Multidisciplinary Approach to Surgical Oncology Patients

M. D. Ray
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To

The Universe

Foreword

If you are really thankful, what do you do? You share.

There is no better way than writing a book to share both, one's knowledge and ignorance. It is indeed a great pleasure to be writing another foreword for such an outstanding book titled, '*Multidisciplinary Approach to Onco Surgical Patients*' that will go a long way in making learning of various aspects starting from rehabilitation, intraoperative and postoperative management to discharge. The book has a vivid and step-by-step approach for a successful outcome in all kinds of Onco Surgical Patients. The science and art of surgery is best learnt by following the instructions from someone with excellence as a motto in life, a quality that Dr Ray has in abundance. This book would serve well for all surgery residents including those going for MS, MRCS, DNB, MCh examinations, and also for those that are training to excel, including younger surgeons in practice to be a complete Surgeon.

The book covers a wide range of topics including pain management, legal aspects and importance of documentation and research in the modern era. It includes practical tips regarding various examinations and fellowships. The book is strongly recommended for all and especially for those with a dream to excel in the field of oncosurgery.

Having written a few books myself, I understand the hard work required in writing such a book and I must complement Dr Ray for such an excellent masterpiece that he has put together for the benefit of all. I wish him and his book a great success and would recommend the reader to be part of this experience.

God bless us all

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Chairman/Editor-in-chief: Indian Journal
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Fellow, Royal Society of Medicine, UK

Joint Editor—Indian Journal
of Surgical Oncology

Governing Council Member—Association
of Surgeons of India (2009–1015)

President—Association of Surgeons of India
(Delhi Chapter-2015)

President—Association of Breast Surgeons
of India (2013–2015)

Hon. Secretary, The Association
of Surgeons of India (2012)

Foreword

It gives me immense pleasure that Dr M D Ray is introducing his new book, '***Multidisciplinary Approach to Onco Surgical Patients'*** for the benefit of young surgical oncologists. After the great success of his earlier two books for the surgery residents, I am sure this one on Surgical Oncology will be highly beneficial to budding surgeons and surgical oncologists.

Dr M D Ray is a highly talented and dedicated surgical oncologist and, in his short tenure, has gained significant popularity in India and abroad by his work and dedication. It is heartening to see one of my very dear students doing so well and continues to do us proud.

Cancer is the epidemic of present days and India has a double challenge of high cancer burden and very high mortality. Cancer care is not just a medical branch but a philosophy as most patients need multimodality treatment. It is the duty of all related with cancer care to educate the general practitioner, specialists of basic specialties and the young oncologists in early detection and handling of initial stages of cancer.

Dr Ray has successfully covered all aspects of cancer care in his new book including investigation, diagnosis, management, surgical issues and rehabilitation. I am sure the book will go a long way in benefitting all its readers in cancer care.

I wish Dr Ray and his book and all the readers all the best for their careers and to him for all his future ventures.

Major Genral (Retd) Prof Sanjay Kapoor
VSM, Onco Surgeon and Deputy Medical Director
TMH, Kolkata

Preface

'Most people, the vast majority in fact, lead the lives that circumstances have thrust upon them, and though some repine, looking upon themselves as round pegs in square holes and think that if things had been different they might have made a much better showing, the greater part accept their lot, if not with serenity, at all events with resignation. I think they are like tram, cars travelling for ever on the self same rails. They go backwards and forwards inevitably, till they can go no longer and then are sold as a scrap iron'.

My sincere effort to write the book is to make students an exceptional personality in the field of surgical oncology through this ***Multidisciplinary Approach to Onco Surgical Patients*****.** I feel the book will help all the medical students both undergraduates and postgraduates and super speciality students to face viva tables and to get through in examination and which is very important to be through the exam door, and that is the *Gateway to enter the field of Surgical Oncology*.

Being an onco surgeon, I know surgeons are weak in antibiotics policy, especially in compromised hepatic and renal function, nutrition, pain managements, etc. I tried to highlight all neglected aspects of a surgeons, which are very important to make a complete surgeon, like the basic concept of surgical and onco surgical disciplines, management of surgical patients from pre-op preparation to discharge, fluid-electrolytes, blood-blood products, nutrition, co-morbidity and pain management, surgical safety, consumer protection act, Medicolegal aspect, importance of documentation, research and publication, etc. Onco surgery is a teamwork and the surgeon is the captain of the team and has to be a perfectionist. I know it is difficult to achieve perfection but if we try to achieve it at least, we can catch the excellence. I remember a short story on perfection. Icannot but mention the story here.

There was a king in India. One day the king asked his sculptor to make two idols to install on pillars of 15 feet height at the front gate. At the end of his stipulated time, he noticed that there is a scratch on the nose and requested king to give him more time to make another one.

King saw the idol and started laughing stating that, you are going to place it 25 feet height. Who is going to see the scratch? The sculptor replies, it's me Maharaj, I will keep seeing it always even after closing my eyes. Being a surgeon, we should be perfect like the sculptor to excel at a task today, not necessary for someone else to notice but for our own inner satisfaction.

Lastly, I will say, prove William Shakespeare's word in Macbeth wrong 'it (life) is a tale told by an idiot, full of sound and fury, signifying nothing'.

Say with me, life is a tale told by a wise full of joy and merry, signifying many things. Welcome for constructive criticism always.

All the best

New Delhi, India M. D. Ray

Suggestions for Success

- Marry/keep constant relation with the right person. This one decision will determine 90% of your happiness or misery.
- Give people more than they expect and do it cheerfully.
- Be forgiving to yourself and others.
- Be generous.
- Have a grateful heart.
- Be persistent.
- Discipline yourself to save money on even the most modest salary.
- Treat everyone you meet like you want to be treated.
- Commit yourself to quality.
- Be loyal.
- Be honest.
- Be a self-starter.
- Stop blaming others. Take responsibility in every area of your life.
- Take good care of those you love.

The basic triad of success:

1. Exercise
2. Meditation
3. Study

It is very very important to realize that valuable man is always far better than a successful man. Always try to be a valuable man in life.

Basic Tips for VIVA

1. Proper dressing, simple, sober clothes.
   Full sleeve apron—well written Exam Roll No over it.
   And do not forget to wear **SMILE AND CONFIDENCE** always, Think at the exam hall 'I tried my level best—nothing to get tense. I know better than anyone else' Take long breathe frequently to avoid anxiety and fear.
2. Take the following things to the exam hall
   - Two pens
   - Stethoscope, Sphygmomanometer
   - Measuring tape
   - Torch
   - Gloves and lignocaine gel
   - Roll made X-ray film
   - 4 tourniquets
   - Hammer
3. Be gentle and polite in exam hall. **Never argue with the examiners never and never**. Not only in examination it is applicable but in all the fields of life too.
4. When a patient is alloted to you in lieu of when you are given a case, go to the patient smiling and introduce yourself. Give him/her a packet of biscuit and tell 'this is my very important exam. Co-operate with me and do not get annoyed please'. Make him/her comfortable and friendly. Take relevant history. Request the patient to tell the same to the examiner which has been told you.
5. Take proper history. You know, perfect history taking will take you through the GATEWAY TO SURGERY. Remember the points for the specific case and write down the long case till case summary and provisional/differential diagnosis.
6. Examination of patient and its findings should be perfect. Do not try to make it as per book, make it whatever it is. Examiners like the truth, not the book knowledge or the manipulation. You know he is more than hundred times experienced than you.
7. Be confident to see the examiners. Say 'Good morning sir', Thank you sir, etc.
8. If the Examiner asks you to tell the history, it is always better to speak history without seeing a case sheet. Have eye to eye contact with examiner. If he asks the summary/diagnosis, tell that thing only. First you listen what examiner is asking you. Take a pause then start speaking—speak

in proper speed, not very fast, not too slow. Give a common diagnosis first. Remember diagnosis of a rare disease will be rarely correct.

9. Always avoid speaking uncommon words, uncommon terms or syndromes.
10. Think for a second which you are going to tell. In exam hall, each word is important which makes you through or may not through the 'Gateway'.
11. **Maintain basic things**. If you do not know the answer, say, 'I don't know sir'. Never stand dumb. And never try to make examiner fool by giving irrelevant answers. If required quote a standard text book or any reference.
12. Lastly I would say the same, '**practice makes perfect**'. Practice case presentation in Clinical Meeting, in front of teachers, friends and above all at home in front of a mirror repeatedly.

Wish you to easily overcome the 'Gateway' to the world of Surgical Oncology

All the best—ever and always.

Dr (Major) M. D. Ray

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I am very grateful to the following personalities for this book:

1. The Universe for giving me a beautiful life.
2. My mother Mrs Saralashree Ray, my wife Anisha Ray and my son Mayukhraj Ray for constant support and suffering for me always.
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Thank you everybody, thank you all.

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Contents

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About the Editor

M. D. Ray Dr M D Ray received his MBBS from Calcutta Medical College and his Master's in Surgery from Army Hospital (R&R), Delhi. He trained in surgical oncology at Army Hospital and Safdarjung Hospital, Delhi. Additionally, he completed his FRCS in Glasgow (UK), his FICS (surgical oncology) in the USA and PhD (molecular oncology) at AIIMS, New Delhi.

Presently, he is a consultant at the Department of Surgical Oncology and a teacher and supervisor for MCh (surgical oncology) students at AIIMS.

He has authored books on surgery and peritoneal surface malignancies and has published several papers in national and international journals. He is also a renowned philosopher and has written more than 25 books on philosophy and literature. He is the recipient of the Rashtriya Gaurav Award for excellence in surgical oncology and has been included in the Limca Book of Records for his excellence in critical surgery. Earlier in his career, he participated in the Kargil War as an Army doctor.

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Concept of Surgery and Basic Principles of Onco Surgery

1

M. D. Ray

1.1 What is Surgery?

1. Surgery is an art of learning not only when to cut but it is more important to learn when not to cut.
2. Surgery is such an act which once done, cannot be reversed.
3. All surgeries are major; there is no minor surgery.
4. Surgery is a science as well as an art. Try to be artistic in surgery and life too.
5. Surgical triad.
   - Measure thrice.
   - Think twice.
   - Cut once.
6. Doing the surgery may be easier, but it is managing the patient which counts finally.
7. The lesser the indication, the greater the complication.
8. In surgery as well as life too there is no question of 'Short Cut'.
9. A surgeon carries success or failure with in self. It does not depend at all on outside conditions or sayings.
10. Many skilled operators are not good surgeons.
11. Attitude for a surgeon may be a small thing, but it makes a very big difference—all the time!

1.2 Basic Principle of Surgery

Concept and Strategy Success in surgical discipline requires clear anatominal knowledge, good planning, clear picturing of the operation and definitely technical skill.

To develop the concept, we should know anatomy, pathophysiology and pathology of the concerned disease.

Think about the merits of alternative treatment options before putting the knife.

When you decide the surgery plan for prehabilitation. Prehabilitation i.e. pre operative preparation including nutritional built up is a very important aspect. Before any major surgery see the following things and calculate the risk of the operation. High risk factors—(i) Age > 65 years, (ii) BMI < 18 or more than >30, (iii) Hb% < 10gm%, (iv) TLC < 4000/cumm or > 12,000/cumm, (v) PT, INR, (vi) Albumin<3gm%, (vii) Co-morbidities like IHD, COPD, HTN, TB and specially Diabetes, (viii) History of smoking and alcohol intake, (ix) Ascites and (x) Patient's mental status and consent—is last but not at all least. Advice for (i) quit smoking, tobacco chewing, alcohol intake etc. (ii) high protein diet with immuno nutrition, (iii) haematinics, (iv) hydration, (v) hygiene, (vi) spirometry 200 times per day and last but not the least Exercise, yoga and meditation half an hour per day minimal.

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Now reflect on the personal experience/concept with complications morbidity, and possibility of mortality.

Review post-operative complications and poor results or mortality of the patients. Criticize yourself, analyse the happenings sincerely and attempt to make an objective appraisal of what went wrong. Think about the poor judgement regarding the selection of the case for the operation.

Please, keep official as well as personal records for the future references, i.e. go through the records before going for the operation of the same type of case. It helps a lot to improve surgeon rapidly.

And persist in a life time study of the published literature in basic science and in clinical surgery.

As per the 'strategy' is concerned, it is advisable that advanced planning of the technical steps of the operation is essentially vital for the safety and efficiency of difficult surgical procedures.

In a word, the operative strategy is that, what the surgeon discusses the day before or ponders the night before the operation.

Anticipating the potential problems and danger points before the operation is the key word for the success than the handling of an awkward situation, in the operation theatre after both the surgeon and patient are in a thick soup.

Remember The main goal of any successful operation strategy is to make the operation easy. Good pre-operative preparation, good exposure, very good light, expert assistants are the essential part of the successful surgery.

If the surgeon is in difficulty, should stop cutting and start thinking why the operation steps seem to be difficult poor exposure, wrong position, bad light or bloody field, etc.

The best surgeon makes always the operation easy, just because of a good operation strategy. And lastly I say, when the surgeon is in real trouble, should call for a help from a more expert colleague.

Remember the proverb 'Asking for a help is not weakness, rather it is strength'. I do not know how much it is practical in our day today life but I know it is more appropriate proverb during a difficult surgery.

And believe me, in surgical discipline, try to be honest, always confess the wrong thing/mistakes you have inadvertently done and be a great critic of yourself.

I personally believe, whatever you try to convince your assistants or colleagues to cover up your mistake or wrong technique, it is you and your conscience will be echoing the fact to you.

Your inner happiness is more important after the surgery than the outer smile. Is not it??

1.3 Outcome of a Surgical Patient

It is more or less equally depends on three phases:

1. Pre-operative preparation 25–30%,
2. Intra operative management 35–40%, and.
3. Post op management 30–35%.

So every phase is important for a successful surgery and no surgery is minor surgery even patient may die on vasovagal attack during biopsy. So take every surgery in a right way.

1. Pre op preparation

I. Confirm the diagnosis first—do the relevant investigations—USG, CT Scan, Endoscopy, etc.

II. Assess the general condition of the patient so called performance status (See the Table 1.1 below).

And decide whether surgery is better or other modality before surgery.

III. If surgery is the choice of treatment, optimize the patient first do the following routine investigations:

(a) Complete blood count (CBC), platelet count, PT, INR (minimum BT, CT). (BT—Bleeding time, CT—Clotting Time).

(b) Sugar (fasting, post prandial or random).

(c) KFT (Urea, Creatinine).

(d) LFT—Total bilirubin, protein, albumin, ALP.

(e) Chest X-Ray (PA View).

Table 1.1 ECOG performance status and Karnofsky Performance Status

ECOG Performance Status	Karnofsky Performance Status
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any self-care; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

(f) ECG.
(g) Viral Markers— HBV, HCV, HIV.
(h) Urine— RE & ME (i) Cardio pulmonary exercise test or pulmonary function test for elderly people and for major surgery.

Get the PAC done along with this investigations. Let the Anaesthetist decide any other investigations required for the general anaesthesia purpose like PFT (Pulmonary function test), CPET (cardio pulmonary exercise test), Echocardiography etc. for correction of co-morbidity opinions may be required from other speciality. Get PAC done in a proper way.

At the level of OPD:

1.4 Start Prehabilitation

(a) Stop smoking, tobacco, alcohol, etc.
(b) Hygiene.
(c) Hydration.
(d) Haematinics.
(e) High protein diet.
(f) Spirometry 100–200 times per day.
(g) Exercise, Yoga, meditation half hour per day.

Start (i) Protein diet or protein supplements,
(ii) Ask the patient to maintain hygiene, and
(iii) Ask for spirometry exercise minimum 100 times/day.

Diabetes, hypertension, COPD to be optimized before admission for surgery.

Make the patient understood about the surgery pros and cons. Take proper consent on admission: review all reports. If the reports are more than a month old, get re-check-up done.

Show the Anaesthetist beforehand.

Write the final plan— Incision, operative procedure. Side— right or left,etc.

Always underline the side and everywhere side to be mentioned like RCC (Rt.) or plan Right Radical Nephrectomy (Rt.).

Take proper consent (A separate Chapter is there for ideal consent).

Never do any procedure without the consent of the patient. Never only on relative or NOK's consent except an emergency where the life-saving procedure is to be performed.

There is very strong legal issue on this even though your intention was genuine towards the benefit of the patients. Few important quotes to be remembered—

1. Safety of the patients shall be the highest law.
2. The good physician treats the disease and the great physician treats the patients who has the disease.
3. Attitude is a little thing but it makes a big difference.

Before surgery every requirements should be in hand starting from drain to any specific item like DJ stent, mesh, connecting plate, etc. and of course blood, FFP, etc.

Never *argue* with Anaesthetist. Maintain everything in a proper harmony starting from nursing staff to all OT staff. To be cool and calm is the main art for a valuable Surgeon.

Maintain sterility property starting from OT temp (ideal 21^0–23^0 C) to cleaning draping, etc.

Hand wash is an important issue (Figs. 1.1 and 1.2). But unfortunately most of us do not bother about this thinking that our hands are always cleaned. Please spend minimum 3 minutes to clean hands with scrub and antiseptics and in a proper manner and use strileum before putting gloves.

Maintain sterility the most important aspect of surgery. By mistake if anything is touched, little too, in your hand please change the gloves, do not try to manage with it.

Always use double gloves. Change the gloves every 3 h because sterility of gloves persists up to 3 hours maximum.

Cleaning of the patient or catheterization to be started with Anaesthetist's consent only.

Catheterize the patient with full sterility. (Fig. 1.3).

Clean the operative part with povidone iodine.

↓

Spirit

↓

Povidone iodine

Minimum contact period should be, of this antiseptic is, 3 min to make the operative surface area sterile. Do not try to start the procedure in hurry.

Remember commonest cause of death in a surgical patient is infection. Infection can take

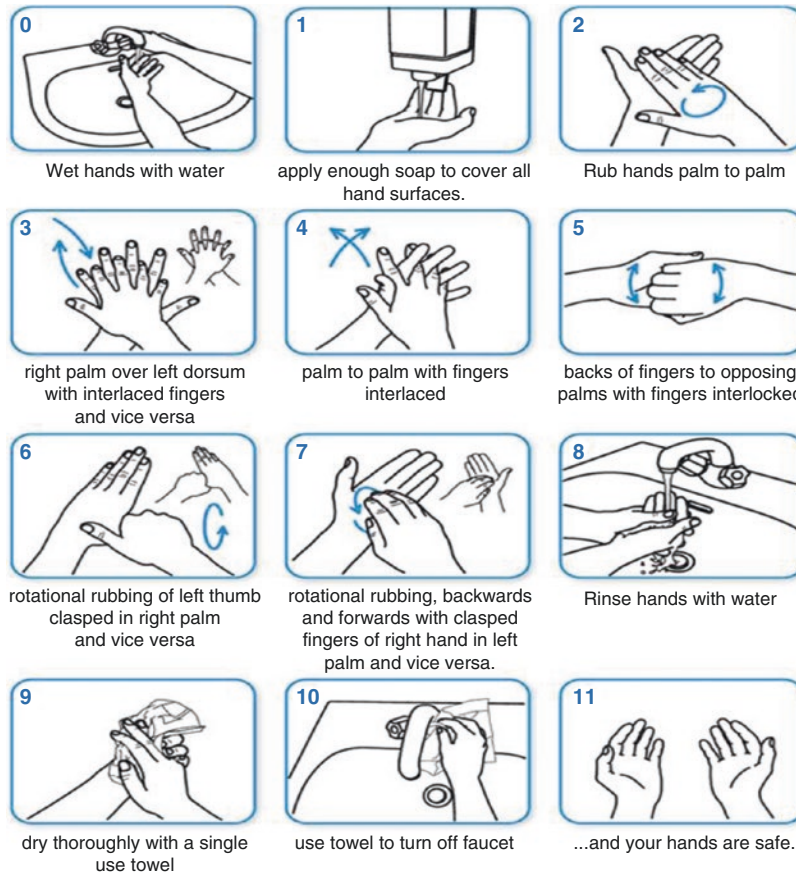


Fig. 1.1 Technique of hand washing before surgery

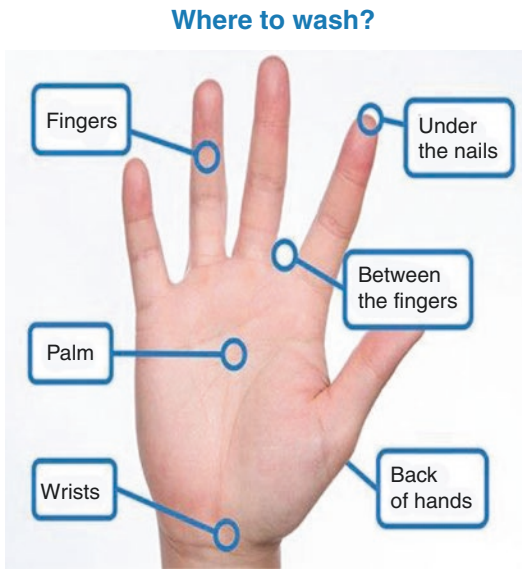


Fig. 1.2 Where to wash properly

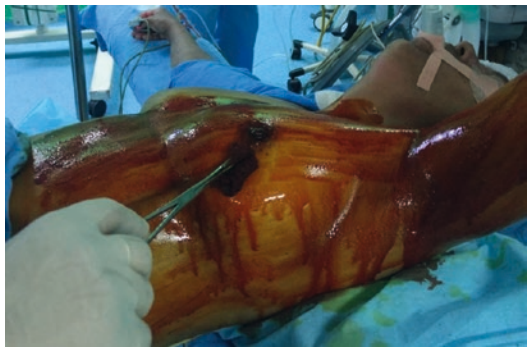


Fig. 1.3 Painting with povidone iodine (as per the present literature Chlorhexidine is the better antiseptic solution)

patient's life and credibility of the surgeon and Anaesthetist. So, beware of infection.

Intra operatively; first and foremost thing is to assess the operability.

If operable, start operating step by step.

Ask Anaesthetist frequently everything is alright? Vitals, haemodynamic stability, etc.

What I personally feel is, complications of a surgery mainly start at the time of surgery. I repeat mainly at the time of surgery.

Tissue handling is an important aspect of surgeon's skill. Its fact that if you do not pay your respect to anyone, nobody will pay due respect towards you too. The same way it happens during surgery. If we pay due respect to the tissues, it will, in return, will respect to the surgeon by making the patient fit to discharge soon and thereby, the Surgeon will be in a comfort zone.

1.5 Post-Operative Period

Post op care is equally important like pre op and intra op.

Look the SOAP

- S— Subjective assessment any complaints from pain site like pain, nausea, vomiting, uneasiness, etc.
- O—Objective— Assessment the patients co-operative. Look at the face of the patient 80% surgeon could assess the patient from the face how the patient is!!

Pulse, BP, Respiration, temperature, pallor, ecterus, oedema and pain (fifth most important vital sign).

See the investigations Hb%, TLC, DLC, PCV, CX Ray. etc.

Assessment of the patients, surgical wounds, drains, abdomen, respiratory system and from the subjective and objective assessment, assess how the patient is?

Expected or any special attention to be paid.

Plan— After the assessment, make the plan, fluid requirement, blood transfusion, any new injection like DVT prophylaxis to start or not, mobilization, physiotherapy, respiratory care, nutrition, etc.

Always make a check list and tick every need when it is completed. Do not try to remember what things to do after round. We like to think that we could remember but more than 90% cases we cannot remember all instructions thereby leave, one/two instruction invariably.

It is always better to make a protocol for your own patients like antiseptic policy, thromboprophylaxis pre op, post op protocol for specific group of patients. Because every setup is different, rate of infection, causative organism, etc. So better to make your own protocol.

At the end of this chapter, I will say our dedication and self-involvement in the management

of surgical patients can only make miracles otherwise, unbelievable negative things will happen usually.

Bricker in 1950 says, 'If we are unable to have a patient in a functional stable, compatible with a comfortable existence, we are morally not justified in performing the operation'.

1.6 Basic Principles of Oncosurgical

Introduction Surgical resection of tumour remains the cornerstone treatment modality, among all the available modalities, which could cure cancers.

Oncosurgical plays an indispensible role in the management of cancer patients across the Globe!

With the advent of chemo, radiotherapy, targeted therapy, the treatment pattern and prognosis have been changed for the best. But in the other way, oncosurgical has to lead the whole journey of a cancer patient, awaring of the potentialities of surgery, chemotherapy, radiotherapy or other newer treatment modalities like targeted therapy, hormonal therapy, etc.

Really it is a true challenge to treat cancer patients as they are often immune compromised owing to various reasons, many a time associated with multiple co-morbidities.

Overall health status, rather than the age alone, to be considered before selection of the patient for a major surgery.

It is to be remembered always that Biology of the disease is the King, selection of the patient is the Queen and our skill and techniques are the Prince and Princess.

Surgery after neodajuvant chemotherapy surgery is little difficult because of demoplastic reaction and oozy field.

Chance of infection is more. Same way after Radiotherapy also, it is difficult to dissect in proper surgical tissue planes because of uniform fibrosis. Delayed wound healing or wound breakdown also not uncommon.

1.7 Diagnosis of Cancer

FNAC (Fine Needle Aspiration Cytology) preferably biopsy, is mandatory initially to obtain tissue for exact histologic diagnosis.

FNAC using 23 gauge needles. It is an established modality for diagnosis in breast cancer, parotid, thyroid.

But few drawbacks are there—as FNAC cannot distinguish between in situ and invasive breast cancer, in thyroid follicular adenoma versus follicular carcinoma as it is unable to detect capsular and vascular invasion.

On the other hand, varieties of biopsy can have more tissue to diagnose clearly the disease, even hormonal status, etc.

1.8 Different Types of Biopsies Are

1. Tru-cut biopsy—With a special needle, which can remove a core of tissue Ca Breast, Sarcoma or any accessible solid tumour. (Figs. 1.4 and 1.5).
2. Excisional biopsy—When the tumour or nodules size are less, removal of whole tumour with a clear margin of surrounding tissue.
3. Incision biopsy—Removing a small wedge of tissue from a tumour either from a surface tumour or from a hollow viscus.
   Oral, oesophagus, gastric, colorectal lesion—this biopsy is preferable.

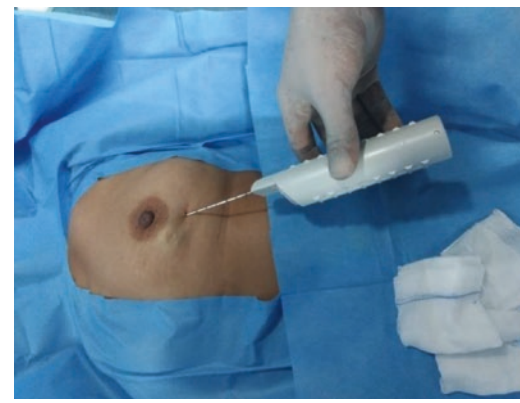


Fig. 1.4 Core needle biopsy being done

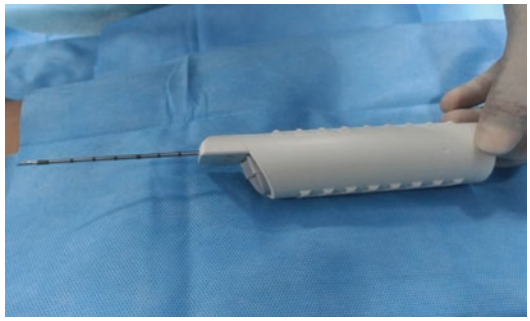


Fig. 1.5 Core biopsy needle

This is one form of Punch biopsy, where a specially designed instrument is used to take the tumour tissue as well as from the normal tissue.

4. Exfoliative cytology—Bronchial lavage, urinary cytology or ascitic fluid cytology for lung, urinary tract or metastatic disease detection, respectively.
5. Frozen Section Biopsy—Gradually coming up in a great way, to take a major decision during surgery, where no confirmed histopathological diagnosis beforehand, frozen section biopsy has got a very important role.

   Negative sentinel lymph nodes, in a frozen section, can raise a decision to avoid axillary lymph nodes dissection, thereby avoiding morbidity like lymphedema.

   Even in Gynaecological malignancies frozen positive for cancer may require extensive surgery.

   Most recently frozen section biopsy may show the better margin assessment.

   In a word, tissue diagnosis is the essential primary step for further progress in cancer management.

   It is to be noted that in few cases FNAC or biopsy is contraindicated like suspected Carcinoma Ovary, Renal cell carcinoma, Parotid tumour, etc.

1.9 Staging Work Up

Initially we have to confirm the diagnosis by

1. USG abdomen and Pelvis. As, USG is easily available, cheaper. It shows initial diagnosis—Solid to cystic mass, organ of origin.

   Apart from these basic, liver mets, ascitis, lymphadenopathy, etc.
2. CT Scan—Almost all solid tumours even in a hollow viscus, CT Scan is the investigation modality of choice.

   In special situation MRI is alternative particularly in pelvis. MRI is preferable in pseudomyxoma peritonei rather than CT scan.

   To detect recurrence after breast cancer surgery. MRI to be done for better delineation of Neurovascular bundles.
3. PET Scan—Now a days PET scan is shown as gold standard and used randomly in most of the centre but one thing is to remember that PET Scan upstage the disease in 30% cases. Even in infection and inflammation PET Scan shows positive. So, the standard indications of PET scan are:
   - Head and Neck Cancer,
   - Oesophageal cancer (Figs. 1.6 and 1.7),
   - Lung cancer,
   - Colorectal cancer,
   - Staging of lymphoma,
   - Melanoma.

   Apart from that
   - Carcinoma Primary unknown where diagnosis not established despite of usual investigations.
   - Ca thyroid where *radio iodine scan is negative to detect recurrence* but thyroglobulin level is beyond normal level.
   - Advanced cases of many cancers, after neoadjuvant therapy to assess the response like Ca Ovary, peritoneal carcinomatosis, GI cancers,etc.
4. Bone Scan—To detect bone mets like in locally advanced Ca breast to stage the disease.

   Suspected bone mets in other cancer like Ca prostate but where alkaline phosphatise is elevated.
5. Tumour markers—So many cases of cancer, Serum tumour marker has got a certain role to establish the diagnosis.

   Like Ca-125 is a marker for Ca Ovary though this is not a specific marker but along with Adnexal mass if it is elevated, it is suggestive of Ca Ovary.

   Same way CEA is a marker for Colorectal cancer. Along with tumour or ulceration in

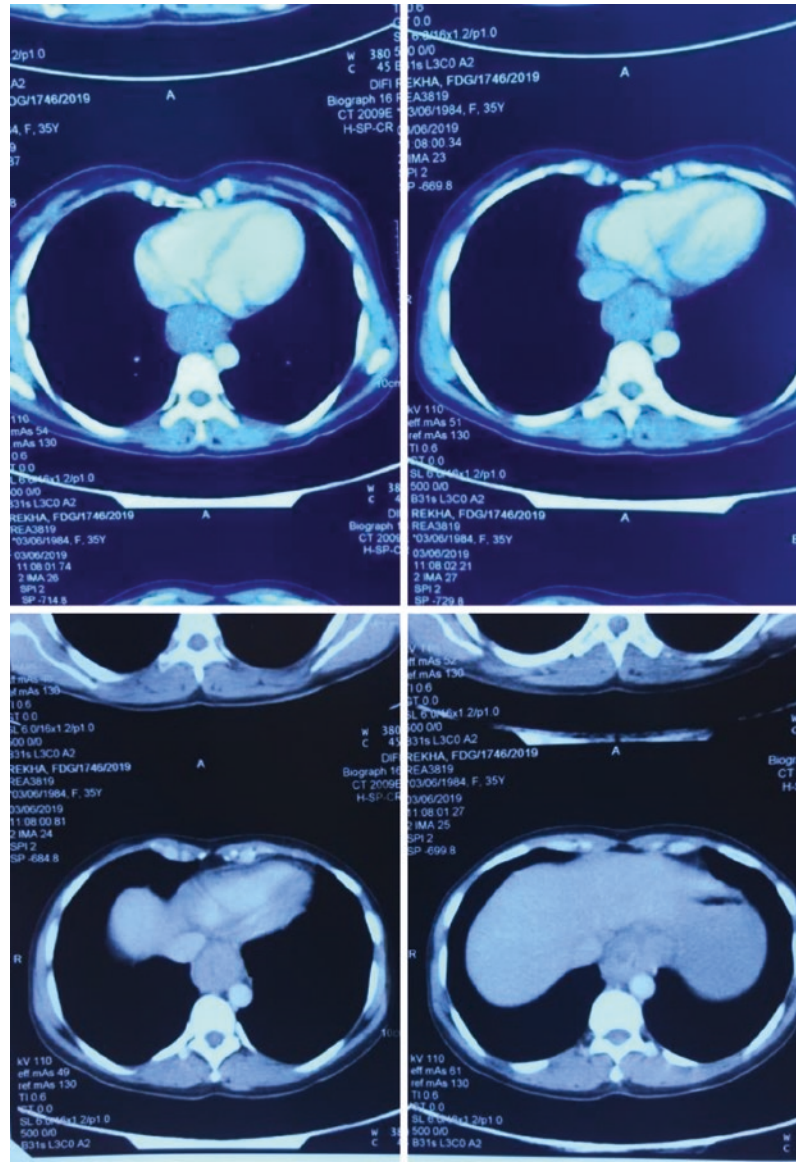


Fig. 1.6 CT images shows circumferential thickening of oesophagus in carcinoma oesophagus

colon or rectum if CEA is elevated, we can establish a diagnosis.

Other common cancer markers are:

- Calcitonin—Medullary Ca thyroid,
- PSA—Prostate cancer,
- Neuroendocrine Tumour—Chromogranin/Synaptophysin,
- AFP—Germ Cell tumours/Liver cancer,
- TTF1—Thyroid cancers, Lung,
- Vermentin—Sarcomas.

1.10 General Work Up

6. Along with the above general work up is very important.

Routine blood test including CBC, LFT, KFT, Sugar F/PP, PT INR, CX Ray-PA, ECG PFT, etc.

Assessment In general, Patient's nutritional status, ECOG score and hydration to be important considerations.

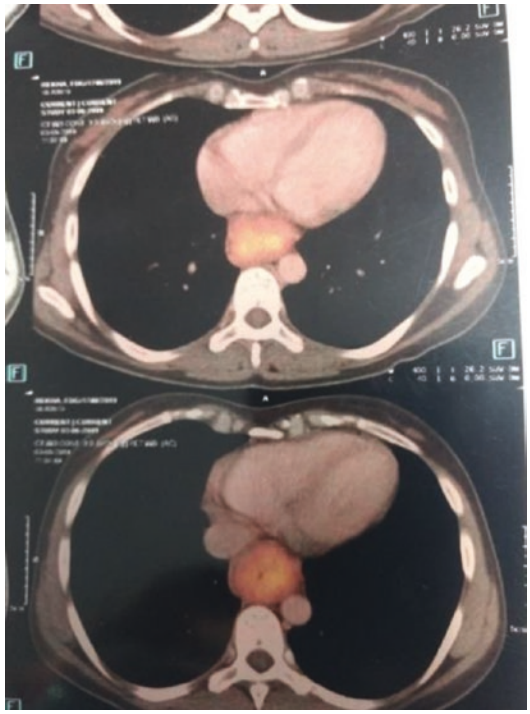


Fig. 1.7 PET image shows increased FDG uptake in case of carcinoma oesophagus

Prehabilitation for minimum 3/4 weeks is equally important factor. (Mentioned before).

Decision about treatment individually or at the multidisciplinary team when multimodality treatment option is there and surgery is not right choice.

1.11 Principles of Operative Oncosurgical

1.11.1 Curative Surgery

Where the margins of the specimen removed are clear of tumour—the total number of lymph nodes excised together with number of involved nodes.

Most of the solid tumours both localized and locally advanced are curable if resection is possible.

Now a days concept of margin has been changed from oral cancer to rectal cancer. Margin positivity is an important aspect both for the surgeons as well as patients. Addition therapy, either re-surgery or radiotherapy, has additional cost and mental burden is main component for both the side.

In oral cancer 2 mm margin and 4 mm depth is acceptable as present days. In rectum, in view of sphincter saving, 5 mm distal margin is considered adequate. In case of renal cell carcinoma, carcinoma ovary there is no NCCN guideline for the resected margin.

Actually what happens—to keep the margin when we cut by diathermy or scissor—the mucosa recedes back thereby actual margin does not reflect when pathologist handles no. 2. Formation itself causes up to 5% retraction of the specimen margin by the time Pathologists cut the section. So, frozen section immediately after specimen removal has being more popularized day by day.

Lymph nodes dissection is an important aspect of cancer surgery. Though most of the study suggest, there is no overall survival in Lymph nodes clearance directly. Positive nodes reflect the prognosis. But few study suggests that there are indirect evidence of LN dissection for better survival as example LNs usually do not respond on completely therapy if we do not remove recurrence rate is obviously high and thereby overall survival will be reduced. So lymph node dissection is an integral part of onco surgical resection like head and neck, breast surgery as well as GI and Gynaecological resections.

Surgery for Metastatic disease—Sometimes surgery is required for metastatic disease to palliate the symptoms; even pelvic exenteration is acceptable to palliate symptoms.

In stomach cancer simple bypass surgery, gastro jejunostomy is enough to relieve from obstructive symptoms.

Cytoreductive Surgery In metastatic RCC, there is a definite role of Cytoreductive surgery. At least 70% of total tumour bulk to be removed as per the definition of cytoreduction surgery. It reduces further disease spread from the primary

site and more over relieves the symptoms like haematuria and anaemia.

In carcinoma ovary FIGO stage III onwards and carcinoma endometrium FIGO stage III & IV debulking surgery has got a definite role.

Surgery for Staging of Cancer Upfront surgery for ca ovary endometrium even Germ cell tumours need exploratory laparotomy for staging along with the primary organ involved by the tumour, lymph nodes dissection, PLND, RPNLD, omentectomy, peritonectomy required.

Surgery for Prevention of Cancer BRCA I, BRCA II positive female with strong family history may be the candidate for prophylactic mastectomy. Heriditary poliposis coli with more than 100 polyps patient should undergo total colectomy around the age of 20 years.

Other surgeries are:

- Reconstructive.
- Rehabilitation.
- Ontological emergency, etc.

Palliative Surgery in GI tract cancer to relieve obstruction where curative surgery is not feasible.

Palliative Surgery is to perform to overcome some symptoms, thereby either resection or bypass surgery is required.

Example: In case of Pyloric obstruction Gastrojejunostomy will provide the bypass of food passage and relieve of vomiting.

Resection of colorectal cancer to relieve from obstruction and bleeding.

But one thing to remember that 'Tailoring' of this kind of surgery to the need of the patient, not for the need of the surgeon without undue morbidity or compromised quality of life.

Margins of Surgical Excision Adequate margin of the excised specimen always an important issue for the surgeon.

Now a days with the advancement of conservative surgery the concept of margin has been changed. Despite of taking adequate margin, pathology reports many a times show positive margin or a close margin because of two common reasons.

1. When we cut the tissue by diathermy the mucosa at the margin recedes back few mm due to contraction.
2. When we merge the specimen into formalin—the margin recedes back due to contraction of mucosa and submucosa up to 50%. So, if we keep 1 cm margin it could show at histopath specimen 0.5 cm.

Now a days the margin concepts are as follows in the 10 most common solid tumours.

1. Oral Cavity 2 mm, depth 4 mm.
2. Breast negative ink surface (no tumour in ink surface).
3. Rectum Distal minimal 5 mm.
4. Colon 3 cm each side.
5. Stomach 2–4 cm both side.
6. GE junction 2–5 cm.
7. Oesophagus 1–2 cm.

No concept margins in Ovary and Kidney.

1.12 Lymph Nodes Dissection

Lymph nodes dissection of respective drainage area of primary tumour to be removed for the following.

1. For staging purpose.
2. For prognosis.
3. For further therapeutic plan.

Till date there are no sufficient data suggestive of survival benefit.

Prophylactic groin dissections in some aggressive cases like melanoma, ca penis, ca vulva show some survival benefit and reduction of nodal recurrence!

1.13 Rehabilitation

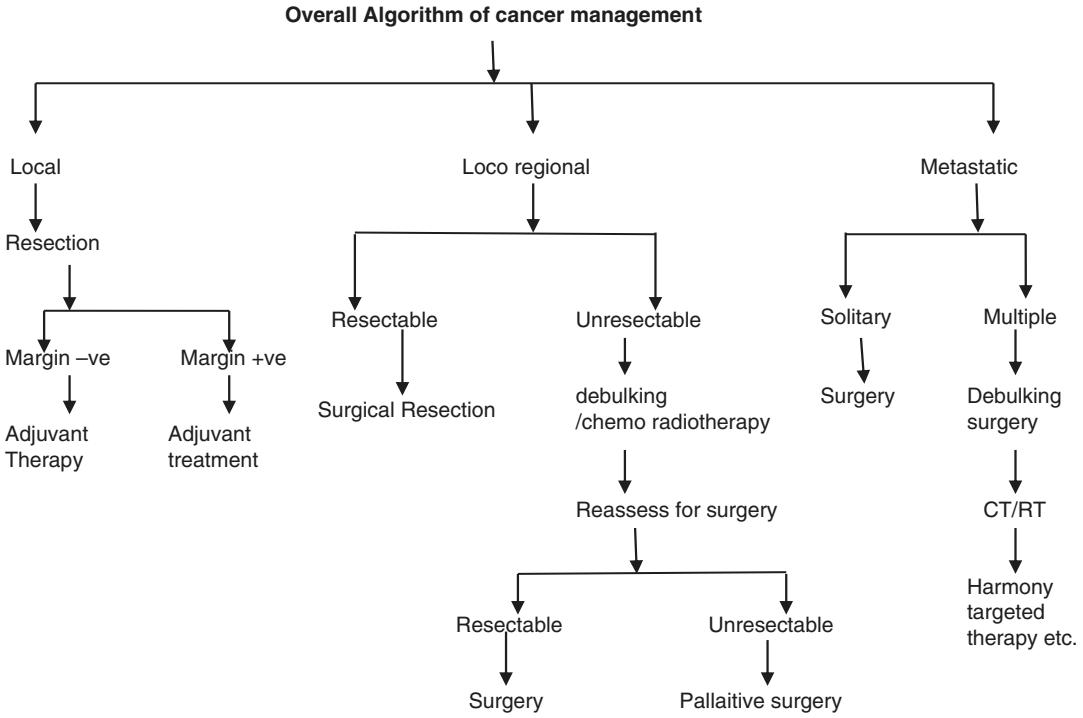
Rehabilitation is important aspect of on surgical resection, breast oncoplasty or prosthesis after mastectomy, artificial limb after amputation, physiotherapy after removal of large masses from the muscle group. Anyway we have to focus on quality of life of cancer patients too.

1.14 Follow up

Follow up is an essential component of cancer treatment.

Usually after a major surgery 3 monthly followup is required for initial 2 years, then 6 monthly for next 3 years, then yearly.

This is important to detect early recurrent disease so that best treatment could be offered at the earliest.



Alternative Treatment Option To tell the truth till date there is no alternate treatment option in cancer apart from surgery, chemotherapy, radiotherapy, targeted, hormonal and immunotherapy.

I always like to reply to patients that you may go for other treatment like homeopathy, ayurvedic but as supportive intent, not as curative.

As far as yoga, gym and physical exercise are concerned, they play a role to prevent the disease, not the cure!

1.15 Overall Complications

Every therapy, starting from surgery, chemo to radiotherapy everywhere some drawback, i.e. some adverse effects are there. It is surgeon's responsibility to make the patients understand the total situation. Patient and party to be fully convinced with the complications, prose and cones of surgery.

We should value the patient choice above all.

2 Basics Principles of Radiation Oncology

Subhash Gupta, K. P. Haresh, and Bharti Devnani

2.1 Introduction

Treatment of cancer requires multidisciplinary team approach. Radiotherapy (RT) is an integral part of the comprehensive cancer care and is required in around 60–70% patients diagnosed with cancer at some point of the time in the course of disease. Sir Wilhelm Conrad Roentgen discovered X-rays in 1895 and since then it is being therapeutically used to treat cancer [1]. This chapter aims to give insight in basic principles of Radiation Oncology for the surgeons.

There are two types ionizing radiation—

- Photons including x-rays and gamma rays.
- Particulate radiation which includes electrons, protons, α-particles, neutrons, negative π-mesons, and heavy charged ions.

2.2 Mechanism of Action

DNA is the principal target of radiation damage. Double-strand breaks are most important biological lesions produced in chromosomes by radiation resulting in cell kill [2]. There are two types of mechanism of cell kill by radiation—

- Direct action—This form of radiation causes direct ionization or excitation of atoms of the target. Radiation impacts the DNA directly in this type of cell kill that is why it is also known as "direct hit." It is the dominant process with high linear energy transfer (LET) particles which are neutrons and alpha particles.
- Indirect action—This is the common method of damage by radiation where radiation interacts with the non-critical target atoms usually water and forms the free radicals. These free radicals then attack the DNA. This free radical mediated injury is known as indirect action of the radiation. The most radiosensitive phase of cell cycle is G2-M phase while S phase is the most radio-resistant phase.

The principle form of photon interaction for therapeutic radiation is by Compton effect. It occurs due to interaction of the photon with the outer shell electrons which are loosely bound to the atom.

2.3 Radiobiology of Radiation Treatment

Radiotherapy is delivered in the fractionated approach; it means the total dose is divided in to a number of daily doses which are generally delivered 5 days a week. Conventional fractionation of radiotherapy is delivered to a dose of

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1.8–2.0 Gy per fraction, from Monday to Friday. There are early reacting tissues including skin, mucosa while some tissues are late reacting like spinal cord, kidney, etc. The aim of fractionation is to maximize the tumor control probability at the same time minimizing the normal tissue complication probability to optimize the therapeutic ratio.

The biological basis of this fractionation is based on "four Rs" [2] of radiobiology as follows-

- *Repair* of sub-lethal damage—There are 3 types of damage by radiation, namely sublethal damage, potentially lethal damage, and lethal damage. Under normal circumstances, the sublethal damage is repaired in 2–6 hours unless other sublethal damage is being incorporated. This time interval between the two fractions of radiotherapy allows the normal early reacting tissue to repair of sub lethal damage repair.
- *Reassortment*—Cells are in different phases of cell cycle and asynchronous at the start of the radiation. G2-M phase is the most radiosensitive phase of the cell cycle while S2 is the most radio-resistant phase. When radiation is given, cells in sensitive phase (G2-M) get killed and the time gap between the two fractions allows the surviving fraction of cells to progress through cell cycle and synchronize to the more radiosensitive phase.
- *Repopulation*—Once the treatment is started, the tumor cells multiply at a faster pace which is known as accelerated repopulation. This is maximum at 4 weeks from starting the radiotherapy. It is prominent for rapidly proliferating tumors of head and neck cancers and lung cancer. The clinical significance of this phenomenon is that treatment breaks in radiation therapy adversely affects the outcome.
- *Reoxygenation*—The remaining viable cells after a fraction of radiotherapy is hypoxic and fractionation restores the proportion of oxygenated cells by allowing time for re-oxygenation. Hypoxia is an adverse feature which leads to radio resistance and poor tumor control. Re-oxygenation between the two fractionations helps in overcoming the negative effect of hypoxia in a multi fractionated treatment.
- *Importance of Oxygen*—Presence of oxygen is very crucial in manifesting biological effects of ionizing radiation [3]. A damage produced by radiation can be repaired by Sulfhydryl (-SH) groups under anoxic conditions. Oxygen fixes this damage produced by free radical and makes it permanent (lethal) damage. Hypoxic conditions increase the metastatic potential of tumor cells and oxygen enhances the radio sensitivity of the cells. Clinical studies have shown benefit in terms of local control in advanced cases of carcinoma cervix and head neck cancer, when the tumor is well oxygenated.

2.4 Altered Fractionation Schedules [4]

2.4.1 Hyperfractionation

Hyperfractionated schedules deliver a RT dose of 1.15–1.5 Gy per fraction twice daily. The intent is to achieve better tumor control with decreased late effects. This fractionation is commonly used to combat the problem of accelerated repopulation especially in head and neck and lung cancers.

2.4.2 Hypofractionation

Hypofractionated RT is utilized for the treatment of breast and prostate cancers where the tumor is slow growing. The dose per fraction is higher than 2 Gy per fraction and radiation is completed is shorter interval of time. The fractionation schedules are designed as per the alpha:beta ratio of the normal tissue and tumor. The fractionation is commonly used in prostate and breast cancer and in palliative irradiation.

2.4.3 Accelerated Radiation Therapy

In this form of treatment, total dose of radiation is given over a shorter period of time compared to standard radiation therapy. Acceleration and

hyperfractionation can be combined, especially in head neck cancers and small cell carcinomas of lung. Accelerated treatment reduces the regrowth of the tumor between sessions, resulting in improved local control. The issue in using such a fractionation lies in the logistics issues as the patient needs to be treated twice a day which causes a problem in high volume centers. Hence, even though it appears to be an appealing modality of dose fractionation, it has not found to have many takers.

2.5 Types of Radiotherapy

Radiotherapy has been conventionally divided into two types [1].

2.5.1 Teletherapy

(Tele-Far) It is also known as External beam radiotherapy and is the most common form of radiotherapy. Tele- When the source of origin of radiation is away from the tumor and radiation is delivered from a distance. Cobalt machines and linear accelerators are being used to deliver the teletherapy by use of photons and electrons.

2.5.2 Brachytherapy

(Brachy- Near) Modality of radiation therapy where radioactive material is placed in or around the tumor [5]. A radioactive source like Ir-192 or Co-60 is the source for gamma radiation in this treatment. This is a type of sealed source radiation therapy (Fig. 2.1).

Brachytherapy is divided into following types based on the location of the implant.

a. Intra-cavitary Brachytherapy—This technique is mostly used for cancers of the uterine cervix and vagina.
b. Interstitial Brachytherapy—This treatment utilizes placement of interstitial needles into the tumor tissue. This method is used in treatment of gynecological, breast, head neck, prostate, penile carcinoma, and sarcomas.

Fig. 2.1 Remote after loading High dose rate Brachytherapy

c. Intraluminal Brachytherapy—The radioactive source is placed into hollow lumen like esophagus, trachea or bile duct. It is especially useful as a boost in esophageal malignancies or as a modality for palliation.
d. Surface (Mold) Brachytherapy—It is used to treat superficial tumors by placing sources on the skin surface. This method is used in treatment of skin malignancies like that of nose, pinna, cheek, scalp and intraoral lesions at hard palate.
e. Intravascular Brachytherapy—The use of this form of brachytherapy is decreasing where sources are placed into vascular lumens.
f. Plaque Brachytherapy: Use of radioisotopes, e.g. Ruthenium has been employed in treatment of ocular tumors like Choroid Melanoma and Retinoblastoma.

Depending on the dose delivered, brachytherapy can be divided into [5] -

- Low dose rate (LDR) brachytherapy—Dose delivered is less than 2 Gy per hour.
- Medium dose rate (MDR) brachytherapy—Dose delivered is 2–12 Gy per hour.
- High dose rate (HDR) brachytherapy—Dose delivered is more than 12 Gy per hour. HDR brachytherapy is most commonly utilized these days.

2.5.3 Unsealed Source Radiation Therapy

Selective Internal Radiation Therapy (SIRT)
This treatment is also known as trans arterial radioembolization (TARE) and used for treating unresectable liver tumors. The procedure involves injecting the Yttrium-90 microspheres into the hepatic artery. SIRT is efficacious in treatment of hepatocellular carcinoma and liver metastasis [6]. An average radiation dose achieved is around 200Gy.

Radionucleotide Therapy (RNT)
Radionucleotide is injected or ingested into the body systemically and based on the material's property concentrated in an organ or site. I-131 for thyroid cancers, Ra-223, Sr-89, Sm-153 for bone metastasis, and Lu-177 for neuroendocrine tumors are some of the example where RNT is used.

2.5.4 Intra-Operative Radiotherapy (IORT)

Intra-operative radiation therapy (IORT) is a technique where radiation is delivered during a surgical procedure directly to the tumor bed. The advantage being precise delivery of a large dose of radiation to the surgical bed with relative sparing of surrounding critical tissues. This is especially helpful in recurrent and residual tumors where dose escalation and reradiation is feasible by IORT which is otherwise difficult with EXRT [7]. The role of IORT has been proven in various malignancies including retroperitoneal sarcomas, pediatric tumors, and recurrent rectal and gynecological cancers. IORT can be delivered using intra-operative electron radiation therapy (IOERT), high dose rate brachytherapy (HDR-IORT), or electronic brachytherapy/low-kilovoltage x-rays (KV-IORT). The advent of mobile linear accelerators and self-shielding devices has further increased the utilization of this technology.

2.6 Intent of Radiotherapy

2.6.1 Definitive/Radical Radiotherapy

Radiotherapy is used as a radical treatment modality with or without concurrent chemotherapy based on the stage of the disease with curative intent. Radiotherapy as a single modality is used in treatment of early stages of head and neck cancers, cervix cancer, while for advanced cases concurrent chemotherapy, e.g. Cisplatin based chemotherapy is used as radiosensitizer. In laryngeal cancers and bladder cancer it helps in organ preservation. The doses range from 60 to 70 Gy by conventional fractionation over 7 weeks. Cervix cancers are being treated by external beam radiotherapy followed by brachytherapy to a total dose of 80–90 Gy for radical treatment [8].

2.6.2 Adjuvant Radiotherapy

When radiotherapy is given postsurgery to eliminate the subclinical risk of micro-metastasis. The suitable time to start adjuvant radiotherapy is between 4 and 6 weeks postsurgery. Intra-operative details and postoperative histopathology is very important for a radiation Oncologist. Post-operative radiation decreases the risk of recurrence and even overall survival benefit in many cancers. It is used in breast cancer, oral cavity, advanced laryngeal cancers, sarcomas, endometrium, and cervical cancers.

2.6.3 Neoadjuvant Radiotherapy

In this approach radiotherapy is given prior to definitive treatment with aim to downsize the

tumor with better surgical outcome. It is being practiced in rectal cancers, locally advanced esophageal cancers, advanced head and neck and breast carcinomas to make surgery feasible.

2.6.4 Extra-corporeal irradiation

Extra-corporeal radiotherapy is used in the management of malignant bone tumors. It helps in limb salvage as a biological reconstruction option in bone tumors, e.g. Ewing's sarcoma and Osteosarcoma. After en-bloc removal of the tumor bearing bone segment, it is irradiated to a dose of 50 Gy in a single fraction and re-implanted back in the body.

2.6.5 Palliative Radiotherapy

Palliative radiotherapy is given for tumor growth restrain and control the symptoms of pain, bleeding, obstruction or compression. It plays an important role in management of metastatic disease. It is given as hypo fractionated approach, most commonly used fractionations are 8 Gy in single fraction, 20Gy/5 fractions or 30 Gy/10 fractions. Some examples of Radiation Oncological emergencies where radiation is used namely- [9].

(a) Superior vena cava obstruction.
(b) Spinal cord compression.
(c) Brain metastasis.
(d) To control tumor bleed.
(e) Obstructive dysphagia from locally advanced esophageal cancer.

2.7 Radiotherapy Volumes Definition

The International Commission on Radiation Units and Measurements (ICRU) Report 50, 62 and 83 [10] has recommended definitions of treatment volumes as-

- The gross tumor volume (GTV) denotes demonstrable tumor. It includes primary tumor GTV-T and grossly involved lymph nodes that is GTV-N. GTV is identified by clinical examination and should be supported by the relevant radiological examinations.
- The clinical target volume (CTV) comprises of the GTV and subclinical disease harbinger of micro-metastasis. This is determined by the radiation oncologist based on the evidence on the patterns of spread and existing contouring guidelines.
- The planning target volume (PTV) is an envelope, which includes the CTV and a margin to encompass for geometric uncertainties. It takes into account the inter and intrafraction motion errors.
- Organs at risk are the non-target normal tissue whose radiation sensitivity influences the treatment planning and dose prescription significantly.

2.8 External Beam Radiotherapy Techniques (Table 2.1) [1, 8, 9]

2.8.1 Conventional 2D Technique

It is the primitive technique to deliver radiation which is largely replaced by CT based planning. Field borders are determined by bony landmarks and orthogonal X-rays of the patient. Beam arrangements are limited and square or rectangular fields are commonly used. It is helpful in palliative treatments due to simplicity of the planning methods.

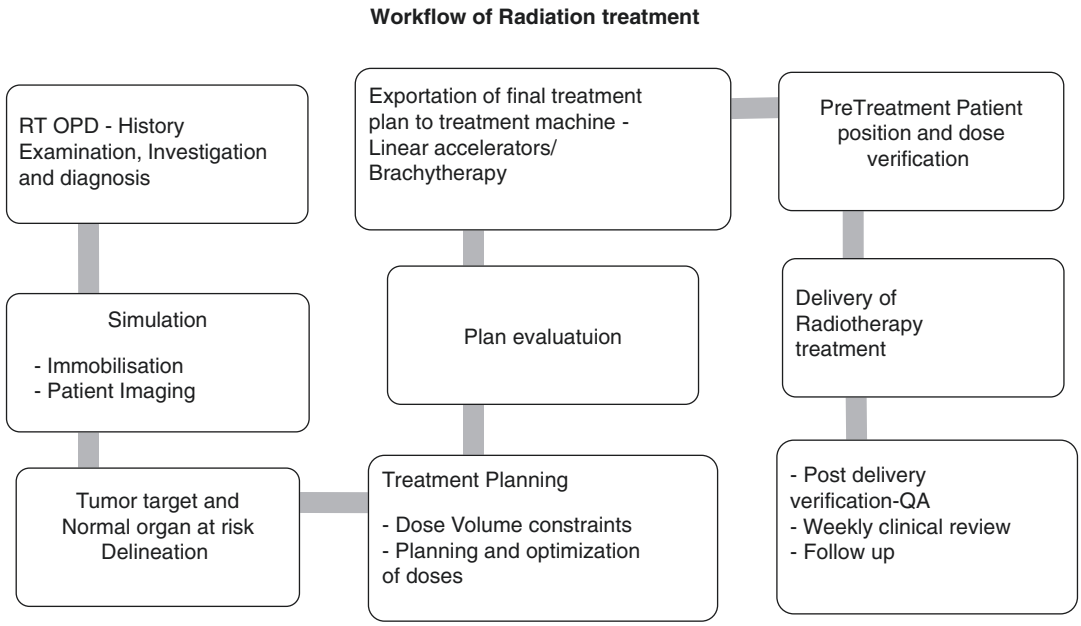
2.8.2 Conformal Radiotherapy

3D Conformal RT (3D-CRT) technique shapes the beams based on 3D reconstructions of the tumor size and shape and the location of nearby normal tissues.

Intensity-modulated radiation therapy (IMRT) changes the intensity of each small beamlet to obtain even more conformal dose distribution and avoidance of normal tissue damage.

Image-guided radiation therapy (*IGRT*) is a method of radiation therapy that incorporates

Table 2.1 Workflow of Radiation treatment



imaging techniques during each treatment session. *IGRT* is used to treat tumors in areas in close proximity to the critical structures and prone for the movement. This technique is required in lung and liver cancer where due to the respiratory motions, there are more chances of intrafraction motion. IGRT helps in precisely delivering the radiation in case of prostate cancer and minimizing the toxicity to the bladder and rectum which are situated are prone for receiving high doses due to variation in filling each day.

2.8.3 Stereotactic Radio Surgery (SRS) and Stereotactic Body Radiotherapy (SBRT)

In stereotactic radiotherapy, ablative doses of radiation are delivered to tumor in a single or few fractions. The technique is based on precise delivery of high dose of radiation to target with minimal injury to the surrounding normal tissues by highly conformal methods. SRS refers to a single-fraction delivery of a high dose to an intracranial target whereas SBRT is hypofractionated treatment applied to extracranial targets.

2.8.4 Hadron Therapy (Particle Therapy) [1, 8, 9]

Proton, Neutron, and Carbon ions are heavy particles which constitute part of Hadron therapy. Proton beam therapy is the most commonly used amongst them. Protons are the positively charged particle which slowly deposit the energy in the tissue up to a certain distance and then deposit their maximal energy also known as 'Bragg peak' with no or minimal exit dose. This helps in sparing the tissues beyond the target. This feature is helpful in reducing the late toxicities especially in childhood cancers like medulloblastoma, ependymoma [11]. Although it is used in almost every site the therapeutic benefit is more pronounced in Choroidal melanomas, Skull base tumors, reirradiation cases and in the tumors which are considered inherently radio-resistant.

2.9 External Beam Radiotherapy Machines [1, 8, 9]

2.9.1 Cobalt-60 Unit

This is a teletherapy machine which utilizes a radioactive source, cobalt-60. The advantage of Co-60 unit is that a simple infrastructure and less power is required, also the maintenance is more cost effective in comparison to Linacs. It is not suitable for deep seated tumors and is associated with more skin toxicities.

2.9.2 Linear Accelerator (Linac)

A linear accelerator is a device that uses high radio frequency electro-magnetic waves to accelerate charged particle such as electrons to high energies through linear tube called the accelerator wave guide. Patient is treated on a movable couch and beam comes out of the gantry which can be rotated around the patient. The principle of linear accelerator was invented by Rolf Wideroe in 1930 and the first patient was treated in 1956 at Stanford University in the USA. Current generation of Linacs have all the advantages of dual photon energy, electron energies, multileaf collimators for beam shaping with improved beam characteristics and image guidance tools in a compact design (Fig. 2.2).

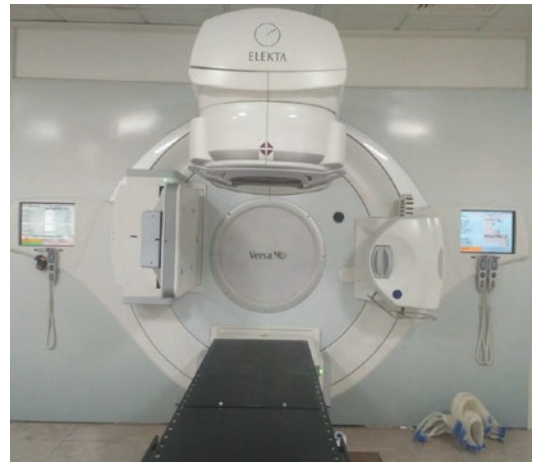


Fig. 2.2 Linear accelerator with advanced technology

2.9.3 Machines to Deliver SRS and SBRT

- *Gamma Knife:* It is a stereotactic radiosurgery unit introduced by Leksell, a Swedish surgeon in 1951 in collaboration with Borje Larrson, a radiation biologist. It has a high precision to deliver high doses of radiation to intra-cranial tumors and used for treatment of Meningiomas, acoustic neuromas and pituitary tumors and brain metastasis [12]. Gamma knife radiotherapy is also useful in benign vascular and functional conditions including arteriovenous malformation, and Trigeminal neuralgia. Historically the unit houses 201 $_{60}$Co sources arranged in a hemispheric array. In the latest system which is named as 'Perfexion' uses 192 $_{60}$Co sources. The gamma knife is not a real knife, instead the highly conformal gamma rays from Cobalt-60 destroy the tumor as a cutting knife.

Linear accelerator (LINAC): LINAC based systems are also used to deliver stereotactic treatment. The advantages of these systems include more patient comfort because of frameless set up and large lesions can be treated using Fractionated stereotactic Radiotherapy (FSRT). Commonly used systems for this kind of therapy includes CyberKnife, NovalisTx, and Brian Lab. The CyberKnife System has a robotic arm with six degrees of freedom and a real time tumor tracking system. Cyberknife can be used for both for SRS and SBRT in comparison to Gamma knife which can be used only for intra cranial lesions [13].

2.10 Reirradiation

Improved treatment techniques have resulted in a longer survival of the patients. Many patients developed local recurrence or second primary in

the irradiated field in the course of their natural history. For years, Reirradiation was an enigma due to risk of normal tissue toxicities and risk of decline in quality of life of the patients. Now there is enough evidence to show that with it is a safe modality if chosen judiciously in carefully selected patient groups. Conformal radiotherapy treatment techniques should be used to minimize the toxicities. Patient and treatment related factors like time elapsed since the first radiation, toxicities from the previous doses and patient's general condition should be considered with maximum care and accuracy [14].

2.11 Common Toxicities of Radiation Treatment

Radiotherapy side effect can be divided into early or late side effects depending upon the time of occurrence.

- Early side effects occur during or within 3 months of radiotherapy. Commonly encountered toxicities are erythema of skin, mucositis, and fatigue depending on the site of radiation. Skin and mucosa are early reacting tissues while spinal cord, kidney, bladder, and lungs are some of the example of late reacting tissue.
- Late effects usually occur post 6 months of radiation for example subcutaneous fibrosis of skin, dryness of mouth, radiation proctitis, and cystitis.

With more conformal radiotherapy techniques both acute and late toxicities are decreasing making radiotherapy a more patient friendly cancer treatment modality.

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Basic Principles of Medical Oncology

3

M. D. Ray

3.1 Introduction

Medical Oncology is an important branch of Oncology which deals with chemotherapy, targeted therapy, hormonal therapy in intend to achieve cure or control of cancers.

It is one of the fastest evolving branches of Medicine. Many cancer is cured by chemotherapy only like germ cell tumour of testis, Paediatric tumours, haematopoietic malignancies, etc.

It addresses metastatic diseases to prevent progression, Chemotherapy is used in the form of neoadjuvant therapy in many locally advanced malignancies.

3.2 History of Medical Oncology

The term chemotherapy was coined by Paul Ehrlich, a Nobel prize winning German-Jewish physician. He was also a known figure for immunotherapy too.

Chemotherapy was first develops at the beginning of twentieth century. It was not originally meant for cancer patients. Actually during the world was I, it was noticed that people exposed to nitrogen mustard, had significantly reduced white blood cells count. This observation led to investigate the agents which can help the growth of rapidly dividing cells like cancer cells. The journey of chemotherapy started at that time.

Over the last two decades combination chemotherapy gains popularity.

As we all know that chemotherapy is an essential part of the treatment of cancer patients. It is used as neoadjuvant, during surgery (HIPEC, PIPAC) or bi directational—(Intra Peritoneal Chemotherapy and I V Chemotherapy together) and as adjuvant therapy.

So many cancers may cured with chemotherapy like—Germ cells tumour, Lymphoma, Childhood cancers, etc.

3.3 Mechanism of Action of Chemotherapy

Before that we should have a look on five stages of cell cycles—G_0, G_1, S, G_2, M phase.

The chemotherapeutic drugs act in the following phases are:

1. G_0-Phase—Resting phase—During rest cells plan for specific function—drug acts—Glucocorticoids for mature lymph nodes.
2. G_1-Phase—called Interphase—in this phage cells synthesize proteins and RNA. Drugs are active in this phase—L-asparaginase.

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3. S-Phase—DNA synthesis occurs in this phase—Drugs act in this cycles are Procarbazine, Antimetabolites.
4. G_2-Phase—Mitotic Spindle cells are produced. Drugs act on this phase are—Taxanes, Vinka alkaloids, bleomycin.
5. M Phase—Mitotic Phase—In this phase, this genetic material segregated in daughter cells after completion of mitosis.
   In this phase protein and RNA Synthesis diminish abruptly.
   Plant Alkaloids are very active in this phase.
   Some drugs are real hero—they do not bother about the phase. They act on both nondividing and dividing cells at any phase.
   - Alkalyting agents, Busulfan, chlorambucil, cyclophosphamide, Dacarbazine, Ifosfamide, etc.
   - Platinum Compounds—like Cisplatin Carboplatin, etc.
   - Steroids also a real hero.

3.4 Basic Principles of Chemotherapy

1. Dose is an important to obtain expected response from chemotherapy. Drug should be administered in maximum tolerable dose.
2. In heterogenous tumour population—combination chemotherapy provide maximum response, chance of development of chemoresistant is less.
3. When tumour load is less, minimal metastasis or micro metastases, the chemotherapeutic agents act better.
4. Drugs to be calculated in maximum tolerable dose. It is also important to calculate the previous exposure of chemo drugs and its toxicity.
5. In case of combined use of multi drugs, the choice of drugs should be such that toxicities do not overlap.
6. Interval between two doses should be consistent. Minimal interval is 3 weeks because bone marrow takes minimal 3 weeks to recover from the side effects of chemotherapy. Longer periods allow tumour regrowth.
7. *Protectants for chemo effects*: Common adverse effects of almost all chemotherapy bone marrow depression.
   - Cardiotoxicity—by Adriamycin.
   - Nephrotoxicity—by Cisplatin.
   - Hemorrhagic cystitis—by ifosfamide, cyclophosphamide.
   - Drugs are also available to protect these organs or help in recovery from the side effects.
   - Cardio-protectants—Dexrazoxone.
   - Uro protectant—Mesna.
   - Nephro protectant—Sodium thyosulphate.
   - Cyto protectant—Amifostine.
   - WBC—rapid recovery by growth factors.
   - GMCSF (Malmogastrim).
   - G-CSF (Filgrastim).
   - Platelets—Oprelvekin can recover platelet counts faster.
8. *Response assessment*: Reduction of tumour size either clinically or radiologically or by both.
   - International definitions of response to chemotherapy.
   - Refractory—tumour relapse <1 month.
   - Early relapse—within 1–6 months.
   - Partial response—tumour recurs within 6–12 months.
   - Sensitive—tumour recurs after 12 months of chemotherapy.
   - *Complete response*—means disappearance of cancer after complete chemotherapy cycles at least for 1 month.
   - *Partial response*—30% or more reduction of tumour size.
   - *Stable disease:* Tumour that is neither growing nor shrinking. It means tumour has not increased in size by >30%.
   - *Progressive disease*: During chemo, the tumour increasing in size rather decreasing.

3.5 Commonly Used Terms and Definition in Medical Oncology

Neo Adjuvant Therapy Chemotherapy using before definitive treatment surgery, to reduce the size and better handling of the tumour.

It is aimed to reduce tumour size as well as to deal the systemic micrometastases.

It may help to conserve the organ like breast conserving surgery, 'Limb Salvage Surgery'.

Adjuvant Chemotherapy Use of chemotherapy after definitive treatment modality, like surgery, radiotherapy or both, is called adjuvant therapy.

It is used to control/prevent the systemic micrometastases like in locally advanced cancers like Ca Breast, colon, stomach, etc.

Induction Chemotherapy Use of chemotherapy as an initial therapy to achieve remission of advanced disease where no alternative treatment modality exists. Example—Acute Leukaemia.

Consolidation Chemotherapy After induction chemotherapy, further use of chemotherapy to prolong the remission period.

Maintenance Chemotherapy Use of low dose, prolonged chemotherapy aiming to prolong the remission or to some extent to achieve cure in patients with remission.

Salvage/Palliative Chemotherapy Use of chemotherapy where other modality like surgery, radiotherapy or earlier chemotherapy fail to achieve any remission.

Metronomic Chemotherapy It is defined as repeated administration of antitumour drug, comparatively low doses, frequently and without a long drug free period.

Site Directed Chemotherapy When a particular organ or space is loaded with tumour, delivering a high dose/concentration of chemotherapy to that particular organ or space to get rid of the tumour.

Example: Isolated limb perfusion in melanoma, HIPEC in Peritoneal Surface Malignancies, hepatic arterial chemotherapy in Hepatocellular cancer (HCC), etc.

3.6 Chemo-Radiation

Concurrent Administration of chemotherapy in the same period of Radiotherapy like Radiotherapy from Monday to Friday and chemotherapy on Saturday.

Alternating Alternate administration of chemotherapy and radiotherapy.

Sequential Administration of chemotherapy followed by surgery or vice versa.

Radiosensitizing Chemotherapy Some chemotherapeutic drugs/agents such as 5 FU or Cisplatin may have synergistic effects if it is applied with radiotherapy called Radio sensitizing drugs.

This radiosensitizing drugs helping RT to achieve its intended goal of locoregional tumour control and thereby it facilitates organ conservation approaches.

Radiomimetic Chemotherapeutic agent like anthracycline may cause dermatitis or mucositis like radiotherapy. This kind of drug is called radiomimetic drug. So, full course of chemotherapy to be completed before starting RT.

Toxicity Chemotherapeutic drugs are definitely toxic as they are blind to differentiate between normal cells and cancer cells.

Bone marrow, GI epithelium, gonads, hair follicles, where the cells division are active, are more commonly affected. The common toxicities are:

(a) *Bone marrow Suppression*: Most common side effects of majority of the chemotherapeutic drugs. On routine haemogram, we could see low blood counts, i.e. Leucopenia, thrombocytopenia, anaemia.

Owing to low immunity of cancer patients, low blood count may be due to infection like in febrile neutropenia.

Spacing of cycles may allow bone marrow to recover or prophylactic growth factors may compensate the reduction.

Antibiotics may require in suspected infection.

(b) *Nausea, vomiting:* It is also as common as bone marrow depression.

Patient may start feeling vomiting (nausea) even before the start of chemotherapy called anticipatory emesis. Nausea, vomiting may occur within 24 hours called early emesis and beyond called delayed emesis.

Prevention: Prophylactic administration of antiemetics like ondansetron, dexamethasone, metoclopramide, aprepitant or any combination.

We use apprepetant 120 mg day before, 80 mg on the day of surgery and another 80 mg on first POD through Rytes tube in a case of HIPEC.

(c) *Alopecia*: The common drugs which may cause alopecia are Ifosfamide, adriamycin, cyclophosphamide, paclitaxel, Vineristine, bleomycin, etc.

Patient may be counselled as the hair loss is usually temporary and reversible. Patient may wear twigs in between periods.

3.7 Organ Toxicities

Cardiotoxicity Adriamycin is very well known for Cardiotoxicity. Other anthracycline may cause cardiotoxicity. It usually manifests as congestive heart failure.

Prevention This drug not to be given to cardiac compromised patients—Prophylactic use of Cardio protectant dexrazoxane.

Before using anthracycline patients should have cardiac check-up.

Nephrotoxicity Classically Cisplatin is the main drug causing nephrotoxicity.

In HIPEC Cisplatin is the commonly used drug. In 4–10% cases, it causes derangement of renal functions. Even dialysis may require 1–2% cases.

Prevention Maintaining hydration, before, during and after this chemo infusion is essential. 1–2 ml/kg/hour may be considered adequate.

During HIPEC, use of sodium thiosulphate injection is important to prevent nephrotoxicity.

Neurotoxicity Peripheral Neuropathy is the commonest among all kind of neuropathy. Cranial nerve palsies, optic neuropathy are other manifestations. The distribution is typically 'Stocking Gloves' and consists of paresthesia, dysesthesias, and loss of proprioception, short time infusion 3 hours or less, chance of neuropathy is 25–75%.

The drugs causing neuropathy are: Cisplatin, methotrexate, Ifosfamide, Paclitaxel, Vinka alkaloids, etc.

It is a relatively difficult aspect to tackle but early detection may prevent permanent damage cytoprotectant like amifostine may be used to prevent neurotoxicity.

For neuropathy pain syndrome—Gabapentin, phenytoin, carbamazepine along with tricyclic antidepressants are useful.

Respiratory Toxicity Bleomycin is well known for pulmonary fibrosis. Initially it manifests as pneumonitis and later lung function is compromised.

Prevention drugs to be avoided in compromised lung function like in Chronic Obstructive Pulmonary Disease (COPD).

Steroid may help to prevent lung fibrosis to some extent.

Gonadal Dysfunction Sterility may be associated with Procarbazine, Cisplatin, Vinblastine, etc.

Semen cryopreservation could be done to pressure for future fertility.

Hepatic Toxicity Few drugs like methotrexate, L-asparaginase may cause hepatotoxicity.

Regular monitoring of LFT may be warning to prevent the toxicity.

Hypersensitivity It is one of the most devastating sudden manifestation of the chemotherapeutic drugs.

Reactions like flashing, hypotension, bronchospasm, urticaria, angioedema, usually develop within 10 min of initiation of the treatment.

90% hypersensitivity develops after the first or second dose.

Anaphylaxis occurs in 2–3% cases. Reactions may be either by Cremophor EL or by the drug itself.

Body Surface Area (BSA) Dose of the drug is the most important aspect of chemotherapy infusion. Dose to calculate based on body surface area.

Nomogram exists for easy calculation of BSA from height and weight (Fig. 3.1).

Mostelar's formula also useful for BSA calculation. The formula is as follows:

$$\text{BSA}\left(\text{m}^2\right) = \sqrt{\text{height x weight}} / 3600$$

Performance Status Scales The important score for cancer management ECOG (Easter Co-operative Oncology Group/Karnofsky scale CY).

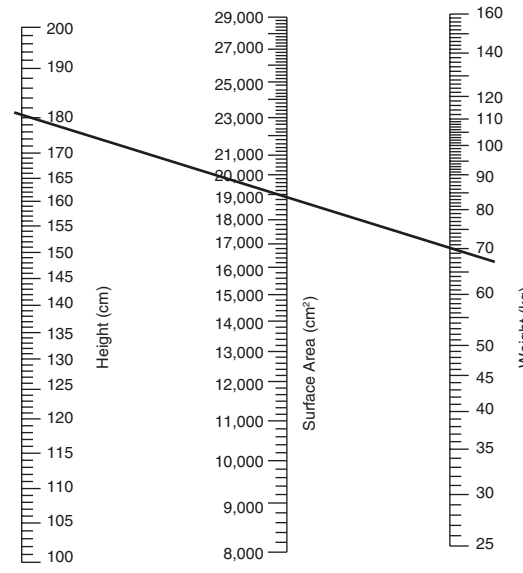

Fig. 3.1 Nomograph for estimating Body Surface Area from Height & Weight

Asymptomatic Normal Activity No complaints, no evidence of 100% disease.

1. Symptomatic but ambulatory, and able to carry out day-to-day activities.
   - Able to carry normal activity occasionally symptomatic 90%.
   - Symptomatic on effort 80%.
2. Symptomatic in bed <5% of the day occasional assistance may be needed.
   - Unable to carry out all day-to-day activities actively 70%.
   - Most personal need is self-cared and occasional assistance may be required 60%.

Treatment either surgery, chemo or radiotherapy to be done on ECOG1 and optimized ECOGII. Karnofsky score 70% and optimized 60%.

4 Pre-Operative Surgical Assessment of Cancer Patients

M. D. Ray

4.1 Introduction

We know preoperative assessment is an important aspect of the management of cancer patients.

Surgeon has to play the key role in the whole process, as surgeon would be solely responsible for his/her own operated patients. It's a fact.

So, I believe 30–35% surgical outcomes depend on pre op assessment and preparation only.

4.2 General Principles

When we see the patient and decide the patient needs surgery then and there we should start prehabilitation.

We see the general condition of the patient, i.e. performance status in the form of ECOG or Karnofsky score.

We advise to quit smoking, alcohol, tobacco, maintain hydration, hygiene, high protein diet, have haematinics do some exercise, yoga, meditation, and respiratory exercise by spirometry.

Do tests to confirm the diagnosis, then staging and general workup.

Next step is to send the patients to Anaesthetist to get the preanaesthetic check-up (PAC) done!!

They usually advice for optimization of comorbid conditions like hypertension, diabetes, COPD, etc. to reduce the risk.

One important thing we have to take care that we should talk to the patients and the caregivers very politely. We should empathical for their mental agony and financial barden because of the disease!

4.3 Preoperative Judgement and Final Decision

Three important questions to be re-assessed (re-evaluated)

- Does the patient adequately investigated for the operation?
- Does the patient really need the operation?
- How much patient is counselled for the operation and what the patient's choice?

Re-assess the medical history, re-visit the CVS and respiratory system.

Medication, Thromboprophylaxis Re-anaesthesia check-up.

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Final discussion with the team and anaesthetists.

4.4 Identifying High Risk Factors

Age > 65 years, severity of the disease, disease burden, systemic disease, co-morbidity chronic kidney disease, stroke, angina are independent predictors of prognosis following surgery (Lee et al. 1999).

4.5 Peri Operative Medications

Aspirin: Usually to be stopped 5 days back. Now a days or low does aspirin 75 mg can be continued, particularly when the chance of bleeding is less.

Clopidogrel—to be stopped 7 days before surgery.

Antihypertensives—to be continued at the early morning in the day of surgery.

Hypoglycaemics: Oral hypoglycaemics like Metformin to with draw 48 hours prior to surgery.

Thyroxin to be continued even in the early morning of surgery with sips of water.

4.6 Pre op Advice to the Patients

Talk to patient and next of Kin minimum 5/10 min. Answer their queries, questions politely. Sometime we may get irritated because of their irrelevant questions but we should not get annoyed to take them in confidence.

We have to remember one thing clearly that our attitude towards the patient is everything. And truly speaking that is more than the successful outcome of surgery.

4.7 Pre op Optimization

Prehabilitation and pre op optimization are two most important tools for surgical success.

Before taking final decision for surgery once we should go through the history, investigations, and final diagnosis. Anything missing or any alternative treatment is better for the patient in that scenario is to finalize!

Even in operation theatre follow surgical check list and final surgical plan.

Talk to Anaesthesiologist once. Tell them your final opinion about the patient.

Team work is the better approach for the management of onco surgical patients always.

Conclusion Pre op assessment and optimization are aims to improve better surgical outcome. Surgeon has to play the most important part in this process because ultimate responsibility comes on to the surgeon only.

5 Pre op Evaluation of Cancer Patients Undergoing Surgeries

Nishkarsh Gupta, Vinod Kumar, Anju Gupta, and Saurabh Vig

5.1 Introduction

Anaesthesiology is unique specialty where the anaesthesiologists routinely expose the patient to risk to facilitate a desired surgical outcome in a holistic manner. Since the demonstration of first anaesthesia, its administration is considered hazardous for the patients. It is important to understand the type and the extent of the risks involved. The patients should have access to truthful knowledge on the possibility of specific complications in the perioperative period, to facilitate informed decision making related to anaesthesia and surgery.

In National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) report observed perioperative mortality of 1.6% and gaps in perioperative management were identified as the single most important factor. The Australian Incident Monitoring Study (AIMS) database has also identified inadequate preoperative evaluation as an important reason for 3% of the adverse events in perioperative period. A comprehensive evaluation and optimisation of comorbid conditions can significantly help in reducing perioperative morbidity and mortality.

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Preanaesthetic evaluation involves assessment for comorbidities before giving anaesthesia for surgical procedures. It is important to ensure that the intended surgical intervention with minimum increase in problems due to existing disorders, avoid new illnesses and ensure speedy recovery after the procedure. Medical comorbidities are a major source of adverse perioperative morbidity and this can be reduced by a properly conducted preanaesthesia check-up. With the increase in longevity more and more patients are presenting to us with multiple comorbidities for surgery. Preoperative screening is required to approximate the associate risk and optimises the patient without causing undue delay in surgery. It provides a patient posted for surgical procedure should be thoroughly screened for any major coexisting diseases that may affect the postoperative morbidity and mortality. We have clear cut guidelines for some of the common diseases like cardiac abnormalities that need to be followed. The preoperative evaluation will help in formulating the anaesthetic plan and if inadequate may lead to anaesthetic complications.

Goals of preanaesthesia evaluation are to:

1. To educate patient and families about anaesthesia and postoperative results.
2. To obtain informed consent.
3. Allay patients anxiety regarding the anaesthesia and surgery.
4. Assess and optimise the patient's medical conditions before surgery.

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5. Reduce the perioperative morbidity and overall hospital stay after surgery.
6. Reduce delays and case cancellations due to unoptimised medical conditions.

A good preoperative optimisation leads to a reduced ordering of laboratory tests, reduced specialist referrals and overall health care costs, decreased patients' anxiety, increased acceptance of alternative techniques of anaesthesia by the patients like regional anaesthesia, decreased hospitalisation and reduced overall costs.

5.2 Risk Assessment

The main aim of a preanaesthesia check-up is to assess the anaesthetic and surgical risk and best optimise it before the procedure.

1. Sources of Anaesthetic Risk.
   (a) Anaesthetic drugs and interventions.
   (b) Mechanical and operator error.
2. Systemic illness that may affect aesthetic technique (patient factors).
   (a) Cardiac: many anaesthesia induction agents and inhalational agents are myocardial depressants. Unoptimised patients with cardiac disease may have accentuated hypotensive response to induction of anaesthesia.
   (b) Autonomic neuropathies, like diabetes mellitus heighten the hypotension following induction of anaesthesia.
   (c) Pulmonary: induction of anaesthesia decreases vital capacity, functional residual capacity and mucociliary clearance. In addition response to hypoxia and hypercarbia is depressed. The patients with preoperative respiratory dysfunction may have postoperative respiratory morbidity like pneumonia, etc.

Though perioperative risk is multifactorial, the patient comorbidities have been found to be major contributor to 30-day mortality. The

Table 5.1 ASA Classification (this is well accepted risk score and should be included)

Class	Systemic Disturbance	Mortality*
1	Healthy patient with no comorbidity except the surgical process	<0.03%
2	Mild-to-moderate systemic disease due to the surgical condition or by other pathologic processes	0.2%
3	Severe disease process that limits activity but is not disabling	1.2%
4	Severe disabling disease that is a constant threat to life	8%
5	Moribund patient not expected to survive 24 hours with or without an operation	34%
E	Suffix to indicate an emergency surgery for any class	Increased

American society of anaesthesiology (ASA) has classified relative risk to conscious sedation and anaesthesia (Table 5.1). This is widely practised and simple reproducible and has been correlated with postoperative morbidity and mortality. ASA status is not based on systemic analysis but on subjective physician assessment of the patient's comorbid conditions. It does not consider the risk due to surgical procedure, e.g. the ASA physical status for a patient with cataract surgery and gastrectomy will be the same if patients have similar heath. Despite its limitations it is still practised in most part of the world.

3. *Surgical risk:* John Hopkins risk classification score categorises the patients into 5 based on severity of surgery and degree of blood loss (Table 5.2). But it is not comprehensive model and tends to ignore patient factors and anaesthetic risk (Fig. 5.1).

- There is no comprehensive risk score that is widely used today. A simple, readily usable and comprehensive risk score is required for better risk assessment.

The *components of a through preanaesthesia examination* should include:

Table 5.2 John Hopkins risk classification system

Category	Type of surgical procedure
1	Minimally invasive procedure; minimal BL*. Minimal patient risk independent of anaesthesia
2	Minimal—Moderate invasive. BL < 500 ml. Slight patient risk independent of anaesthesia
3	Moderate to significant invasive. BL 500–1500 ml. Moderate patient risk independent of anaesthesia
4	Highly invasive. BL > 1500 ml. Major patient risk independent of anaesthesia
5	Highly invasive. BL > 1500 ml. Critical patient risk independent of anaesthesia. Postoperative ICU stay with invasive monitoring

BL: blood loss

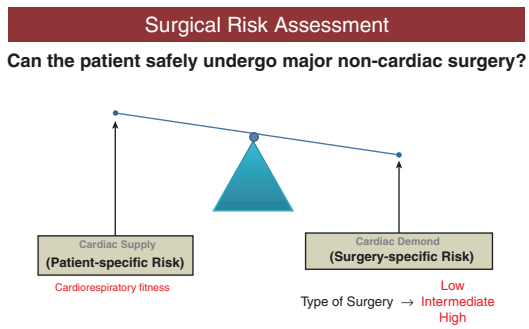

Fig. 5.1 Risk assessment

History and Physical Examination A detailed medical record and examination is mainstay of a good preanaesthetic check-up. Patients posted for elective surgery should undergo a detailed and relevant evaluation of the cardiac and pulmonary function, kidney disease, endocrine, musculoskeletal and other relevant to anaesthesia care. Various societies including ASA periodically publish and update guidelines for preoperative assessment of patients. The focus of the assessment should be to detect comorbidities and formulate strategies to optimise them before the surgery. The criteria to optimise will also depend upon the need of surgery.

The history and examination should be done as a routine with special emphasis on:

- Detailed history to include major systemic illness,
- A detailed record of all drugs taken by the patient,
- history of any allergies to drug or other substances,
- any untoward reaction to previous anaesthetic,
- previous surgery and hospitalisation,
- any difficulties faced during previous anaesthetic (like difficult airway, tracheostomy, difficult intravenous cannulation, etc.).

The patients come in contact with the surgical speciality before anaesthesia personnel. So, they have a better rapport with the patient and a through history related to preanaesthesia check-up should be taken at the initial contact with the patient. Nowadays several questionnaires have been designed for preoperative screening of the patients that may help in finding any associated diseases. Questionnaire may help to find significant medical issues while screening. Another advantage of the questionnaire is that they can point towards a systemic disease so the advanced testing and consultations can be advised in the first visit itself to reduce the delay in surgery. In case the patient is illiterate then they can take help of their relatives a staff nurse may help them to do so (Table 5.3).

The patients are often unaware when they visit the preanaesthesia clinic regarding what will be done during the visit. All patients should receive instructions from treating surgeon to visit the preanaesthesia clinic (PAC) with details of the drug prescription that patient is taking. He should always come to PAC after normal meal and after taking all medications advised to him. It is often seen that patients omit morning dose of antihypertensives and are found hypertensive on their PAC visit. This may make it difficult for the

Table 5.3 A suggested pre-screening questionnaire (the form is not exhaustive but indicative of a model form, needs to be customised as per the set up)

Have you ever felt any of the following? (if 'yes', please tick and give details)
• Have you ever experienced severe pain or pressure around the chest lasting for 30 min or more?
• Do you have puffiness in your feet or ankles sometimes?
• Do you have breathlessness while routine activity or exercise or sleeping at night?
• Do you sometimes get calf pains while walking?
• Pain in chest, palpitations or blackouts
• Any H/o high blood pressure
• Any H/o prolonged fever with joint pains
• Do you hear any wheezy or whistling sound from your chest?
• Have you been told that you snore during sleep?
• Do you cold, cough or any other respiratory symptoms in past 6 weeks?
• Any H/O of diabetes or thyroid problem?
• Any H/O convulsions or fits
• Have you or anyone in family had any bleeding through vagina, rectum or minor injuries etc.?
• Are you taking blood thinners like aspirin recently (last 2 weeks)?
• Are you anaemic or taking iron pills?
• History of dyspepsia or heartburn
• Do you smoke, or drink alcohol or abuse any other drug? (if 'yes' how many a day?)
• Do you have loose teeth?
• Do you have any implants or pacemaker?
• Women; are you pregnant?
• Are you or any medicines? (like inhalers, eye drops, herbal remedies, etc.). Please give details
• Please provide details of previous anaesthetics
• Any previous chemotherapy or radiation therapy?
• Do you need the services of an interpreter?
• Signature of the patient: Signature of the doctor
This form to be filled by the patient with the help of a doctor, before coming to PAC clinic. It will help us to plan the perioperative care

anaesthesiologists to opine for surgical scheduling. The PAC should be scheduled within 72 h to 30 days of scheduling the procedure.

Laboratory Testing The preoperative tests should be ordered selectively to guide perioperative care. The indications for additional tests should be mentioned clearly based on information available and surgical risk. Also, test should be done if it will affect the management. In case the patient does not have any medical history other than the disease per se, he should be advised minimal laboratory investigations necessary depending on his/her age and surgery planned. Recent studies have suggested that up to 60% of regularly requested tests may not be indicated clinically. An abnormal test may be present despite any disease in the patient (false positive). This may add to confusion and delay the treatment of the patient. A false-positive result may distract the physician from clinically more significant problem, cause a delay and may eventually harm the patient. So, we should be cautious in ordering medical test and have our own guidelines for preoperative medical testing in the patients. The surgical risk of the patient will govern any laboratory testing (Table 5.4). An ASA I patient undergoing a simple mastectomy is dif-

Table 5.4 Common laboratory tests suggested for patients undergoing surgery (all tests should be after last chemotherapy and/or radiotherapy if the patient is receiving such treatment)

S. No	TEST	Target group
1	ECG	> 40 years, major severity at ≥3; any cardiovascular or severe renal disease.
2	CXR	> 30 years, CVS, respiratory, renal disease
3	Hemogram	All ages (Hb), major surgery, ASA gr > II
4	KFT	Older than 50 years, major systemic illness
5	Electrolytes	Diabetic patient, patient with a history of excessive fluid and electrolyte loss, e.g. diarrhoea, diuretics, vomiting, colostomy, etc.
6	Pregnancy test	Women who may be pregnant
7	LFT	Liver disease, age > 60
8	Blood sugar	DM, age > 40 years (routine)
9	HB1AC	Diabetic patient
10	PT/PTTK	h/o of coagulation or liver disease, major surgery, anticoagulant drugs
11	ABG, PFT	Associated cardiac or pulmonary disease
12	Viral markers	All major surgeries should be tested for viral markers (HIV, hepatitis B, hepatitis C)

ferent form that undergoing a pneumonectomy. So, additional testing may be required in patients with major surgeries and long duration surgeries. The surgeon and anaesthesiologist as a team should agree and decide to make their own protocols for preoperative testing to avoid any delays and confusion. The patients should be referred for preoperative assessment only after the preoperative testing based as per need to minimise the delay.

5.3 Cardiovascular Issues

The American College of Cardiology/American Heart Association and from the European Society of Cardiology regularly come up with guidelines and update on preoperative optimisation of patients with cardiac disease for surgery. The patients planned for noncardiac surgery should be assessed for perioperative cardiac event risk based on detailed perioperative examination. In absence of any clinical findings the indications for cardiovascular testing to diagnose coronary artery disease are the same as in any other patient. In patients with suspected heart disease additional cardiac evaluation (echocardiography or 24-hour ambulatory monitoring) should be performed only if additional testing will help in establishing the diagnosis and treatment plan for cardiac optimisation before the surgery.

Many risk assessment tools have been developed to grade cardiac risk. The commonly used tools today are revised cardiac risk index (RCRI) and Gupta's index. Risk indices should be customised according to the setup to quantitate preoperative risk.

RCRI is a tool used to estimate a patient's risk of perioperative cardiac complications. It includes the surgical risk, history of ischemic heart disease or congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin and preoperative serum creatinine level higher than 2.0 mg/dL.

The frequency of major cardiac complications (nonfatal MI, nonfatal cardiac arrest, death, etc.) increases if the number of risk factors is more. The patients with no risk factors have 0.4% incidence of major cardiac event, whereas patients with three or more factors have a risk of 5.4%.

Gupta and colleagues have used data collected by the NSQIP (National Surgical Quality Improvement Program risk) based on type of surgery, dependent functional status, abnormal creatinine level, ASA physical status, and increasing age.

5.4 Pulmonary Issues

Perioperative pulmonary problems are quite common in the postoperative period. Post op pulmonary complications contribute significantly to peri operative morbidity and mortality 25% deaths within 6 days of surgery are because of respiratory complications. American College of Physicians has suggested that additional preoperative and postoperative interventions may be required to avoid complications in patients with:

- increased age (> 60 years),
- chronic obstructive lung disease,
- heart failure,
- significantly reduced exercise tolerance,
- functional dependence.

Other risk factors associated with increased pulmonary morbidity include:

- Smoking (current and > 40 pack-year),
- Neck, thoracic, upper abdominal, aortic or neurologic surgery,
- Long procedures (>2 hrs),
- General anaesthesia,
- Albumin <3 gm/dl,
- Exercise capacity <2 blocks or one flight of stairs,
- BMI >30.

Simple measures like smoking cessation and incentive spirometry in the perioperative period, nutritional build-up of the patient, antibiotic to cure respiratory infection and bronchodilataion for better pulmonary toileting will help in reducing postoperative pulmonary morbidity.

5.4.1 Preoperative Preparation for Thoracic Surgeries

The respiratory function needs to be evaluated objectively before planning lung resection surgery. Spirometry is the commonly available test and should be done in all such patients (Fig. 5.2).

FEV1 is primary value to determine resectability and predicts pulmonary reserve. It is a strong predictor of pulmonary complications. A minimum FEV1 > 2 Lt is acceptable for pneumonectomy and a FEV1 > = 1.5Lt acceptable for lobectomy . For FEV1 values less than these cutoff, the preoperative management needs to be individualised, additional testing of the respiratory system and cardio respiratory reserve needs to done in consultation with respiratory physician.

Spirometry tests only respiratory mechanical function (delivery of oxygen to distal airways). But adequate delivery does not ensure the exchange at the alveolar level. So additional testing is required to ascertain optimal functioning lung parenchymal function. Traditionally arterial blood gas analysis has been used to ascertain lung resectability (PaO2 > 60 mm Hg and Pa CO_2 < 45 mm Hg). Diffusion capacity of lung carbon dioxide is the most useful test to detect the gas exchange at lung.

5.5 DLCO Good Predictor of Mortality and Morbidity

- DLCO<60%- mortality rate – 24%.
- DLCO<40%- higher mortality and morbidity.

Estimated Postoperative FEV1 and DLCO values less than 40% (predicted postoperative function = Pre op func ×[% of function contributed by the lung that will remain postoperative period]) leads to an augmented risk of respiratory complications postoperatively.

The cardiopulmonary interaction is important in preoperative assessment. Nowadays Cardio pulmonary exercise testing (CPET) is done and tests the cardiopulmonary reserves before planned surgery. Maximal oxygen consumption (VO2max) is the most useful predictor of postoperative pulmonary complication. A VO2max of

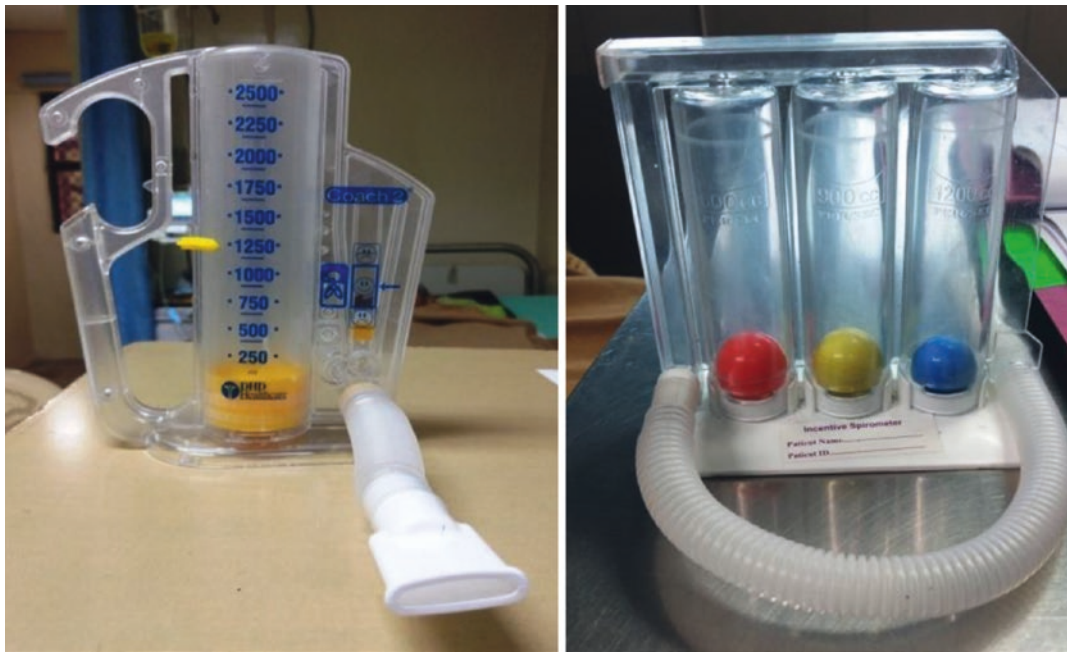

Fig. 5.2 Spirometer

less than 10 ml/kg/min increases the risk of morbidity and mortality and a value of >20 ml/kg/min is associated with minimum complications. This has not gained widespread popularity because of the cost concerns. A number of other tests like 6 minute walk test and ability to climb five flights of stairs (V02max 20 ml/kg/min) have a reasonable good estimate of cardio pulmonary reserves and can be used as surrogate markers in case of non-availability of CPET machine. CPET can also be used to objectively guide preconditioning of patients to improve their cardio respiratory reserve before surgery.

The patient risk for postoperative pulmonary complications should be considered in tandem with the procedure related risk factors for planning optimisation before surgery.

Preanaesthetic evaluation in patients of haematological disorder: Three most common clinical situations seen include anaemia, bleeding risk, and oral anticoagulation management.

Anaemia Anaemia is the most common defect seen in preoperative patients. It is an important modifiable risk factor affecting perioperative morbidity and often asymptomatic. The patients may complain dyspnoea, or palpitations, loss of energy. The preoperative evaluation should be able to identify the aetiology and duration of anaemia along with related symptoms and therapy. Additional investigations like complete blood count, serum iron studies vitamin B_{12}, and folate levels may be needed classify anaemia. The patient's cardiorespiratory reserve and amount of blood loss expected should also be considered before planning for surgery and transfusion in the preoperative period. Patients with normovolemia anaemia without considerable cardiac risk or expected surgical blood loss can be safely managed without transfusion. Perioperative transfusion is rarely required if the haemoglobin concentration is >10 g/dL.

5.6 Coagulopathies

- Coagulopathies may result due to inherited or acquired disorders of platelet and clotting factors. It may also be due to organ dysfunction or medications.
- The bleeding time and clotting time are not routinely done for every preoperative patient and history of the patient for bleeding disorders is more reliable.
- A detailed history of easy bruising, bleeding with minor procedures, need to be taken. The patient's medications should also be reviewed, and the use of anticoagulants and antiplatelet drugs should be noted.
- Any history suggestive of coagulopathies should prompt detailed coagulation studies before surgery.
- Patients with coagulation abnormalities may need a consultation with a haematologist. (Fig. 5.3).

Anticoagulants It is common to find the patients on anticoagulants requiring surgical intervention electively or on urgent basis. The risk of arterial or venous thromboembolism in case the drug is discontinued should be balanced against the risk of bleeding due to drugs. In addition, residual effect of anticoagulants may be catastrophic because it may cause haematoma following neuraxial blockade and lead to paraplegia.

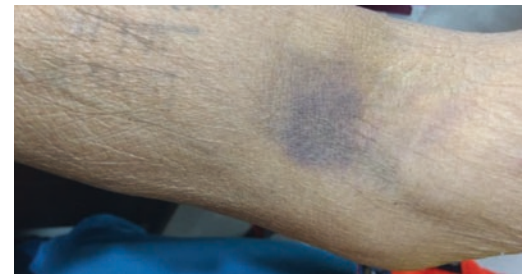

Fig. 5.3 Echymosis

Low dose aspirin is considered safe in the perioperative period. Warfarin should be stopped to allow the INR to fall to the range of 1.5 or less.

Recently many patients are receiving newer oral anticoagulants which are direct, selective, and reversible inhibitors of factor Xa or factor IIa. The drugs should be stopped for duration equivalent to two half-lives before planned surgery.

In patients with higher thrombosis risk, bridging therapy with heparin may be considered.

In case of any doubt regarding the perioperative status of the anticoagulants a specialist consultation with the haematologist and/or a cardiologist should be taken to further evaluate the patient.

Gastrointestinal Issues Aspiration of gastric substances is potentially disastrous pulmonary complication of surgical anaesthesia. We should have policies according to our setup regarding preoperative fasting status of the patients. Most current guidelines support fasting from solids (and non-human milk) for a period of 6 h or more and clear liquids are allowed up to 2 h before anaesthesia, irrespective of type of anaesthesia. There is no benefit in limiting fluid intake (of any kind or any amount) more than 2 h before induction of anaesthesia in fit patients. A maltodextrin-based liquid in the preoperative period to reduce preoperative fasting has been suggested to reduce the surgical stress response and improve outcomes. Routine usage of stimulants to decrease the risk of aspiration is not recommended. Some of the patients may have symptoms of GERD and are at increased risk of aspiration. Such patients should receive non-particulate antacids like sodium citrate and gastric motility stimulating agents like metoclopramide to reduce the chances of aspiration.

Liver Disease It is common for liver disease patients to undergo surgery. Moreover, asymptomatic patients may also undergo surgery and they have a heightened risk of morbidity and mortality. These are the questions which need to be addressed.

What are the risks of anaesthesia in patient with acute liver disease for emergency surgery?

What are the risks of anaesthesia in patient with chronic liver function impairment?

How can these risks be minimised?

The increased risk of surgery and anaesthesia in patients with liver disease is due to the numerous synthetic and metabolic liver functions. Deficiency of any of these functions increases perioperative risk of surgery. We need to identify such patients, stratify the risk, and optimise them as far as possible. Appropriate perioperative management of these patients is vital for case selection for surgical management to improve outcomes (Table 5.5).

A thorough history and physical examination including earlier blood transfusions, excessive alcohol or illicit drug use, history of jaundice, or hereditary liver disease, or previous reactions to anaesthesia should be taken to rule out liver disease. Associated cardiovascular symptoms (like poor exercise tolerance, oedema, and orthopnoea), respiratory symptoms (dyspnoea, ascites, pleural taps), and gastrointestinal symptoms (bleeding, haematemesis, melaena, piles Sepsis / urine output) may also point towards liver disease.

The physical examination should be done to identify signs of liver disease like jaundice, ascites, palmar erythema, etc. Muscle mass, cyanosis, clubbing, temperature. Cardiovascular

Table 5.5 Evaluation of Liver function tests

1. Cell damage: Aspartate aminotransferase (AST), alanine aminotransferase (ALT)—However, no correlation between levels and damage.
2. Biliary tract conjugated hyper bilirubinaemia, gamma-glutamine transaminases, alkaline phosphatase.
3. Impaired synthetic function.
• Albumin (half-life >20 days).
• Pre-albumin (half-life ~1.5 days).
• Clotting factors V, VII, (half-life ~1.5 days).
• Prothrombin time increases.
4. Imaging: Ultrasound abdominal (portal flow, pressure, ascites) and cardiac (myocard wall movement, pericardial effusion), upper GI endoscopy, endoscopic retrograde cholangiography and computed tomography.

system: pulse rate, venous pressure, BP, oedema Respiratory System: rate, effusions, sputum. Unconscious patient: Venous access (existing + potential). Various biochemical tests may be required to further evaluate liver disease. The routine liver function assessment is not recommended if history and examination is not suggestive of a liver disease. If there is inexplicable elevations of aspartate aminotransferase and alanine aminotransferase levels to more than three times normal or with any rise of total bilirubin concentration, a thorough investigation should be done.

Based on the history, examination and laboratory tests the surgical risk can be graded by using indices such as the Child Turcotte Pugh score or Model for End-stage Liver Disease score. Mortality rates for patients undergoing surgery increases with increase in Child class and varies from 10 (Child Class A) to 82% (Child class C) cirrhosis.

Kidney Disease *Renal* damage with proteinuria or a GFR less than 60 ml/min/1.73m^2 for 3 or more months is considered as kidney disease (Table 5.6).

Table 5.6 Stages of Chronic Kidney diseases

Stage	Description	GFR, mL/min per 1.73 m^2	Action
1	Injury to kidneys with normal or decrease in GFR	>90	Manage comorbidities, decrease progression
2	Injury to kidneys with mild decrease in GFR	60–89	Estimate progression
3	Moderate decrease in GFR	30–59	Evaluate and treat complications
4	Severe decrease in GFR	15–29	Prepare for renal replacement therapy
5	Renal failure	<15 (or dialysis)	Kidney transplant

Patients with renal disease have multi systemic involvement. These patients should be screened for:

1. *Cardiac disease:* Patients with CKD may have hypertension and CAD leading to presence of angina, MI. Exercise tolerance and METS needs to be evaluated preoperatively. Renal impairment (S. Creatinine >2 mg/dL) is a clinical cardiac risk factor for surgery as per AHA guidelines 2007. Also, heart failure may be present and patients may have presenting as shortness of breath, orthopnoea, PND, pedal oedema. A thorough evaluation is warranted for same.
2. *Anaemia may be present d*ue to decreased erythropoietin production, bone marrow fibrosis secondary to hyperparathyroidism, and increased haemolysis. Always look for pallor, tachycardia and systolic murmur.
3. *Platelet Dysfunction:* Due to decrease platelet adhesiveness and aggregation. Also, Heparin used during dialysis can cause heparin induced thrombocytopenia. Also, patients may have thrombasthenia with normal PTT and platelet count.
4. *Gastrointestinal Involvement:* common symptoms include anorexia, nausea, vomiting, diarrhoea, and hiccups. Also patients may associated malnutrition, liver dysfunction (due to chronic venous congestion), viral hepatitis (due to dialysis), and muscle ulceration.
5. *Neurological involvement (Uremic Neuropathy):* patients with chronic renal failure may have polyneuropathy, decreased mental ability, central nervous symptoms (like myoclonus, confusion, seizures, coma), and autonomic dysfunction.
6. *Pulmonary involvement* in renal patients includes pulmonary oedema and pleural effusion with decrease in lung compliance and increased VQ mismatch leading to hypoxia.
7. Depending on the history and examination additional investigations and nephrologist's opinion should be sought for best possible optimisation before the surgery.

5.7 Preoperative Optimisation

1. *Patient with Chronic Renal disease treated conservatively.*
   - Dialysis not needed for euvolemic patients who respond to diuretics and do not have significant electrolyte imbalance or bleeding problems.
   - Those with congestive heart failure or pulmonary congestion should be evaluated to rule out cardiovascular disease.
2. *Patients already on dialysis:*
   - Patients on haemodialysis should have dialysis within 24 hours before surgery. One should avoid elective surgery on the same day of haemodialysis because possible rapid fluid shifts, electrolyte abnormality, and disequilibrium. However, surgery should not be delayed more than 48 hrs after dialysis due to possibility of fluid overload and acidosis.

In a patient on dialysis the following should be recorded:

- Weight (pre-dialysis and post dialysis).
- Last dialysis session.
- Volume of fluid normally removed (Pre-dialysis—Post-dialysis weight).
- Electrolytes.
- Blood urea and creatinine levels pre-dialysis.
- Daily fluid intake and amount of urine output.
- Sites of current or old AV Fistula.
- Presence of peritoneal dialysis catheter.

5.7.1 Preoperative Evaluation for Endocrinal Disorders

Patients with endocrinal system problems may present for endocrinal surgery. Also, patient for endocrine system disorder may present for non-incidental non-endocrinal surgery. Moreover, many endocrine disorders often occur in concert with another to produce recognised syndromes of endocrinopathies such as MEN syndrome. The common endocrine diseases (thyroid disorder and diabetes mellitus) and preoperative considerations are discussed here.

5.7.2 Diabetes Mellitus

Preoperatively, it is important to differentiate between hyperglycaemia as a marker of acute illness and its potential as a reversible, treatable, and independent variable of outcome.

Currently, a target HbA1c of <7% for patients with DM. Lower level of HbA1c is related with reduced microvascular complications and neuropathy. An elevated HbA1c is related with a greater risk of cardiovascular events, an increase in postoperative infectious complications, an increase in gastric fluid volumes. Chronic hyperglycaemia—stiff joint syndrome, reducing joint mobility (cervical, atlanto-occipital), and contributing to a difficult laryngoscopy. Peripheral neuropathy with preexisting sensory deficits may complicate attempts to assess the adequacy of a regional anaesthetic. Additional tests may be needed depending upon involvement of the other systems. At present there is no data to suggest a cut off value of blood glucose to cancel an elective procedure because the association between preoperative blood glucose (BG) values and postoperative complications after surgery is not established clearly. In general, preoperative BG levels above 200 mg dl^{-1} [is] lead to an increased risk of cardiovascular morbidity and overall 30 day mortality. A single morning glucose value or even multiple readings taken only after an overnight fast do not adequately reflect a diabetic patient's long-term glucose control. An estimation of glycaemic control can be obtained through an examination of blood glucoses at different times of the day over a course of weeks or an HbA1c. (Table 5.7) Moreover if the patient comes for elective surgery and is diagnosed as a diabetic on the workup should be evaluated thoroughly for the systemic involvement instead of taking a call on biochemical values only.

Table 5.7 Preoperative evaluation of the patient with diabetes

System	Common Symptoms	Additional tests
Cardiovascular	MI, silent Other risk factors for CAD BP, HR, orthostatic hypotension Peripheral pulses (monitoring)	Provides information about ischemic cardiac disease and serves as a baseline for comparison should hemodynamic complications develop.
Neurologic	History of stroke, peripheral neuropathy, autonomic dysfunction Motor, sensory neurologic examination	
Gastrointestinal	Gastroparesis Gastroesophageal reflux	
Renal	Renal dysfunction Diuretic and/or dialysis dependence Volume status, skin turgor, mucus membranes, neck veins	Kidney function tests (urea, creatinine, electrolytes) provide information about volume, osmolarity, and acid-base status.
Endocrine	Glucose control, history of diabetic ketoacidosis or hyperosmolar coma, presence of other endocrine disorder (MEN syndrome)	Blood glucose provides information about glucose control and serves as a marker of illness. Hb1Ac information about long-term glucose control and associated complications.

Table 5.8 Recommended standard for BS control for patients with diabetes mellitus (BS in mg/dl)

Index	Good	Acceptable	Fair	Poor
Fasting BS	≤ 100	≤ 120	≤ 170	>200
Post prandial BS	≤ 120	≤ 150	≤ 200	> 235
Glycosylated Hb	≤ 6%	≤ 8%	≤ 10%	> 10%

Diagnostic Testing A single morning glucose value or even multiple readings taken only after an overnight fast do not adequately reflect a diabetic patient's long-term glucose control. An estimation of glycaemic control can be obtained through an examination of blood glucoses at different times of the day over a course of weeks or an HbA1c (Table 5.8).

5.7.3 Implications for Perioperative and Anaesthetic Management

The anaesthesiologist should know which type of insulin the patient is taking. In order to simplify perioperative glucose control, the anaesthesiologist should consider discontinuing all oral agents on the day of surgery and use insulin therapy for glucose management. The medical regimen is designed in consultation with physician or endocrinologist.

Suggestions/ recommendations for patients with DM scheduled for surgery:

- Surgery of DM patients should be planned as the first case.
- Pre, intra-, and postoperative blood glucose levels should be determined.
- Up until day of surgery—continue all insulin regimens as scheduled.
- *In Type I diabetics take one-third to one half of daily morning insulin should be given in morning.*
- *Type 2 diabetics take none or up to half dose of long acting or combination (70/30 preoperations) insulins on the day of surgery.*
- *In patients with an insulin pump basal infusion rate should be continued.*
- Discontinue all rapid and short acting insulins on the day of surgery.
- Long acting sulfonylureas such as chlorpropamide may be discontinued several days before surgery, especially if prolonged fasting is anticipated.
- Shorter acting oral agents should be discontinued on the day of surgery.
- Metformin should be discontinued on the day of surgery.

Prolonged fasting—supplement glucose containing solutions to meet the basal need of glucose in perioperative period.

Thyroid Disorders In general, successful management of overt thyroid dysfunction has been correlated with an improved survival. In patients with severe thyroid dysfunction myxoedema coma or thyroid storm may occur due to surgical stress (Table 5.9).

Patients with thyroid disease should be assessed for the systemic effects of hyperthyroidism or hypothyroidism (Table 5.10). A recent thyroid function test post alteration in treatment is necessary to ascertain the level of control. Patients should be as close as possible to clinical and biochemical euthyroid before going to surgery.

Table 5.9 Preoperative evaluation of the patient with Hyperthyroidism

General	Hyperkinesis, warm moist skin, carpal tunnel syndrome, tremor
CVS	Palpitations, tachycardia, atrial fibrillation, systolic HTN
Neurologic	Fatigue, weakness, nervousness, tremor, proximal muscle weakness
Gastrointestinal	Change in appetite or bowel movement frequency, weight loss despite increased appetite
Endocrine	Increased perspiration, irregular menses
HEENT	Eyes signs, tracheal deviation, goiter, dysphagia, chronic cough, dyspnoea, orthopnoea, hoarseness

Table 5.10 Preoperative evaluation of the patient with Hypothyroidism

General	Slow movements, slow speech, dry sallow skin, nonpitting oedema, cold intolerance
CVS	Bradycardia, diastolic hypertension, low voltage ECG, enlarged cardiac silhouette on chest radiograph
Pulmonary	Hypoventilation
Neurologic	Fatigue, sleepiness, depression, paresthesis, delayed DTR
Gastrointestinal	Weight gain, constipation
Endocrine	Irregular menses, menorrhagia

TSH levels monitor thyroid function but can mislead like in patients with thyrotoxicosis or pituitary disease. Several drugs and pathologies affect protein binding so values of free hormone concentrations (free T3 and free T4) should be done.

Thyroid function tests may be less useful in some situations such as nonthyroidal illness, previously known as 'euthyroid sick syndrome', subclinical hyperthyroidism, altered protein binding, and medications like dopamine and glucocorticoids. Clinical and end organ measures like ECG and Electrolyte levels may be helpful in these conditions. In the preoperative period, hyperthyroid patients have a risk of thyroid storm and hypothyroid patients may have a decreased cardiac output. So, an endocrinology consult should be taken for non-euthyroid patients who require urgent or emergent surgery.

Perioperative Medical Consultation After thorough preoperative check-up specialist medical consultations may be required for optimisation of the patients. The perioperative team should balance the risk of doing the surgery against the risks of delay. The preoperative consultations are not taken for getting the patient 'cleared' for surgery but to stratify the risk involved for the proposed procedure. Consultant-to-consultant communication between anaesthetists, surgeons, and specialist physician is essential, particularly the benefits of surgery may be outweighed by the risks to the patient.

The general goals of these consultations are to identify unknown comorbidities and risk of medical complications and optimise medical condition as far as possible. The perioperative team should clearly state the need for consult, treatment goals, benefits of the intended procedure and urgency, the possible risks and other treatment options available.

Based on the assessment and analysis of the specialist, the final decision should be taken by the perioperative team in consultation with the patient. The additional advantage with perioperative consultation is that, the specialist who has seen the patient in the preoperative period and in

case of a complication the patient can be consulted for management.

Key Points

- Preoperative assessment is an important component of surgical management of patients.
- It should be done comprehensively and needs a team effort.
- A preoperative questionnaire may help to detect the comorbid conditions early and help in reducing unnecessary visits to the hospital for PAC.

Safe anaesthesia and surgery require an optimal balance between comorbidities management and surgical management. A balanced approach should be taken to prevent unnecessary delays, and safe conduct of surgery.

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6 Perioperative Management of co-Morbid Conditions in Cancer Patients

Rakesh Garg and Sikhar More

6.1 Introduction

Onco-surgical patients are usually complex, of long duration, associated with extensive tissue handling and blood loss with fluid shifts. More and more number of patients are undergoing surgeries with one or more comorbidities like coronary artery diseases (CAD), hypertension (HTN), diabetes mellitus (DM), thyroid disorder and other associated comorbidities. Management and planning for perioperative care in view of associated comorbidities remains a challenge. The complex onco-surgeries require inter-disciplinary co-operation for an effective preoperative evaluation and optimisation of a patient with significant comorbidity. At a time where medical information is grown vast and boundless, it is difficult if not entirely impossible for even the most astute surgeon and anaesthesiologist alike to keep up with rapidly changing concepts in other medical specialities.

The aim of this chapter is to address issues relevant to the peri-procedural and perioperative evaluation, optimisation, risk stratification and planning of care of patients who have associated comorbidities.

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6.2 Cardiac Diseases

The most frequently encountered cardiac comorbidity is CAD and valvular heart diseases. Perioperative management of such patients is a significant challenge with respect to optimising the functional capacity, effects of concurrent medications with array of drugs which may include anticoagulants and whether or not to undertake a procedure like revascularisation to decrease the perioperative risk.

The perioperative risks of various cardiovascular events in patients with cardiac comorbidities scheduled for non-cardiac surgeries are greater than patients without any cardiac comorbidities. The risks include increased occurrence of coronary events like myocardial ischaemia/infarction, heart failure, stroke or death. The associated factor for such adverse outcomes relates to both the patient-related and surgery-related factors. The assessment of these factors allows for optimal optimisation, risk stratification and appropriate care in the perioperative period to effectively manage such untoward events.

6.2.1 Preoperative Evaluation

The professional bodies have presented various framework and guidelines for preoperative assessment and optimisation of patients' condition for their comorbidities. The American

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College of Cardiology and the American Heart Association (ACC/AHA) have collated various recommendations in their document for assessment and optimisation of patient with cardiac comorbidities preoperatively scheduled for non-cardiac surgery [1]. The salient features as per these guidelines for preoperative evaluation of patients with cardiac comorbidity and planned for non-cardiac surgery are summarised below [1]:

- Patients undergoing non-cardiac surgery with associated cardiac comorbidities need to be assessed preoperatively in a timely manner and attempt to optimise the cardiac status need to be done.
- The preoperative assessment should include details of the symptoms like chest pain, dyspnoea, syncope, and palpitations. Also past history of cardiac diseases like coronary artery disease (CAD), valvular, or cardiomyopathic disease, hypertension (HTN) and diabetes mellitus (DM) should be elicited. Patients with cardiac comorbidity may have associated renal, neurological or vascular abnormalities. So, these patients need to be assessed for these systems as well as they also affect overall perioperative outcome.
- The assessment of cardiac functional status provides useful information for optimal perioperative outcome. Important parameter for assessment of functional status includes its representation in the terms of metabolic equivalents (MET) (1 MET is defined as '3.5 mL oxygen uptake/kg per min, which is the resting oxygen uptake in a sitting position'. The other assessment tools that have been used to assess functional status of the patient include 6 min walk test, climbing two flight of stairs at a specified pace, walking four block, etc.
- Patients' history should guide appropriate physical examination and may focus on assessment of cardiovascular system examination. The focus should include blood pressure recording and its charting, auscultatory findings of respiratory and cardiovascular system, examining the body for impact of cardiovascular morbidity like ankle oedema, vascular flows, etc. During such examination, findings of evidence of heart failure or a murmur hints for the occurrence of major concern for cardiac disease and thus should be further evaluated by the specialists.
- A preoperative 12 lead electrocardiogram (ECG) provides baseline screening of the heart status including any ischaemic event or electrical disturbances in conduction system for arrhythmias. Also, the preoperative ECG shall be useful to compare any changes in ECG pattern during the perioperative period for fresh insult to the heart.
- Based on the history, examination and ECG; various risk predicting models can then be applied to predict the possibility of an adverse cardiac event. The most common tool used for risk prediction is the revised cardiac risk index and has been well validated for its use for perioperative period. The other tools has also been proposed and are validated and include the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) risk model or the myocardial infarction or cardiac arrest (MICA) calculator.
- Based on above-mentioned assessment tools, the risk stratification can be done as either 'low risk' whose estimated risk of major adverse cardiac events is <1% or 'higher risk' if the risk of major adverse cardiac events is >1%. Low risk patients require no additional cardiovascular testing and may proceed for surgery. 'Higher risk' patients are those who require further cardiovascular evaluation and may benefit from a cardiologist referral and further testing in the form of stress testing, echocardiography or 24-hour ambulatory monitoring.

6.2.2 Recent Myocardial Ischaemia or Unstable Angina

Patients undergoing surgery soon after an acute coronary event remain at increased risk for occurrence of major adverse cardiac event in the perioperative period. In case of an urgent or emergent

surgery, prevention, detection and treatment of ischaemia are of utmost importance. The ACC/AHA recommends waiting for four to 6 weeks after myocardial infarction (MI) before an elective non-cardiac surgery is planned. In selected patients, the cardiologist may advise coronary revascularisation prior to surgery.

6.2.3 Recent Percutaneous Coronary Intervention (PCI)

Patients who have undergone percutaneous coronary interventions (PCI) recently have an increased incidence of major adverse cardiovascular events during the perioperative period. These patients remain at risk of stent thrombosis and are kept on dual anti-platelet therapy after the placement of the stents, specially the drug eluting stents. The anti-platelet therapies remain advantageous of preventing stent thrombosis but also increase the risk of bleeding in the perioperative period, if they are continued. So appropriate risk vs benefit assessment needs to be done for the urgency of surgeries for patients on these drugs. The non-urgent and non-cardiac surgeries need to be postponed for at least 6 months or preferably 1 year to avoid above-mentioned concerns.

6.2.4 Perioperative Medication Management

- *Beta blockers:* Beta blockers are one of the common drugs administered to cardiac patients. Patients should continue these drugs in the perioperative period in similar doses as being taken them earlier. The primary benefit is to minimise tachycardia and hypertension associated with the catecholamine surge due to the stress of surgery.
- *Statins:* Patients taking statins should continue this therapy throughout the perioperative period. The cardiologist may also initiate statins in otherwise naive patients. It is also recommended to start statins as soon as possible after the surgery.
- *Aspirin:* The patients with cardiac diseases may be on low dose aspirin and this may be continued in the perioperative period except in surgical cases of high risk of bleeding like neurosurgical interventions or retinal surgeries.
- *Angiotensin-converting enzyme (*ACE*)* inhibitor *and an angiotensin receptor blocker (*ARB*):* These drugs need to be administered as per routine especially for patients with coexisting heart failure. Since these drugs have a risk of precipitating hypotension, some clinicians withhold the morning dose if large perioperative fluid shifts are anticipated. These may also be withheld if there is evidence of haemodynamic instability, hypovolaemia or acute elevation of creatinine.
- Patients with cardiac diseases may also be on certain other drugs like calcium channel blockers, diuretics, digoxin, etc. These drugs are generally continued in perioperative period but we need to monitor for their side effects like electrolyte disturbances.

6.2.5 Perioperative Myocardial Injury

The myocardial ischaemia with or without infarction in the perioperative period has a poor outcome in patients with prior underlying cardiac disease. The mortality rates are high of around 15–25% after a perioperative MI. It is also emphasised that almost 65–93% of patients of perioperative MI may not manifest frank cardiac ischaemic symptoms. The underlying pathology for the perioperative MI may be due to dynamic plague rupture, erosion, ulceration or fissuring (type 1) or due to an imbalance between myocardial demand supply (type 2). The type 2 PMI has been considered more important in the perioperative period because of its adverse outcome. Following factors in the perioperative period may contribute to the same:

- Sympathetic and cortisol surge related to surgical or anaesthetic stress, pain, anaemia or hypothermia.

- Increased heart rate and blood pressure episodes which exacerbate vascular stress.
- Procoagulant state of surgery.
- Inflammatory cascade due to surgical trauma.
- Perioperative hypoxia or hypercarbia.

Therefore amelioration of stress response is pivotal in prevention of such an episode. This may be accomplished with combination of various factors like minimally invasive surgical techniques, effective intra and postoperative pain management, meticulous detail to blood and fluid therapy. The diagnosis of perioperative MI requires a high level of suspicion as most such cases are asymptomatic. Any deterioration in haemodynamic variables and/or ECG changes should alert the attending clinician. The quantitative serial measurements of the cardiac biomarkers like troponin T and I are useful to make the diagnosis. Transthoracic or transoesophageal echocardiography may also be used for monitoring of MI. The diagnosed patients of MI should have cardiology consult and decision for appropriate definitive diagnostic intervention like coronary angiography and further management is required at priority.

6.2.6 Perioperative Management

After a meticulous preoperative workup and medication management, a few specific points need to be focused on for proper management of such patients.

- Care should be taken to maintain the cardiac work load as close to baseline as possible. Any increase in myocardial oxygen demand could lead to decompensation and risk of ischaemia. The clinical implication is to maintain heart rate, blood pressure, preload and after load as close to the patients' normal.
- Preoperative anxiety can lead to tachycardia—a mild anxiolytic like alprazolam or midazolam can be used.
- Additional monitoring included use of blood pressure by invasive tool and even more advanced tool like measurement of continuous cardiac output parameters remains useful in perioperative period.
- Large amount of blood loss triggers compensatory tachycardia and is tolerated poorly. A more liberal transfusion threshold may be considered if the patient is hypovolaemic.
- Ocular surgery, dilation of sphincters and peritoneal stretching may result in reflex bradycardia and so can stimulation around carotid arteries.
- Fluid and blood management are of vital importance as compensatory mechanisms are limited. Both hypovolaemia and fluid overload can lead to disastrous consequences. Restrictive and goal directed fluid therapy using cardiac output monitors, inferior vena cava size and variation with breathing, response to passive leg raising and urine output can all be used to judge adequacy of fluid replacement. Electrolyte abnormalities may trigger malignant arrhythmias.
- Multimodal and meticulous analgesia is vital as pain triggers a stress response leading to increases in tachycardia and increase in after load.

6.3 Hypertension

Hypertension (HTN) is one of the most frequently encountered conditions in the surgical patient. The prevalence of hypertension in India is 28%–32% in the urban population and 27.6% in the rural population [2]. Chronic hypertension impacts various organ systems and this is the primary factor that leads to an increase in surgical morbidity and mortality, rather than arbitrary readings of blood pressure.

6.3.1 Pathophysiology: [3]

- Persistent hypertension leads to remodelling of smaller resistance arteries initially and later involves the larger conduit vessels as well.
- The net result is loss of elasticity and stiffening of vessels, which eventually leads to widened pulse pressure due to systolic pressure

summation and loss of diastolic augmentation.
- Therefore there is significant loss of vascular adaptive mechanisms and wide fluctuations in blood pressure may occur preoperatively.
- Hypertensive patients have impaired autoregulation and organ perfusion occurs at pressures higher than normal. The autoregulation curve is shifted to the right and hypotensive episodes are tolerated poorly. When combined with the fact that vascular compliance also tends to be poor, such patients are at particular risk of organ hypoperfusion even with moderate levels of surgical bleeding.

6.3.2 Perioperative Considerations [4]

6.3.2.1 Target Blood Pressure

The consensus of a target blood pressure of <140/90 mmHg has been recommended by most guidelines in ambulatory patients and chronically elevated blood pressures are independent risk factors for a variety of adverse health outcomes, the same may not be true for the perioperative period. A meta-analysis concluded that there was no evidence to show that admission blood pressures <180/110 without organ damage were associated with adverse postoperative outcomes [5]. However, data on the long-term consequences of poorly optimised blood pressure during the perioperative period is scarce but there is some evidence that shows that even short duration of haemodynamic alterations can have long-term impact. The following can be taken as a guide to target blood pressures:

- Reliable and reproducible documentation of BP <160/100 may safely proceed for surgery without additional testing.
- Blood pressure > 160/100 but less than 180/110 may undergo further evaluation of end organ damage.
- BP > 180/110 should undergo formal evaluation by a cardiologist and treatment should be initiated preferably a few weeks prior to surgery.
- Beta blockers, if indicated, need to be initiated at least a week before surgery and continued. There is currently no consensus regarding perioperative ACE inhibitors and the decision is usually based on the clinicians' preference.
- Sympathetic stimulation leads to exaggerated increase in blood pressure, which is common during laryngoscopy and intubation, surgical incision and other intense surgical stimuli such as sternotomy and rib retraction. Thus it is essential for the surgeon to ascertain with the anaesthesiologist a proper depth of anaesthesia and adequate analgesia during such periods.
- In patients of uncontrolled hypertension, perioperative hypertensive surges are observed due to various perioperative surgical stimulus. These can lead to bleeding at times either from the surgical sites or even non-surgical sites like brain haemorrhage or on the other end perfusion deficit. Occurrence of MI is also associated with these surges. The surge in blood pressure is common during carotid surgery, abdominal aortic surgery, and other intraperitoneal and intrathoracic surgery, laparoscopy, renal transplantation and major trauma (e.g. burns).
- Due to the relatively higher perfusion pressures and altered vascular adaptive mechanisms, it is vital on part of the surgeon and anaesthesiologist alike to have a relatively lower threshold for intraoperative blood loss. It is also risky to deliberately lower the blood pressures to manage bleeding or for a cleaner surgical field. Episodes of exaggerated hypotensive response are also common during induction of anaesthesia, sudden relief of raised intra-abdominal tension in acute abdomen, during caesarean delivery and release of pneumoperitoneum during laparoscopy. Therefore communication between the surgeon and the anaesthesiologist is of paramount importance for timely anticipation and management of such wide swings in blood pressure during intraoperative periods.
- Postoperatively, the anti-hypertensive medications are resumed as the patient begins to tolerate enteral feeding and further follow-up

with the physician could be done on outpatient basis.
- In patients with poorly optimised blood pressures who are undergoing emergent surgeries, the perioperative blood pressures are controlled with parenteral vasodilators or beta blockers. The anti-hypertensive therapy needs to be resumed in postoperative period at the earliest.

6.3.3 Diabetes Mellitus (DM)

Diabetes Mellitus (DM) is an frequently encountered comorbidity in cancer patients requiring surgical interventions. It is a complex syndrome of glucose metabolism with multisystem implications that significantly confound postoperative morbidity and mortality. Patients with DM require holistic assessment including history, examination and relevant investigations as these patients remain at risk of multiple adverse events related to cardiovascular and renal outcomes. Also, patients with DM may have associated asymptomatic cardiovascular or renal compromise and may precipitate in perioperative period. The cornerstone of perioperative management is good glycaemic control in the face of complex interplay between surgical stress, anaesthesia, altered meal schedules and nutritional intake along with treatment regimens for diabetics.

6.3.4 Preoperative Evaluation

The key principles of preoperative evaluation of a diabetic patient are:

- Confirm the type of DM as the different types may manifest with different adverse events preferentially. The type 1 DM is associated with increased risk of diabetic ketoacidosis. So management of such patients requires optimal use of insulin to prevent this catastrophic adverse event.
- The presence of DM may lead to impact on other body organs and systems like eyes (retinopathy), kidney (nephropathy), nervous system (neuropathy, autonomic neuropathy) and cardiovascular (CAD, peripheral vascular disease, HTN).
- Patients should be assessed for the status of glycaemic control including glucose levels and its variations on day to day basis. The glycated haemoglobin (A1C) levels give an overview of glycaemic status over last 3 months.
- Detailed history of diabetes therapy, including oral hypoglycaemic agents, insulin type, dose and timing.
- The surgical parameters like type and extent of surgical intervention need to be assessed as they may influence the overall outcome in patients with DM undergoing surgery. A detailed history along with clinical examination targeting the end organ damage of diabetes needs to be carried out. This should include documentation of peripheral and autonomic neuropathy. Laboratory investigations include a baseline blood counts, renal function tests to rule out diabetic nephropathy, blood sugar charts and glycosylated haemoglobin (HbA1c). The HbA1c levels of greater than 8% need to be optimised preoperatively for elective surgeries. Increased blood sugar levels affect the overall surgical outcome in terms of increased morbidity like delayed wound healing, risk of infection, etc. Various studies have also shown HbA1c as an independent predictor of complications post-surgery.

6.3.5 Effects of the Surgical Stress Response

Surgery and general anaesthesia initiate a neuro-endocrine stress response which alters various secretory and metabolic effects. These factors lead to impaired glucose utilisation by the cells, insulin resistance, impaired insulin secretion, increased lipolysis. These in turn further led to hyperglycaemia and ketosis, at times.

6.3.6 Perioperative Glycaemic Management [6]

The general goals of glycaemic management in these patients are:

- Prevent hypoglycaemia/marked hyperglycaemia.
- Prevent ketoacidosis/hyperosmolar states.
- Optimal fluid and electrolyte balance.

Various guidelines have been published by eminent organisations for the perioperative glycaemic management, including Association of Anaesthetists of Ireland and Great Britain, Society for Ambulatory Anesthesia, Joint British Diabetes Society, Australian Diabetes Society. Although there are differences in recommendations, a general outline is described below (Table 6.1).

The modification of insulin regimens perioperatively is complex and needs to be individualised according to the nature and timing of surgery, whether enteral feeding will be resumed postoperatively and the glycaemic control:

- The type 1 or 2 diabetics with high daily dose requirements of insulin should be considered for fraction of their daily insulin dose even for the day of surgery as it helps in glucose metabolism in stress period and avoid occurrence of ketosis.
- Long acting insulins like glargine (Lantus), detemir, NPH and premixed insulin (e.g. 70/30) should be continued at 80% of their daily dose the evening before surgery. Short acting insulins like lispro can be continued at their regular dose.
- Long and intermediate acting insulin may also be administered in the dose of 80% of their daily requirement. Blood sugar levels need to be monitored.
- Blood glucose targets in the perioperative period should be between 90 and 180 mg/dL. Slightly strict range of up to 140 mg/dL may be preferable in patients undergoing cardiovascular or neurological surgeries.
- Perioperative management of blood sugar levels has undergone a paradigm shift in the recent years. The subcutaneous 'sliding scale' approach of insulin administration looks to correct hyperglycaemia after it has occurred and is no longer recommended in hospitalised patients. Rather intravenous sliding scale therapy or a variable rate insulin infusion with regular human insulin should be used. Even more contemporary approaches advocate administration of a part of the daily dose of insulin prophylactically via the subcutaneous route throughout the perioperative period covered by slow administration of dextrose solutions. This approach has two advantages—first it is a preventive approach that reduces the incidence of hyperglycaemia rather than treating it; second, it also prevents ketosis triggered by the lack of insulin in patients with higher daily dosage of insulin. Any further episodes of hyperglycaemia that may occur may be treated with variable dose insulin infusions (VRII) which may be administered via a number of 'regimens' [7].
- Fixed dose regimens involve the addition of a pre-fixed dose of insulin depending on the blood glucose levels to a fixed volume of dextrose and infused over a period of time. Examples include the Alberti (GKI) regimen and the Vellore regimen. These regimens are

Table 6.1 Management of oral hypoglycaemics

Drug	Perioperative modifications
Metformin	Avoid on day of surgery. May be continued for surgeries without major fluid shifts, risk of renal failure and where oral feeds can be resumed early.
Sulphonylureas	Stopped on the day of surgery
DPP iv inhibitors—Sitagliptin, vildagliptin	As such no contraindication for its continuance in perioperative period.
GLP1 analogues	As such no contraindication for its continuance in perioperative period.
Pioglitazone	As such no contraindication for its continuance in perioperative period.

Table 6.2 Variable rate insulin infusion (IV sliding scale)

IV insulin sliding scale	
Prepare insulin in concentration of 1 U/mL to be used via a syringe pump, or 8 U can be added in saline bottle to be used as controlled infusion. Monitor capillary sugar hourly	
Blood sugar (mg/dL)	Reaction
<70	Initiate hypoglycaemia protocol
70–140	No action needed
140–199	2 U/ hour IV insulin
200–249	4 U/ hour IV insulin
250–299	6 U/hour
300–350	8 U/hour
>350	10 units, check correct administration. Look for evidence of DKA

considered to be inherently safe as insulin and dextrose are always administered together but involve repeated changing of the IV bottles. Truly variable rate insulin infusion involves administration of insulin via an infusion pump on a 'piggyback' with a dextrose infusion. Although more convenient than fixed dose infusions, there is a risk of insulin being administered without dextrose and thus the risk for hypoglycaemia.

- All patients should have their morning blood sugars, urine ketones and serum electrolytes measured on the day of surgery. Patients already on insulin may receive a fraction of the dose at this time, and those found to be hyperglycaemic should be started on a VRII. For patients who are well controlled may have their blood sugar checked every 2 h intraoperatively and every 4–6 hourly thereafter. Patients with poor control and those receiving insulin should have their blood sugar monitored hourly intraoperatively and every 1–2 hours thereafter (Table 6.2).

6.4 Thyroid Disease

Thyroid dysfunction is a commonly occurring entity especially in females and of advancing age. These patients may undergo thyroid or non-thyroid surgery and there are various mechanisms that may complicate the perioperative course.

Diagnosis of thyroid dysfunction is made by biochemical measurements of thyroxine (T4) along with thyroid stimulating hormone (TSH). 'Free T4' is considered to be more reliable than total (bound to thyroxine binding globulin + free) and should be requested whenever feasible. Although the prevalence of thyroid dysfunction is high in general population, it is not recommended to routinely screen all surgical patients preoperatively. Only those with symptoms suggestive of hypo or hyperthyroidism and those known to have thyroid disease should undergo thyroid function testing.

6.4.1 Hypothyroidism

Manifestations that may impact the surgical course include:

- Decrease in cardiac output mediated by reduced heart rate and contractility due to systemic hypometabolism.
- Respiratory muscle weakness and altered response to hypoxia and hypercarbia.
- Reduced gut motility may result in constipation and ileus.
- Hypothyroid patients may also have anaemia of varying degrees.
- Metabolic and electrolyte abnormalities that may occur include hyponatraemia due to reduced free water clearance and reversible increases in creatinine.
- Hypothyroid patients are prone for hypothermia as body heat production is reduced in presence of hypometabolism.

Normal levels of TSH are 0.5–4.70 mU/ L, T4 are 4.5–12.5 mcg/dL and T3 are 0.8–2 ng/ mL. Small variations in 'normal' reference range are common between different labs and are dependent on the reagent and the method used. Moderate/subclinical hypothyroid condition, defined as normal T4 with TSH > 4.5 mU/L but less than 10 mU/ L does not contribute to periop-

erative outcome and such patients may proceed for surgery without significant risk to perioperative outcome. Overt hypothyroidism (low T4 or TSH > 10 mU/L) is required to be treated and euthyroid status should be confirmed before elective surgery. Patients taking thyroxine supplements should receive the same dose on the morning of surgery.

In case of emergent surgery, patients with overt hypothyroidism should receive full dose of thyroxine (1.6 mcg/kg) orally before surgery with informed consent about the incidence of postoperative complications. Severe hypothyroid patients like myxedema coma should be given intravenous thyroxine (not available in India) while supportive therapy is put into place to optimise intravascular volume, cardiac function, body temperature, respiratory function and electrolyte balance. Stress dose of steroids should also be administered as Addison's disease is common in severely hypothyroid patients.

6.4.2 Perioperative Management

- The effects of hypothyroidism are reversible with thyroxine supplementation. It is, therefore, prudent to treat the condition to avoid acute decompensation whenever feasible.
- Thyroxine has a long half-life of 7 days, and patients on long-term exogenous thyroid supplementation may be allowed to miss a couple of doses if the surgical conditions demand. However a maximum of 5 days can be allowed before IV levothyroxine supplementation becomes necessary.
- A full blood count to rule out anaemia, renal function and serum electrolytes should be documented before surgery. All hypothyroid patients should also have an ECG to rule out rhythm abnormalities. Echocardiogram may be required to ascertain cardiac function in patients who report poor effort tolerance. Chest X-Ray may be done to look for effusions.
- Postoperatively course may be complicated by cardio-respiratory dysfunction. Cardiac monitoring with continuous ECG and haemodynamic parameters including pulse rate, blood pressure may be required as per patient assessment. Such patients will also benefit from perioperative respiratory muscle training, deep breathing and incentive spirometry along with steam inhalation to prevent pulmonary complications.
- Disorders of water and electrolyte balance may also occur and judicious use of balanced fluids is vital. Serum electrolytes including calcium should be ascertained in the postoperative period.
- Temperature monitoring to prevent hypothermia and appropriate timely rise of warming blankets and fluid warmers are important in these patients.
- Referrals with endocrinologists are usually not required for patients on thyroxine who are euthyroid. Subclinical or frank hypothyroid patients require specialist referral for optimisation and continuation of the treatment.

6.4.3 Hyperthyroidism

The clinical status of the patient with hyperthyroidism along with biochemical status aids in decision-making for the surgical intervention. Patients who have subclinical hyperthyroidism do not have over symptoms and they are diagnosed incidentally based on thyroid profile (low TSH with normal levels of free T4 and T3). These patients can be taken up for surgical intervention with appropriate care in perioperative period. However cardiovascular manifestations if present may be controlled by perioperative use of beta adrenergic blockers. Patient with untreated or poorly controlled hyperthyroidism have a risk of precipitation of 'thyroid storm'—a life threatening emergency with an acute event such as surgery. Hence elective procedures are best delayed until euthyroid status is ascertained. For emergent surgery, the preoperative treatment of hyperthyroidism should be initiated as soon as possible. For control of cardiovascular function, beta blockers are the drug of choice unless contraindicated. A short acting beta blocker (like esmolol) may be administered and if tolerated well longer

acting drugs (propranolol or atenolol) may be used.

Antithyroid drugs like propylthiouracil and methimazole are used to decrease the synthesis of thyroxine. Rapid control of thyroid function may be obtained with use of beta blockers and iodides along with antithyroid drugs.

Patients with a large goitre are potential candidates for difficult airway especially if long-standing and with retrosternal extension. Preoperative neck radiographs of CT scans provide valuable information about the extent of compression and airway anatomy. Emergency surgical airway access is also difficult in such cases. Long standing airway compression may weaken the tracheal rings and lead to 'tracheomalacia'. Prolonged intubation may be required in such cases and consent should be sought preoperatively.

6.4.4 Perioperative Management

- Specialist consultation is inevitable for optimising thyroid and cardiac function preoperatively in patients who have poor control. The drugs like beta blockers or calcium channel blockers need to be continued prior to surgery. Patients undergoing thyroid surgeries for the same have their antithyroid drugs stopped postoperatively.
- Invasive cardiac monitoring including central venous catheters, arterial catheters and other advanced cardiac output monitors may be required as per patient assessment and based on systemic effects of hyperthyroidism. The hyperthyroid patients have a high cardiac output state, heart rate, widened pulse pressure and reduced systemic vascular resistance. May even precipitate myocardial ischaemia.
- Tachyarrhythmias especially atrial fibrillation is common in this population.
- Dyspnoea may occur due to increased oxygen demand, carbon dioxide production or respiratory muscle weakness.
- These patients may be malnourished due to increased gut motility, malabsorption and hyperdefaecation.
- Temperature monitoring and fluid and electrolyte balance need special attention in these patients.

6.5 Chronic Obstructive Pulmonary Disease (COPD)

COPD and its subtypes (emphysema and chronic bronchitis) are important risk factors for postoperative pulmonary complications (PPCs), prolonged mechanical ventilation, longer ICU and hospital admissions, and mortality after surgery. The COPD has been defined as 'COPD is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. The airway limitation (pulmonary component) is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases and is not fully reversible' [8].

6.5.1 Preoperative Assessment

The assessment of the patients with COPD needs to include following considerations:

- Assessment of severity of disease and its symptoms. Airflow limitation is assessed by lung function studies, typically post bronchodilator FEV1/FEV1 $\geq$ 80% represents mild obstruction, between 50–80% represents moderate obstruction, between 30–50% is severe obstruction and $\leq$ 30% is very severe obstruction [8].
- To look for evidence of acute exacerbations like dyspnoea at rest, wheezing, change in amount and type of sputum production and other signs and symptoms of respiratory infection.
- Patients with FEV1 < 50% should have assessment of baseline pulse oxymetry and arterial blood gas assessment to stratify the severity in the preoperative period. In those with pre-existing hypercapnia, perioperative ventilation is targeted at the same levels of PaCO2.

- Interventions to optimise pulmonary condition:
  - Optimisation of treatment of poorly controlled patients: Patients with poorly controlled symptoms may benefit from an escalation of the bronchodilator therapy, short course of systemic steroids and antibiotics if indicated.
  - Smoking cessation: Although ideally smoking should be stopped for four to 8 weeks for complete benefit and reducing pulmonary complications, but nevertheless it is advisable to counsel the patients for stop smoking any time prior to surgery.
  - Preoperative muscle training: Inspiratory muscle training like deep breathing exercises and self-administered incentive spirometry is easy, cost effective and helps to reduce pulmonary complications.
- Preoperative medication management:
  - Inhaled beta agonists, anticholinergics and steroids are continued in perioperative period as per schedule.
  - Patient may require steroid replacement in the perioperative period, specially those who were on steroids as hypothalamic–pituitary–adrenal function suppression occurs. These patients include those patients who have received prednisolone>20 mg/day or its equivalent (dexamethasone 2 mg/day, methylprednisolone 16 mg/day, hydrocortisone 80 mg/day) for more than 3 weeks during the previous 6 months.

6.5.2 Perioperative Management

- Sedation and analgesia: The benzodiazepines and opioids should be judiciously used for adequate analgesia and anxiolytic as these patients are prone for respiratory depression. Anxiety and pain can lead to increased respiratory rate and hyperinflation due to breath stacking and worsen dyspnoea in a COPD patient.
- Controlled ventilation: COPD patients may require invasive or non-invasive ventilation in the postoperative phase due to a variety of reasons. However mechanical ventilation carries the risk of dynamic hyperinflation, auto-PEEP and worsening of V/Q mismatch if adequate time for expiration is not provided, and inspiration begins without complete expiration.
- High FiO2 oxygen supplementation should be avoided in such patients as they are dependent on a hypoxic ventilatory drive. Sudden high FiO2 supplementation may cause loss of this drive and further worsening of respiration.
- These patients should benefit from nebulised beta agonists like salbutamol or salmeterol, anticholinergics like ipratropium and steroids like budesonide alone or in combination although overzealous administration may result in systemic effects.
- Incentive spirometry should be continued postoperatively along with steam inhalation and chest physiotherapy.
- Once the acute stress of surgery has passed and the patient is able to generate good inspiratory power, regular aerosolised or powdered inhalers should be reinitiated.

6.5.3 Surgical Factors

- *Site:* The functional residual capacity (FRC) is reduced proportional to proximity of surgical site to the diaphragm. Surgical interventions at thoracic, upper abdominal and subcostal incisions have a propensity of postoperative pulmonary complications than surgery in the lower abdomen or extremity.
- *Position:* FRC is further reduced in the supine, Trendelenburg, lithotomy (Fig. 6.1) or lateral decubitus position. Prone position has little or no effect on FRC and may also be beneficial.
- *Open vs laparoscopic approach:* Although laparoscopic approach has the benefit of less pain reduction in FRC in the postoperative period, the CO2 used for pneumoperitoneum may cause significant rise of PaCO2 in patients with COPD. The anaesthesiologist may not be able to treat hypercapnia with the usual compensatory adjustments of mechanical ventilation (e.g. a faster respiratory rate) due to the need for a prolonged expiration time in COPD patients. In addition, pneumoperitoneum

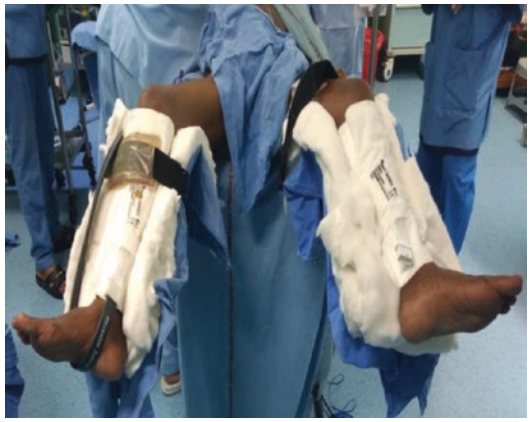

Fig. 6.1 Lithotomy position

increases intra-abdominal pressure, which may cause cephalad shift of the diaphragm, increased intrathoracic pressure, worsening V/Q mismatch and hypoxemia. In patients with severe COPD, it may be necessary to use intermittent desufflation and/or lower insufflations pressures to minimise the adverse effects of pneumoperitoneum.

- *One lung ventilation:* It may not be feasible to completely collapse one lung in patients with lung hyperinflation and parenchymal damage. Small amounts of PEEP on the non-ventilated lung may be essential to maintain the normal gas exchange function. The surgeon should be prepared to work alongside a partially inflated lung or with intermittent inflation.

6.5.4 Chronic Renal Disease

Chronic renal disease is a condition wherein decline in the glomerular filtration rate (GFR) secondary to various reasons such as diabetes, hypertension, glomerulonephritis and polycystic kidney disease. The GFR < 60 mL/min/1.73m^2 for more than 3 months is a diagnostic criteria for chronic renal disease [9].

6.5.5 Pathophysiology

Patients of CKD have impact on various organ systems and the pathophysiological changes include:

- *Cardiovascular system:* The patients of CKD are prone for salt and water retention, anaemia, accelerated atherosclerosis, altered lipoprotein metabolism, and uremic pericarditis. These patients have increased calcification in heart and vascular structures leading to valvular heart disease and calcified atherosclerosis. The renal hypertension and associated left ventricular hypertrophy cardiomyopathy and heart failure are also manifested. The autonomic dysfunction is also manifested in patients of CKD. The cardiovascular impact of AV shunts includes steal syndrome, heart failure and limb ischaemia.
- *Haemostasis and coagulation:* The CKD lead to various blood related abnormalities. These include thrombotic phenomenon including vascular access thrombosis, uremic thrombocytopathy, and various changes include uraemic thrombocytopathy, and prothrombotic tendency.
- Patients may manifest metabolic acidosis due to metabolic abnormalities.
- *Musculoskeletal system:* The CKD patients have increased risk of bone resorption, renal osteodystrophy along with muscle wasting and growth retardation. CKD patients are also at risk of rhabdomyolysis.
- *Endocrine system:* Due to systemic effect patient with CKD may have endocrinal changes including diabetes mellitus, hyperparathyroidism and vitamin D deficiency.
- *Gastrointestinal system*: CKD patients have delayed gastric emptying due to gastropathy, increases chances of nausea and vomiting and absorption abnormalities leading to malnutrition.
- *Immune system:* The CKD leads to suppression of immune response overall related to uraemia and drugs.
- *Fluid and electrolyte homeostasis*: The deranged renal function leads to fluid and electrolyte abnormalities like increased serum potassium, volume overload, etc.

6.5.6 Preoperative Evaluation

6.5.6.1 History

- Establish cause of renal failure and its duration.

- Treatment being received—conservative/on renal replacement (haemodialysis/peritoneal dialysis).
- Ascertain fluid restrictions and daily urine output.
- Enquire about comorbidities: hypertension, diabetes, ischaemic heart disease, etc., and treatment.
- Exercise tolerance, anaemia, LVF, electrolyte disturbances, symptoms of gastro-eosophageal reflux.

6.5.6.2 Examination

- Detailed general and systemic physical examination with focus on cardiovascular system.
- BP in standing and sitting position for autonomic neuropathy.
- Presence of flow murmurs secondary to anaemia or pericardial rub secondary to uraemic pericarditis, ankle or sacral oedema, lung crepitations.

6.5.6.3 Investigations

- Full blood counts: Normocytic, normochromic anaemia/infection.
- Clotting studies if uraemia is severe.
- Renal function tests are mandatory prior to surgery—BUN, creatinine, electrolytes.
- ECG: ischaemia, arrhythmias, LVH and hyperkalemia.
- Chest X-ray: Pleural effusions, cardiomegaly, pulmonary oedema.
- ABGs to evaluate the acid base status.
- Baseline LFT if undergoing a major surgery.

6.5.7 Renal Risk Assessment and Prevention

Patients treated conservatively: The cause and duration of CKD, and whether the elevations in BUN and creatinine are prerenal, renal or postrenal in origin should be established. Patients who are euvolaemic, diuretic responsive with no significant electrolyte abnormality need not undergo dialysis preoperatively. If there is evidence of volume overload, congestive heart failure, progressive oedema; dialysis may be imminent and it may be useful to place a dialysis catheter intraoperatively.

Further deterioration of renal function can be avoided by avoiding the use of nephrotoxic drugs. These may include substitution or dose modification of antibiotics (aminoglycosides, acyclovir, amphotericin), NSAIDs (diclofenac). Iodinated radiocontrast material can cause acute kidney injury and worsening of renal status. The use of drugs like dopamine, n-acetyl cysteine, sodium bicarbonate for ‘renal protection’ is not currently recommended.

6.5.7.1 Patients on Renal Replacement Therapy

Patients on haemodialysis usually require preoperative dialysis within 24 hours before surgery. Patients with peritoneal dialysis should be switched with haemodialysis in those who are undergoing abdominal surgery. Postoperative dialysis requirements should be ascertained with the nephrologist. Complications like volume overload and hyperkalemia may require emergent dialysis.

Daily fluid intake and output should be closely monitored and overzealous administration may result in fluid overload and pulmonary oedema. Analgesic management in the perioperative period is often a challenge as NSAIDs are known to be nephrotoxic and opioids like pethidine and morphine have the risk of accumulation of their metabolites. Regional anaesthetic techniques are safe provided coagulation function is optimised.

Patients with CKD have cardiovascular abnormalities and increased atherosclerosis along with electrolyte imbalance. These abnormalities place these patients at increased risk of perioperative MI. So it is desirable to monitor these patients accordingly and any change in parameters should have index of suspicion for the MI and managed accordingly.

So, adequate assessment of patient including history, physical examination along with relevant imaging and blood investigations is paramount for optimal outcome of surgical intervention in patients with associated comorbidities.

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7 Proper Counselling and Consent of Patient for Medicolegal Aspects and Importance of Documentation

Amitabha Mandal and M. D. Ray

7.1 Introduction

Earlier it was believed that revealing information to patient and giving all information regarding a fatal disease may lead to mental instability and depression. So physician used to conceal actual facts and provide minimum information about a fatal disease for better management of patient. Physician was the absolute authority to decide treatment without proper prior information to patient. In modern day practice this philosophy is no longer acceptable. Patient has all the right to know about his disease and he is the ultimate decision maker regarding his or her treatment. Concealing information may lead to court proceeding against physician. In a case in the USA a patient consented for operation in the right ear, but during surgery surgeon noticed that, the condition of left ear was much worse than right one. He operated on left ear, later the surgeon was summoned to the supreme court of Minnesota in 1905, and was found guilty [1]. In another case in 1914 a surgeon removed a malignant tumour against patient's will. The surgeon was found guilty by the court [2]. The crux of this judgement was that every human being of an adult age and sound mind has the right to decide about what should be done to his body.

In present day proper counselling of patients before any surgical intervention and taking informed written consent is utmost important for surgeon, from medicolegal point of view. Counselling is a confidential speech between patient and the doctor about the disease, possible treatment options, outcomes and complications related to the treatment that may help the patient to take proper decision along with the doctor regarding the further treatment plan. It is a continuous process starting from the establishment of diagnosis and will continue till the treatment completed.

Another aspect of modern day surgery is taking proper consent before any surgical intervention. There are many forms of consent like, implied consent, expressed consent, informed written consent. The last one is the most important for surgeon from medicolegal point of view. Another aspect I want to highlight is the record keeping. Properly conserved record not only help for patient follow-up and further treatment, research, but also help surgeon to defend himself during any court proceeding.

7.2 Counselling

Definition "Counselling is a confidential dialogue between a patient and doctor, helps patient to take proper decision regarding his or her illness". Patient should be informed about the dis-

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ease, possible treatment options, outcome of treatment, risk and benefit associated with each treatment. A doctor should reveal all treatment related facts to patient and relatives honestly. The facts should be explained in legible words and preferably in patients own language or best understandable language.

7.2.1 When to Start Counselling?

Counselling is a continuous process starts during the patient's first visit, and it will continue till the end of the treatment.

First visit: At first visit after proper history taking and complete physical examination, patient should be informed about the provisional diagnosis, possible differential diagnosis and investigation required to reach a final diagnosis.

Subsequent Visit:
After final diagnosis, following are to be explained to patient and attendant—

(a) Nature of the disease.
(b) Possible treatment option to be explained in patient's language.
(c) Outcome of treatment.
(d) Risk and benefit of each treatment option.
(e) Nature of surgery.
(f) Risk associated with surgery.
(g) Possible blood loss during surgery.
(h) Arrangement of blood product before surgery.
(i) Cost of the treatment.
(j) Waiting list of the department and delay in starting treatment.
(k) What will happen if any delay occurs in initiation of treatment.
(l) Hospital stay.
(m) Time required to return to normal lifestyle.
(n) No oral intake after surgery for how many days.
(o) Disability if any may occur after surgery.
(p) Co-morbidity and its effect on surgery.

For Cancer Patient Following Should Be Kept in Mind
(a) Risk of disease recurrence.
(b) Possibility of negative histopathology report after surgery.
(c) Chance of inoperability.
(d) Need for NG tube feeding after surgery for oral cancer patient.
(e) Fertility issue after chemotherapy and surgery like hysterectomy, oophorectomy and orchidectomy.
(f) Chance of limb salvage, and functional impairment after surgery in case of extremity sarcoma.
(g) Improving nutritional status before surgery, particularly in case of esophageal and gastric cancer.
(h) Impairment of sexual function after surgery like abdomino-perineal resection (APR), RPLND.
(i) Need for temporary and permanent stoma.
(j) Functional, sexual, social and psychological aspects of stoma.
(k) Need for long-term follow-up and importance of follow-up in picking up recurrence at earliest.

Special Situations In case of radical surgery like cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS + HIPEC), exenteration surgery, details of procedure, risk associated with surgery, possible benefit from surgery, functional impairment after surgery to be explained.

After Admission in Hospital for Surgery Patient and attendant should be explained in detail by the operating surgeon or operating team, about the nature of surgery, possible time required for surgery, chance of inoperability, possible blood loss, risk associated with surgery, need for blood transfusion and hazards related to transfusion, need for mechanical ventilation, ICU stay, nosocomial infection, ventilator associated pneumonia, ICU psychosis, wound complications, negative histopathology, risk of

disease recurrence, time period to be remained nil per mouth, time required to recover, possible hospital stay.

For Specific Cases

(a) Oral cancer—following to be explained—NG tube feeding, difficulty in speech, loss of mandible, need for flap, type of flap, possibility of flap necrosis, development of orocutaneous fistula, facial disfigurement after surgery, bad cosmesis.
(b) Thyroid surgery—risk of recurrent laryngeal nerve injury and voice change, risk of hypocalcaemia in post-operative period.
(c) Esophageal cancer—gastric conduit necrosis, cardiac arrhythmias, changes in feeding habit after surgery.
(d) Gastric cancer—loss of reservoir capacity of stomach and need for modification of feeding behaviour.
(e) Pancreatic cancer—pancreatic fistula formation.
(f) Colorectal cancer—change in bowel habits, sexual impairment, need for temporary and permanent stoma.
(g) Radical cystectomy—permanent urostomy.
(h) Penectomy—loss of penis, reconstruction option, impairment of sexual function.
(i) Orchidectomy—chance of being infertile.
(j) Oophorectomy—infertility.
(k) Hysterectomy—inability to conceive.

Type of anaesthesia, risk related to anaesthetic drugs, need for mechanical ventilation and complication associated with it, ICU stay and complication related to it, to be explained in details by anaesthesia team. After explaining everything to patient and attendant, surgeon should record all those things and take an informed written consent from patient and attendant. Surgeon should answer every query of patient related to surgery.

During Discharge Patient should be explained about the restriction in life style if any needed, dietary modification if needed, date, time and place of follow-up.

7.3 Consent

Starting with a story—A Perimenopausal lady medical officer by profession underwent diagnostic Laparoscopy for evaluating chronic pelvic pain. During diagnostic lap—the surgeon found that there is a chocolate cyst along with features of endometriosis. The surgeon decided to do hysterectomy to relieve her symptoms but no consent was taken before. But during the procedure, he arranged to take consent from her husband and mother for hysterectomy and surgeon did it without any malintention.

Ultimately when the medical officer came to know the fact, she filed a case that without her consent, her uterus has been removed.

Court found guilty of the surgeon and fined for his basic mistake.

So, without proper consent of the patient, surgeon should not take his own decision, even for the betterment of the patient unless it is life-threatening emergency.

Definition As per sect. 13 of "Indian Contract Act 1872"—consent is defined as—When two or more persons agree upon the same thing in the same sense they are said to consent.

Necessity of Consent Before performing any surgery or intervention surgeon should take an informed written consent from patient, husband or wife or parents in case of minor, as per Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations 2002, vide regulation No. 7.16.

Modes of Consent

1. Implied consent.
2. Expressed consent.
3. Informed consent.

1. Implied consent: It is the most common mode of consent in general and hospital practices. Most of the physician works on the basis of implied consent. It is either by words or behaviour of the patient or by circumstances under which treatment is given. When a patient comes

to a doctor for treatment, patient volunteers for history taking and physical examination without any objection. In this case the consent is implied. In such situation no separate consent is required. Physical examination is restricted to inspection, palpation, percussion, auscultation only. Procedures not more complex than giving an injection, doing an ultrasonography, implied consent is sufficient. For physical examination like per vaginal examination, per rectal examination, or drawing blood samples from patient, require expressed consent, either verbal or written.

2. Expressed consent: Anything other than implied consent is expressed consent. It can be verbal or written. Verbal consent when taken in the presence of a disinterested third party is as valid as written consent. But obtaining written consent is preferable for easy proof and reproducibility. Anything more than inspection, palpation, percussion, auscultation, like vaginal or rectal examination require expressed consent in the presence of a disinterested third party. Written consent is required in the following situations:

(a) Major diagnostic procedure.
(b) General anaesthesia.
(c) Surgical procedure.
(d) Intimate examinations.
(e) Determining age, potency, virginity.
(f) Medicolegal case.

3. Informed consent: In modern day practice it is a common scenario that a doctor is being convicted by patient, claiming that he or she was not informed about the nature of the disease, complication. It is occurred frequently when a treatment modality fails, complication arises after surgery, or disease recurs, or a patient died. So the concept of informed written consent arises. The surgeon's role is to disclose honestly all the facts related to disease and treatment. After understanding everything from doctor, the patient's role is to decide what to be or not to be done with his or her body. Informed consent is right to patient. So the patient and attendant should be explained about the following facts before proceeding for any treatment or surgery: (a) Nature of the disease. (b) Possible treatment options. (c) Risk and benefit associated with the treatment. (d) Complications related to surgery. (e) Risk of cancer recurrence. (f) Chance of inoperability. (g) Chance of success of treatment modality. (h) Prognosis and outcome of treatment.

After explaining all those facts a written consent will be obtained from the patient and the attendant. In certain circumstances disclosure of facts can be restricted to patient—

(a) If patient is wish for.
(b) May affect the psychology of the patient.
(c) When complication is trivial.

7.3.1 What Is Legally Valid Consent?

Consent is said to be valid when

(a) When given by a patient of valid age, or by parents or guardian in conscious, and stable mental condition.
(b) Informed expressed written consent.
(c) Given voluntarily.
(d) Knows all the facts related to surgery.
(e) Given before the procedure.
(f) Given without fear, fraud or force.
(g) Given in front of two witnesses.
(h) Signed by the doctor, patient, attendant/guardian, witness.
(i) Written in patients own hand writing.

7.3.2 Who Can Give Consent?

1. Any patient who is fully conscious, mentally sound above 12 years of age can give consent (Sect. 88, 90 IPC 1860).
2. As per Sect. 13 of Indian Contract Act, 1872 a person above 18 years of age can enter into a contract. As the doctor patient's relationship is a contract, 18 years of age is considered as age of giving written consent.
3. < 18 years of age—consents to be taken from parents or legal guardian.
4. For unconscious patient—consent to be taken from the parents or local guardian.

7.3.3 What Is Loco Parentis?

When a child is sick and needs emergency treatment, but parents are not available for giving consent, the person in charge of the child can give consent (like—school teacher). In contraceptive sterilization consent of both husband and wife is necessary. In case of organ donation, after death of the person, consent of spouse is necessary.

What is blanket consent? If a consent taken on a printed form, which almost mention everything about what to do on patient without mentioning specifically is called blanket consent. It is legally inadequate.

7.3.4 What Is Proxy Consent or Substitute Consent?

All the above-mentioned types of consent can take the shape of proxy consent, like parent for child, close relative for unconscious, unsound patient, and consent given by loco parentis.

7.3.5 What Is Informed Refusal?

After knowing all the facts related to treatment patient can refuse to take treatment.

7.3.6 What Is Paternalism?

Is an abuse of medical knowledge in such a way that a patient is deprived of his ability to make a rational choice. Doctor should not practice paternalism.

When consent is not valid?

When consent is not required?

7.4 Documentation

Proper documentation of medical fact is very important from treatment as well as medicolegal point of view. Documentation of patient's history, diagnosis, investigation advised, treatment proposed, date of visit, any event occurred during treatment is necessary. Proper documentation of facts will help a physician to follow-up the patient properly and review the case quickly. From medicolegal point of view it will save a physician in court case.

Main aspects of documentation:

1. Follow up of patient.
2. Research.
3. Medicolegal purpose.

Things to be noted during OPD visit: The doctor should document the following things in legible handwriting

(a) Date and time of visit.
(b) Patients' particulars.
(c) Case history.
(d) Drug allergy.
(e) Positive findings.
(f) Investigation suggested.
(g) Treatment advised.
(h) Possible drug reaction.
(i) How to take medications.
(j) Where to go in case of any emergency.

Physician should mention "*diagnosis under revision*" until a final diagnosis is reached. What other disease to be ruled out should be mentioned in patient's history sheet. In a difficult case to which specialist you are seeking referral should be mentioned. When a patient counselled about the disease and prognosis, should be documented in case sheet. When patient's condition is critical, and in case of grave prognosis, patient should be counselled, and signature of the patient in presence of a witness should be taken in the case sheet, for proof that, you have told them everything about the disease.

In case of critical case, when risk and benefit of the treatment to be weighted, after explaining the risk of treatment, and possible benefit from the treatment, signature from patient and a close relative to be taken.

After Final Diagnosis Following facts to be noted in the case sheet: (a) Diagnosis (b) Plan (c) Justification for such plan (d) Implementation of Plan.

Before Surgery Following things to be mentioned in the consent form and to be signed by the patient and attendant in presence of a witness: (a) Diagnosis (b) Surgery planned (c) Possible complications related to surgery (d) Possible risk related to anaesthetic drugs and General Anaesthesia (e) Need for ICU stay, ventilator support (f) Long-term complications (g) Risk of recurrence (h) Need for re operation (i) Need for stoma creation (j) Chance of positive margin (k) Risk related to blood transfusion.

During Hospital Stay If any event happens should be documented, like (a) drug reaction (b) blood transfusion reaction (c) morbidity during hospital stay (d) complication occurred after surgery (e) measures taken to such complication (f) positive culture report (g) wound infection (h) whether visited by consultant on not (i) discussed with consultant or not.

During Follow-Up Following to be documented (a) any recurrence (b) investigation suggested to detect recurrence (c) counselling of patient about the recurrence (d) prognosis explained or not.

If a patient provides an unreliable history, refused for physical examination, refused to take treatment, ignore the advice given by doctor, not taking medicines prescribed by doctor, taking medicines irregularly, leave against medical advice, lost to follow-up, refusing admission should be recorded in case sheet.

Preservation of Records Every doctor should preserve the records of each and every patient for a period of 3 years from the date of commencement of treatment, in a standard proforma. Hospital and nursing home should maintain the record for a minimum of 3 years. This is necessary, because if any case lodged against a doctor or an institution these documents can be produced to competent authority. In case of minor and new born record should be preserved for 3 years after attaining 18 years of age. If any patient, authorized attendant or legal authorities request for treatment related documents, the same should be provided within 72 hours.

Few Examples of Negligence in Surgery

1. Performing surgery when contraindicated.
2. Performing surgery—when lack of reasonable skill—performing cytoreductive surgery and HIPEC without prior training.
3. Delay in surgery—delaying surgery in case of bowel perforation, abscess, appendicitis.
4. Performing surgery without proper infrastructure: performing esophagectomy or commando surgery without proper ICU facility.
5. Leaving swab, instrument inside the abdomen, or wound.
6. Going beyond the area of consent: Surgeon performed cholecystectomy during appendectomy without prior consent.
7. Inadvertent burn: cautery burn during surgery, burn occurred by hot saline.
8. Performing surgery in wrong limb.

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8 Surgical Safety Checklist: Relevance and Importance

Babul Bansal and M. D. Ray

We do believe that a patient dying of surgical error be a rare occurrence. However, a report published by the Center for Disease Control and Prevention (CDC) suggests that in the year 2013, number of patients dying of 'medical errors' (251,000) in the USA alone is half the number of those succumbing to cancer (585,000) and eight times that due to motor vehicle accidents (34,000) [1]. According to World Health Organization (WHO), in developed countries, 50% of all adverse events occurring in hospitalized patients are related to surgical care, half of which in turn are considered preventable [2].

Globally, an estimated 234.1 million surgeries are conducted every year, of which approx. seven million results in a major complication and one million patients die during or immediately after surgery. 50% of these adverse events are preventable [3]. The usual excuse for surgical errors is that operating room is a high risk and complex environment and therefore prone to high error rates. An example of another high risk and complex system is the aviation sector. There were an estimated 3.8 billion passengers who flew in commercial aircrafts in the year 2016 alone [4]. And the number who died in accidents were a paltry 278 in contrast to the estimated 500,000 preventable deaths among 234.1 million patients undergoing surgery [5]. Therefore, aviation sector despite being a complex and high-risk system has managed to achieve a low error rate.

Among major reasons for the high error rates is our failure as surgeons to recognize that we can make mistakes and as a result, surgical safety is seldom a priority. Although surgical procedures are meant to treat morbidity, unsafe surgical procedures can cause substantial harm.

3 major types of surgical errors are—

- *Action based errors*—these are due to a lack of skill.
- *Decision based errors*—these are due to faulty knowledge or judgement.
- *Communication based errors.*

The science of 'safety' is based on a premise that everyone makes mistakes and that specific processes can be implemented to prevent mistakes or minimize their adverse impact. 'Swiss Cheese' model is a popular paradigm in the arena of surgical safety [6]. It represents several layers of system which are designed to prevent medical errors from happening. In this model, latent medical error is represented by a beam of light and system vulnerability by holes in cheese. Figuratively, medical error occurs if the beam is able to navigate through the mass of cheese. Therefore, if enough systems with vulnerabilities, although in differing axis, are put up, then it

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will be hard for the latent errors to manifest as a clinical error.

'Never Events' refer to errors which are clearly identifiable, preventable and have serious consequences. They indicate a real problem in safety mechanisms of a healthcare facility. In surgical parlance, Never Events refer to—

- Wrong surgery—Wrong patient, side or procedure.
- Foreign object retention during surgery.
- Death during surgery or in immediate postoperative period.

The general approaches to risk reduction during procedures performed in an operating room (OR) include review of patient's informed consent, timeouts, checklists, surgeon-led briefings, technique to minimize distractions and disruptions, cognitive aids for emergencies, formal handoff procedures and debriefings.

In 2004, the World Alliance for Patient Safety (WAPS) was introduced by WHO to address the issue of patient safety, in response to the World Health Assembly adopting resolution 55.18 urging WHO for the same [7, 8]. The Alliance organizes programmes to improve patient safety around the world every year and formulates a 'Global Patient Safety Challenge' to address a particular patient safety issue every 2 years.

The focus of the first challenge was to control health care-associated infection, while the focus of second challenge (launched in January 2007) was 'Safe Surgery Saves Life' [9]. The latter challenge defined ten objectives which should be met by every surgical team—

1. Correct procedure on correct patient at correct site.
2. Protect patient from pain and prevent harm from anaesthesia.
3. Maintenance of airway and respiratory function—to recognize and prepare for life-threatening loss.
4. High blood loss—to anticipate and prepare for such a situation.
5. Allergic or adverse drug reaction should be avoided.
6. Risk of surgical site infection should be minimized.
7. Retention of foreign objects in body after surgery should be prevented.
8. All surgical specimens should be appropriately labelled.
9. Effective communication and exchange of critical patient information should be ensured.
10. Routine audits of surgical volume, capacity and results should be undertaken.

'WHO Surgical Safety Checklist' (SSC) was developed as a result of this challenge. SSC was designed to help surgical teams to minimize the occurrence of adverse events [10]. SSC is a simple and practical tool for use by surgical teams to improve the safety of the operations and reduce unnecessary surgical morbidity and mortality. It operates by reinforcing safety standards and promoting better communication and teamwork among team members. Each item on the list is placed on the basis of clinical evidence or on recommendation of a team of experts. The Checklist is not comprehensive but simple, widely applicable and measurable. Modifications to Checklist so as to fit local practice may be required.

The WHO Surgical Safety Checklist (*see* Fig. 8.1) was validated after a multicentric trial spanning 5 continents was conducted between October 2007 and September 2008. The results were published in New England Journal of Medicine [11]. Implementation of Checklist resulted in a significant reduction in complications and death rates.

A single person, preferably a circulating nurse, should be made responsible for the implementation of checklist [12]. The Checklist is divided into three phases—Sign In (before induction of anaesthesia), Time Out (after induction but before surgical incision) and Sign Out (during or immediately after wound closure and before removing the patient from the operating

SIGN IN (Before Induction of Anesthesia)	**TIME OUT** (Before Skin Incision)	**SIGN OUT** (Before patient leaves Operating Room)
Patient has confirmed – - Identity - Site - Procedure - Consent Site Marked/Not Applicable Anesthesia safety check completed? Pulse Oximeter on patient and functioning? Does patient have a – - Known allergy? - Difficult airways/aspiration risk? - Expected risk of >500cc blood loss? If yes, are appropriate blood products and fluids planned?	All team members have introduced themselves by name and role? Surgeon, Anesthesiologist and Nurse verbally confirm – - Patient - Site - Procedure Anticipated Critical Events - **Surgeon** reviews – What are the critical or unexpected steps, operative duration, anticipated blood loss? - **Anesthesia team** reviews – Are there any patient-specific concerns - **Nursing team** reviews – has sterility (including indicator results) been confirmed? Are there any equipment issues or any concerns? Has antibiotic prophylaxis been given within the last 60 minutes? Is essential imaging displayed?	Nurse verbally confirms with the team – - The name of the procedure recorded - That instrument, sponge and needle counts are correct (or not applicable) - How the specimen is labelled (including patient's name) - Whether there are any equipment problems to be addressed Surgeon, anesthesiologist and nurse review the key concerns for recovery and management of this patient.

Fig. 8.1 WHO Surgical Safety Checklist

theatre). In each phase, the Checklist coordinator must confirm that the items on checklist are satisfactorily completed before the team proceeds further.

- *'Sign In' phase*—The phase is implemented before induction of anaesthesia. The Checklist Coordinator verbally confirms with the patient (when possible) his or her identity, procedure, site of surgery and the consent for procedure. The coordinator also visually confirms if the operative site has been marked (if appropriate) and that a pulse oximeter is functional. The coordinator will verbally review with the anaesthesiologist the estimated risk of blood loss, anticipated airway difficulty or allergic reaction and whether a full anaesthesia safety check has been completed. The presence of surgeon is not essential for completing this part of the Checklist but it is desirable as the surgeon will have a better idea of the estimated blood loss or other complicating factors.
- *'Time Out' phase*—This phase is implemented after induction of anaesthesia but before surgical incision. The operating theatre team members introduce themselves by name and role, if not already introduced earlier. Immediately before incision, the team verbally confirms the identity of patient, surgical plan and site of procedure. The team also verbally discusses in brief the critical events anticipated to occur during surgery, confirm that essential imaging is displayed and prophylactic antibiotics have been administered within last 60 minutes.
- *'Sign Out' phase*—This phase is implemented during or immediately after wound closure but before transferring the patient out of the operating room. During this phase, the team reviews the surgery that was performed, confirms the instrument and sponge counts and labelling of any surgical specimens obtained for laboratory examination. Any equipment malfunctions or issues that need to be addressed for future surgeries are also reviewed. At the end, key plans and concerns regarding postoperative management and recovery of the patient are discussed before transferring the patient outside the operating theatre.

The Checklist can be modified to suit local practices, with respect to degree of familiarity among the surgical team, the processes and culture prevalent in the institution. However, in essence, each and every element of the Checklist should be followed. Safety steps should not the removed just because they cannot be implemented due to lack of facilities or logistics.

Several studies worldwide have confirmed the efficacy of WHO surgical safety checklist. Klei et al. demonstrated a decrease in crude mortality from 3.13% to 2.85% in their hospital after implementation of SSC [13]. Weiser et al. reported an improvement in complication rates from 18.4% to 11.7% and in death rates from 3.7% to 1.4% among patients undergoing urgent surgical procedures [14].

The beneficial effects of the WHO Surgical Safety Checklist in reduction of perioperative morbidity and mortality indicate that improved communication due to checklists might improve outcomes in other spheres of medicine as well.

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9 Post op Fluid, Electrolytes, and Nutritional Management: Present Perspective

M. D. Ray

A good proverb is there, "Less you eat you will be malnourished. More you eat more you are diseased." So balance in life as well as any management is important.

As per the fluid and electrolytes management is concerned like others evidence-based treatment is always logical. I feel it is always better to die in logical way rather in the way of baba ji or guru ji wants!!

NICE (National Institute of Clinical Evidence) plays an important role in the practice of Medicine.

We know successful outcome of surgical patients depends on pre op preparation 30%, intra op care 40%, and post op care is 30%. And fluid electrolytes balance plays an impeccable part in surgical patients' outcome.

Technology has arrived in surgical arena in a big way in a short time. Many options are now available in treating surgical disease. Old is not always gold and everything at the cutting edge is not the last word. We must continually study the pros and cons, the efficacy of the old and the new, before discarding the old or embracing the new. The high-quality evidence from many sources will guide clinicians to discard unsubstantiated practices and follow the proven ones.

In industry when the quality improves, the cost comes down. But with introduction of technology, health care costs started spiraling and it has become a problem of global concern. The only answer is defensible practice according to the guidelines suggested by evidence-based surgery. The clinician has an important role to play in implementing the guidelines in everyday practice and also when faced with uncertain situations.

Every surgeon must constantly exert and improve in his area of work, to bridge a gap between his results and the best possible.

Few basic points I like to highlight:

1. Intravenous fluid administration constitutes an integral part of the clinical outcome. Fluid therapy has important role in maintenance of intravascular volume adequacy, hemodynamic stability, and delivery of oxygen. But adverse effects are underestimated. According to one survey, half of physicians were unaware of the composition of the fluids that they were prescribing and administering.
2. Consequences of Inappropriate Fluid Therapy.

In elderly, injudicious fluid administration can lead to dire consequences. United Kingdom National Confidential Enquiry was done in 1999, into perioperative Death report which concluded "errors in fluid management (usually excess fluid) were one of the most common causes of avoidable perioperative morbidity and mortality" at age extremity[11].It also stated that "fluid management in the elderly is often poor; they should be accorded the same status as drug

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Table 9.1 Risks associated with inappropriate fluid therapy

Hypovolemia Risks	Fluid Overload Risks
Hypotension and Tachycardia	Delayed bowel recovery and chance of anastomotic leak
Compromized function of multiple organs and failure consequently	Persistent hypertension
Renal function impairment and failure	Peripheral edema
Shock and its consequences	Poor wound healing
Headache, giddiness, weakness, Confusion, etc.	Respiratory distress or failure

prescription." Multidisciplinary reviews are needed to develop good local working practices. (Table 9.1).

9.1 Effects of Aging on Renal Function, Fluids, and Electrolytes

Inappropriate fluid administration places elderly patients more at risk to adverse consequences in comparison to young patients, because of reduced physiologic reserve. These patients also have multiple comorbidities such as elevated blood pressure, coronary vessel disease, and congestive heart disease[13]. The prevalence of chronic kidney disease in the Medicare population is about 8%.

Aging leads to progressive deterioration of renal and cardiovascular system. There is increased incidence of systolic/diastolic dysfunction and vascular stiffness as person ages. There are various changes in renal function also which are as follows:

1. Renal vascular dysautonomy.
2. Senile hypofiltration.
3. Tubular dysfunction.
4. Medullary hypotonicity.
5. Tubular frailty.

Body composition also changes with age. Age-related loss of muscle mass leads to a 10% to 15% decrease in intracellular fluid content. Although total fat content goes down, the amount of fat as a percentage of total body weight increases. Total energy expenditure also falls.

The clinical consequences of these changes are profound. The aging kidney is more vulnerable to injury, less able to accustom hemodynamic changes, and cannot deal perturbations of salt and water. Reduced GFR and decreased tubular function tend to reduce ability to concentrate urine, the result of which requires an increase in the obligatory urinary volume necessary to excrete waste products. On the other hand, the drop in GFR diminishes the potential to excrete excess water, making the aged prone to overload of fluid and pulmonary edema. Aged patients become more prone to hypoosmolar states (hyponatremia) if given excess quantity of hypoosmolar fluids.

Hemodynamic changes that lead to dehydration may be muted, especially in hospitalized elderly patients, and signs of dehydration may be nonspecific (impaired cognitive dysfunction, minimal confusion, weakness, apathy, dizziness) and may be attributed to other etiologies or aging itself.

It is imperative to monitor electrolytes in elderly patients who are receiving IV fluids. Alterations in plasma sodium concentration generally indicate a deficit or an excess of water rather than changes in balance in sodium. A small change of even 1 mmol/L in plasma sodium concentration reflects a loss or gain of 280 mL of water in a 70 kg man. However, about half the amount of change in fluid can cause a similar change in sodium concentration in a 45 kg woman, and thus is more easily overloaded by injudicious use of fluids.

9.2 Role of Medications in Fluid and Electrolyte Balance

Many elderly patients take multiple medications—for a variety of comorbidities, such as those listed earlier—that may have significant interactions with each other. These drugs often interfere with fluid and electrolytes, as well. Thiazide diuretics and serotonin reuptake inhibitors, for example, have been shown to cause hyponatremia by either causing direct sodium loss, release of ADH, or potentiating of the effects of ADH. Aldosterone-blocking agents

like spironolactone, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers can lead to hyperkalemia. It is prudent to check electrolytes periodically in patients taking these medications. Diuretics can cause significant dehydration. Some clinicians recommend dosing diuretics in out-of-hospital patients based on daily weight, rather than on routine basis, to avoid dehydration. (Figs. 9.1, 9.2, and 9.3).

Fig. 9.1 Fluid therapy

Fig. 9.2 Total parenteral nutrition

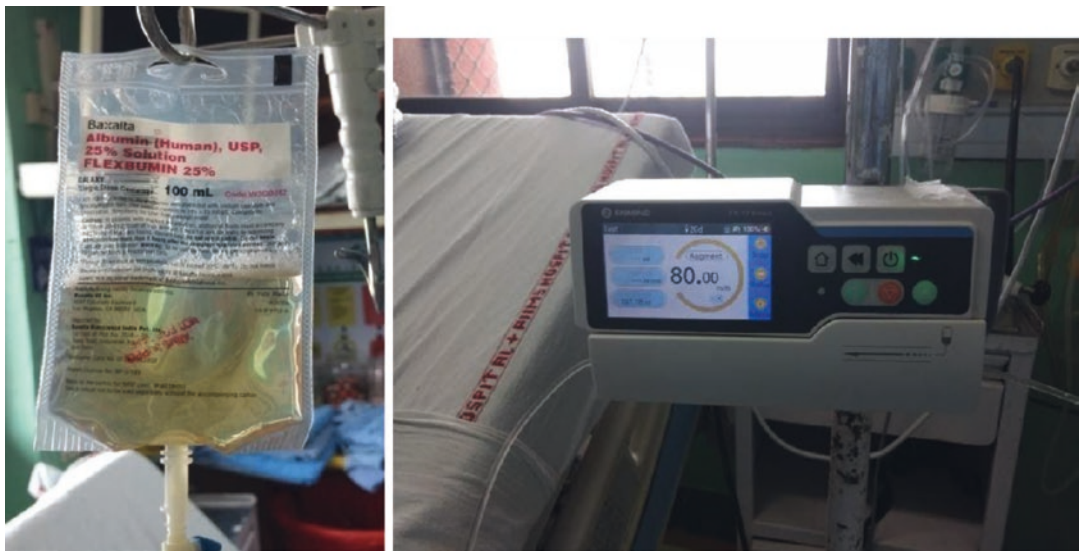

Fig. 9.3 Albumin infusion and Infusion pump

Administration of diuretics and hypertonic saline should be avoided, as it may cause rapid changes in serum sodium and water level which will lead to neuronal demyelination and fatal outcome.

9.3 Choice of Fluids in the Perioperative Period

Typical Properties of Commonly Used IV Solutions						
	Sodium, mmol/L	Potassium, mmol/L	Chloride, mmol/L	Osmolarity, mOsm/L	Weight Average, MolWtkD	Plasma Volume Expansion
Type of Fluid[a]						Duration, h[b]
Plasma	136–145	3.5–5.0	98–105	280–300	–	–
5% dextrose	0	0	0	278	–	–
Dextrose 4%	30	0	30	283		
saline 0.18%						
0.9% "normal" saline	154	0	154	308	–	0.2
0.45% "half normal" saline	77	0	77	154	–	
Ringer's lactate	130	4	109	273	–	0.2
Hartmann's solution	131	5	111	275	–	0.2
Gelatine 4%	145	0	145	290	30,000	1–2
5% albumin	150	0	150	300	68,000	2–4
20% albumin	–	–	–	–	68,000	2–4
HES 6% 130/0.4	154	0	154	308	130,000	4–8
HES 10% 200/0.5	154	0	154	308	200,000	6–12
HES 6% 450/0.6	154	0	154	308	450,000	24–36

British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP) for fluid management recommends that "when crystalloid resuscitation or replacement is indicated balanced salt solution Ringer's lactate/acetate or Hartmann's solution should replace 0.9% normal saline, except in cases of hypochloremia, for example, from vomiting or gastric drainage."

9.4 Restrictive or Liberal Fluid Therapy

Although goal-directed fluid therapy in perioperative elderly patients is not studied specifically, it is associated with improved outcomes. A primary goal of fluid therapy is to maintain optimal preload which inadvertently results in achieving adequate cardiac index/stroke volume for a particular clinical scenario. It is difficult to find accurately the fluid status in perioperative setting.

Central venous pressure or pulmonary artery wedge pressure, which are the static measures of preload, have been commonly used to guide fluid therapy. But, these are not particularly accurate[21]. Dynamic indices like systolic pressure variation (SPV) by pulse pressure variation (PPV), stroke volume variation (SVV) and pleth variability index may be better predictors of volume status[22].

Marik et al., in their meta-analysis of 29 studies involving 685 patients, showed that dynamic indices correlate better with cardiac index and stroke volume than static indices. Correlation coefficients for dynamic indices (PPV, SPV, and

SVV) were 0.78, 0.72, and 0.72, respectively; area under the curve (AUC) was 0.94 to 0.84. For static indices, AUC was 0.6 to 0.55[22]. To determine fluid status, British guidelines recommend flow-directed monitors. However, these are small studies (average, n = 23 patients) and results may not apply to elderly patients. Still, goal-directed therapy, which also requires the use of inotropes, has been recommended for intraoperative fluid management by some authorities in the United Kingdom and Europe.

9.5 Summary of British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients

	Recommendation	Level of Evidence
1.	Balanced salt solutions (e.g., Ringer's lactate/acetate or Hartmann's solution) should replace 0.9% saline, whenever crystalloid resuscitation or replacement is indicated to avoid risk of hypochloremic acidosis in practice routinely, except when there is hypochloremia (e.g., from vomiting or gastric drainage).	1b
2.	4% dextrose, 0.18% saline, and 5% dextrose are optimal sources of free water for maintenance therapy, but may result in life-threatening hyponatremia if used in excessive amounts, especially in children and elderly. These solutions are appropriate only in significant free water deficit (e.g., diabetes insipidus), but not in other conditions.	1b
3.	Adult patients need sodium 50 to 100 mmol/d, potassium 40 to 80 mmol/d in 1.5 to 2.5 L of water by the oral, enteral, or parenteral route for maintenance. Additional amount is given only to correct deficit or when there is ongoing losses. Clinical examination, regular weighing, and fluid balance charts should be done for monitoring when possible.	5
Preoperative fluid management		
4.	Fluid and electrolyte derangements can occur due to mechanical bowel preparation. Hartmann's or Ringer's lactate or acetate-type solutions are used to correct it.	5
5.	Gastric aspiration/vomiting can lead to excessive losses preoperatively and to be treated with crystalloid solution that comprises necessary potassium supplement. Hypochloremia is treated by 0.9% saline, with added potassium to avoid sodium overload. Lose of fluid from diarrhea/ Ileostomy/small bowel fistula/obstruction/ileus should be replaced with Hartmann's or Ringer's Lactate or acetate-type solutions. Excessive diuretics can lead to "saline depletion," which is better managed with a balanced electrolyte solution like Hartmann's.	5 and IIa
6.	Preoperative treatment with IV fluid and inotropes should be given in high-risk surgical patients to achieve adequate cardiac output and delivery of oxygen for improved survival.	1b
7.	Flow-based measurements should be used to diagnose preoperative or operative hypovolemia, though it is logistically difficult in many centers currently. Clinical features are also an important indicator to determine hypovolemia. Hypovolemia is clinically diagnosed by pulse rate, capillary refill, venous (JVP/CVP) pressures, peripheral perfusion, Glasgow Coma Scale, acid–base and lactate levels, when direct flow measurement is not possible. A low urine output should be always interpreted in context of patient's cardiovascular parameters.	1b

9.6 Conclusion

Renal function declines progressively in the elderly. Approximately 8% of Medicare patients have chronic kidney disease. In view of the deleterious effects of fluid and electrolyte imbalance on perioperative outcomes, administration of fluids and electrolytes should receive heightened attention in elderly patients. Clinicians must consider fluids as medications and administer them as such, and an improved understanding of the composition of fluids and their physiologic effects is critical.

In a hospitalized, inactive, afebrile, and elderly patient, there is diminution of fluid need. Dehydration in elderly patient may be due to decreased thirst response, regular diuretics usage, and limited functionality. Underhydration and overhydration are both deleterious. However, few studies in the elderly have specifically addressed the issue of fluid management in the perioperative period. More research is needed in this area.

Acute Pain management in Onco Surgical Patient: Overview

10

Somnath Bagchi

Pain is a complex multifactorial phenomenon which has a biological basis, huge psychological component, and a great social impact (Biopsychosocial model of pain) [1]. Broadly speaking pain can be classified into three broad categories—acute pain, that is the pain immediately following an operation or injury so it has an identifiable temporal and causal relationship to injury or disease, cancer pain which happens due to metastasis, invasion of tissues or inflammation from cancer and the third type of pain is chronic non-malignant pain like headache, backache, fibromyalgia or neuropathic pain. Chronic pain usually starts after tissue healing often without any specific identifiable cause in most cases persists beyond 3 months of the initial injury. Many scholars present a view that is acute and chronic pain may represent a continuum rather than distinct entities. In this chapter, we will limit ourselves to the definition of pain, the pathophysiology of acute postoperative pain, the assessment of the patients in pain, management of the postoperative patients and some challenges you will face in the ward. The aim of this chapter is not to impede the freedom of the clinician but to provide him with guidance to form a robust, evidence-based and acceptable working protocol. It will help the clinical staff to manage patient more proficiently and establish standardized care which can be audited against a standard to improvise and compare the outcome.

10.1 Introduction

International Association of the Study of Pain (IASP) [2] defines pain as 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'. The old view was pain is beneficial as it warns us about the problem but contrary to the old view, it has been demonstrated that pain is not equal to damage. Pain is a stressor and it threatens homeostasis with a neurohumoral adaptive response which harms the patient. It is now established that the contribution of psychological factors in acute pain is as important as chronic pain [3]. So our aim should be to reduce preoperative anxiety, anxiety or depression by proper counselling and reduce the stress response to improve outcome.

The table below summarizes some of the salient systemic effects of acute pain, for example, following a laparotomy.

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Cardiovascular	Stress leads to increase in sympathomimetic amines like adrenaline and nor adrenaline causing an increase in heart rate, cardiac contractility, systemic vascular resistance and blood pressure. This leads to increase stress on the heart as it has to work more with less diastolic time for perfusion of cardiac muscles. This produces the oxygen supply-demand mismatch of the cardiac tissues causing myocardial ischaemia.
Respiratory	During operation, there is positive pressure ventilation of the lungs contrary to the normal negative pressure aspiration of air and oxygen. This disturbs the alveoli function leading to accumulation of protein-rich exudates in the dependent portions of lungs which are ideal for bacterial growth. So it is mandatory to have deep breathing exercises in the postoperative period to mobilize this fluid and prevent chest infection.
Renal	The effect of the activation of the renin–angiotensin system leads to sodium and water retention by active transport in the distal tubules. This leads to poor urine output and extracellular accumulation of water and tissue oedema. In compromised patients with low GFR (<50 mL/min/1.73 m^2) this can lead to postoperative acute renal failure.
Pancreas	Inhibition of insulin release and increase in glucagon leads to poor glucose homeostasis. Neoglucogenesis by the liver is also promoted by cortisol leading to further catabolism and increase in blood sugar levels.
Haemopoietic	General anaesthesia predisposes to Virchow's triad of venous stasis, abnormal coagulation and intimal damage; Immobility due to pain increases the chance of DVT and PE with fatal consequences [4].
Psychology and cognitive effects	Anxiety and pain are positively correlated [5]. The stressor effects of unrelieved pain have the potential to increase anxiety levels and interfere with activities of daily living, such as diet, exercise, work or leisure activities and to interrupt normal sleep patterns causing varying degrees of insomnia. Pain also results in a distressing cognitive impairment, such as disorientation, mental confusion and a reduced ability to concentrate [6].
Gastrointestinal	The override of the sympathetic system leads to a decrease in gut motility—paralytic ileus—postoperative nausea and vomiting. The GI mediated release of serotonin and its effect on the chemoreceptor trigger zone are also responsible for nausea and vomiting.
Immune system	Increased catabolism with negative nitrogen balance leading to dysfunction of T and B lymphocytes that increases the susceptibility to infection and poor wound healing. There is also the release of Interleukin-1 which stimulates the release of sympathetic mediators.

10.2 Pathophysiology of Acute Postoperative Pain

It is important to understand the basics of the pain pathway and know some of the neurotransmitters to understand the rationale behind the use of pain medications. The pain pathway has four important components: transduction, transmission, perception and modulation.

When pain is inflicted by a surgical incision at the tissue there is a degradation of cells with a release of chemicals [7] like histamine, prostaglandins, H+ ions, cytokines (IL1, TNF), chemokines (e.g. CCL3) and neuropeptides (substance

P) which stimulates the free nerve endings or nociceptors. Activation of the nociceptors leads to the development of action potential at nerve endings in a process called transduction (conversion of chemical to electrical energy). The pain impulse in the form of the action potential is now carried to the brain in a process called transmission. The impulse is carried by medium diameter, relatively fast, lightly myelinated A-delta and thin, slow conducting, unmyelinated C nerve fibres (both are first-order neurons) to a specific area of the grey matter of the spinal cord called substantia gelatinosa (Lamina II & III). (The grey matter in the spinal cord is divided into layers I to X known as Rexed laminas—see Fig. 10.1.)

The first-order neurons end at the lamina II and III and the second-order neurone starts. Most of the second-order neurone crosses over at this level to the opposite side and ascends as lateral spinothalamic tract (Lateral Pathway). Some second-order neurones do not cross, they ascend in the same side as fasciculus gracilis and cuneatus to the nucleuses of midbrain. These fibres (Medial Pathway) are important for fear, aversion and psychopathic components of pain perception and suffering.

Most fibres end in thalamus from where the third-order neurons arise. The third-order neurons go from the thalamus to various places of the brain including the sensory area of the brain so we can perceive (feel) the pain. Third-order neurons from thalamus also go to the areas like periaqueductal gray and locus coeruleus from where descending inhibitory tract begins and goes to the dorsal horn of the spinal cord. This completes the feedback loop of the pain. Some nerve fibres from the spinal cord and also from thalamus go to other areas of the brain like the medulla, brainstem, hypothalamus and amygdala (spinoreticular, spinomesencephalic, spinoparabrachial tracts). These are important to integrate the pain sensation with other responses like arousal, autonomic and emotional responses which leads to the expression of pain sensation and contribute to the suffering of pain.

A few words about the importance of dorsal horn is mandatory at this point.

The dorsal horn is the major site where modulation of pain signals happens.

- There is a complex interplay of the peripheral nervous system (the receptors and nerves) and central nervous system (brain and spinal cord).
- There are a huge number of excitatory neurotransmitters like glutamate, aspartate, calcitonin gene-related peptide which propagate

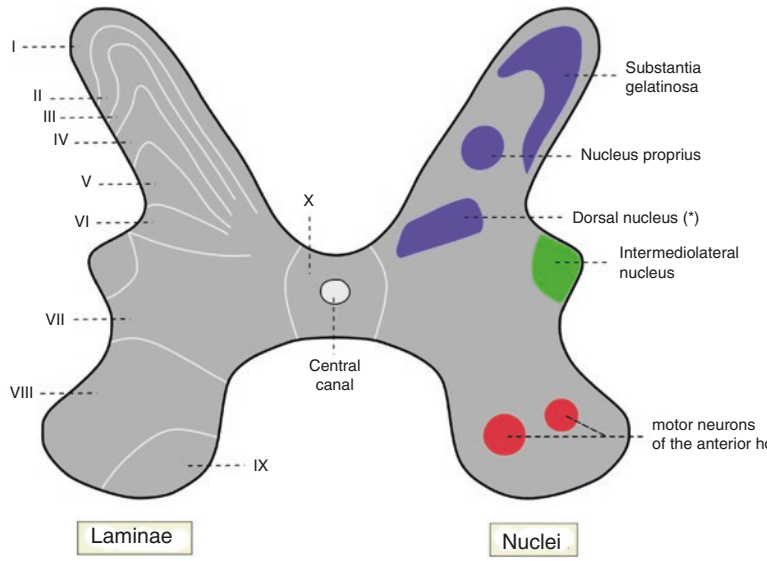


Fig. 10.1 https://en.wikipedia.org/wiki/Rexed_laminae

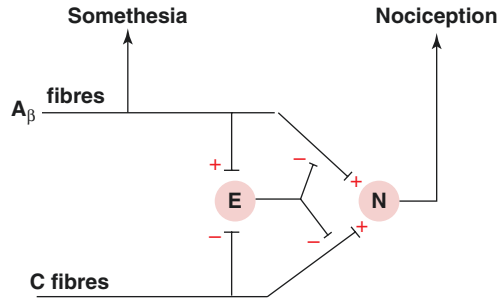


Fig. 10.2 Gate Control Theory of Pain: https://www.anaesthesiauk.com/article.aspx?articleid=100119. *E* Encephalinergic Interneuron

the pain signal and a host of inhibitory neurotransmitter like GABA and glycine which inhibit the pain propagation.

- On this dorsal horn the descending inhibitory fibres from periaqueductal gray and locus coeruleus terminates try to stop the pain (Inhibitory pathway).
- The dorsal horn is also influenced by non-nociceptive peripheral inputs by moderately myelinated, fast A Beta fibre which carries touch sensation. They can occupy the receptors and prevent excitatory neurotransmitters to activate it or can stimulate inhibitory interneurons and block the transmission of pain. This is the basis of the Gate Control Theory of Pain [8].
- The other inhibitory influences at this level are by higher-order brain function (e.g. distraction, cognitive input). These inhibitory mechanisms are activated by the brain to modulate the controlling responses to reduce the excitatory activity of C fibres.
- Thus, analgesia may be achieved by either enhancing inhibition (e.g. opioids, clonidine, antidepressants) or by reducing excitatory transmission (e.g. local anaesthetics, ketamine) (http://fpm.anzca.edu.au/documents/apmse4_2015_final) (Fig. 10.2).

Perception of pain is a complex phenomenon which involved recognizing of the intensity, quality and influence from medial pathway, defining and responding to pain. This brings us to the concept of global pain which is the resultant pain of all the conflicting influences in the spinal cord.

The concept is depicted as follows:

$$\text{Global Pain} = \underset{(\text{Lateral Pathway})}{\text{Pain intensity}} + \underset{(\text{Medial Pathway})}{\text{Pain suffering}} - \underset{(\text{Inhibitory Pathway})}{\text{Pain Suppression}}$$

It is a result of neural activity and is where pain becomes a conscious experience. Perception takes place predominantly in the cortex, but the limbic system and reticular systems are also involved. This becomes more important as the pain becomes chronic. The complex interaction between the various excitatory and inhibitory inputs alters the pain perception in a process called Modulation. A schematic diagram of the various projections is given in Figs. 10.3 and 10.4. Apart from modulation, pain is also influenced by culture, previous pain experience, belief, mood and ability to cope. The individual variation to pain makes it a dynamic experience and pins the importance that there cannot be a fixed plan to manage all patients. The same procedure in the same cohort of patients will elicit a different response. So, the treatment should be individualized and tailored to the requirement of the patient.

This brings us to the next section a careful assessment of the pain.

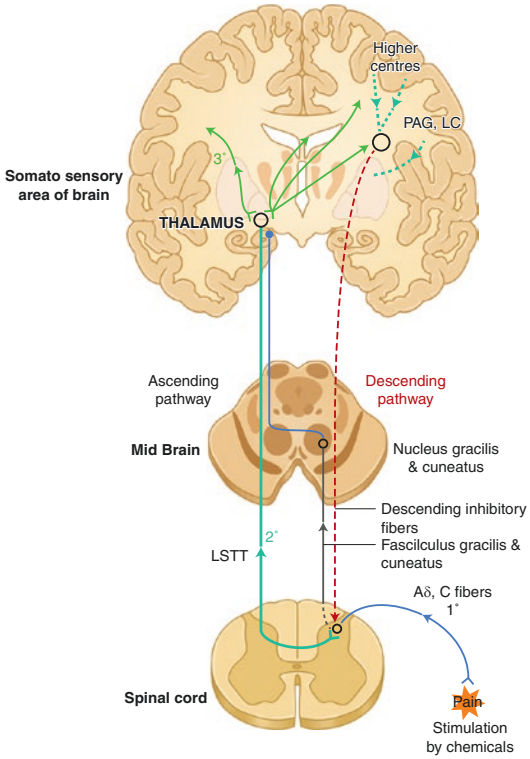


Fig. 10.3 The Afferent and Efferent Pain Pathways

10.3 Assessment and Documentation of Pain

Pain is a subjective phenomenon. So, it is reported by the patient and the assessment aims to find out the severity and quality of pain experienced by patients. When we assess the intensity of the pain we try to assess the Global pain.

Various scales have been used to assess pain but the main criteria to select one which is familiar to all staff, reliable, reproducible and easy to use in the postoperative period. I am going to explain here is an 11 point 0–10 Numeric Pain Rating Scale which is most commonly used in

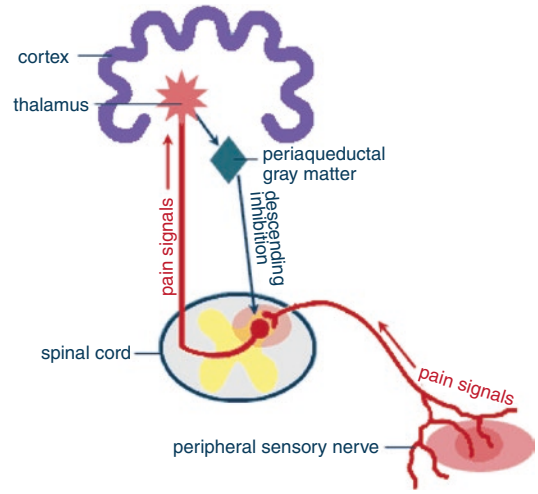
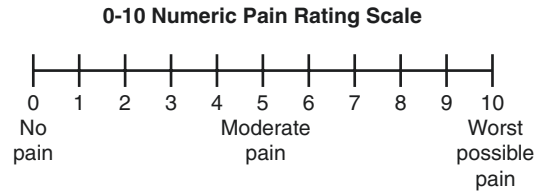
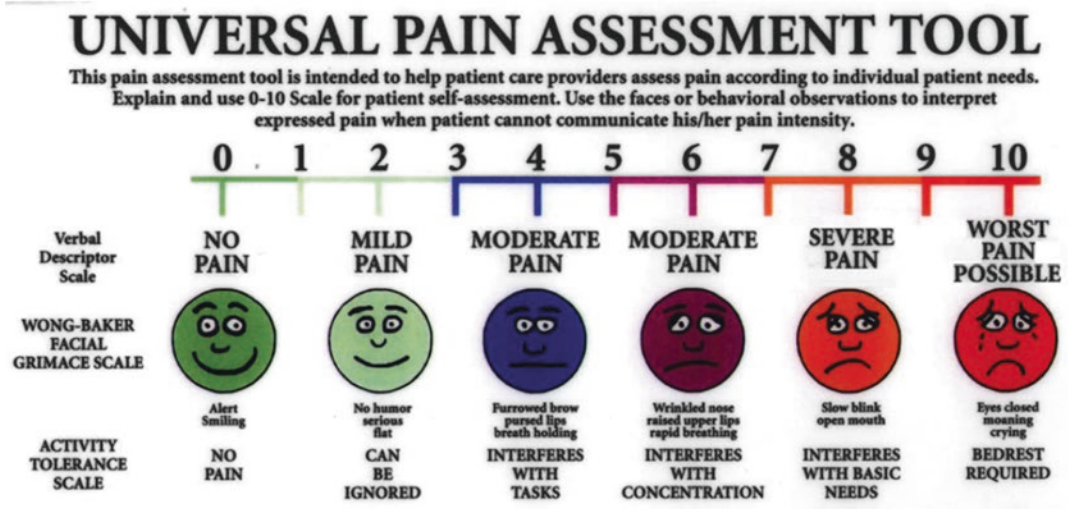


Fig. 10.4 A simple Diagram of the main pain Pathways. https://brainchemist.wordpress.com/2010/11/28/pain-sites-of-origin-pathways-and-neurotransmitters/

our unit. It is a 10 cm line with 0 to 10 written on it. 0 implies there is no pain at all, while a score of 10 means the maximum pain imaginable by the patient. The clinician aims to reduce the pain by 50% or keep it below a score of 3. A simple 4 point scale where no pain (= 0), mild pain (= 1 to 3), moderate pain (= 4 to 6) and severe (= 7 to 10) can also be used in patients who cannot comprehend it intellectually.



For children under 5 years, Wong–Baker FACES Pain Rating Scale is used. Recently a universal pain assessment tool is introduced which incorporates both the aspects.



For postoperative patients, it is important to assess the dynamic pain as well. It is important to use additional medications to manage pain during deep breathing, early mobilization or during procedures like dressing changes.

Along with routine vital signs and pain scores, we need to assess the side effects of medications. It is important to ask patients specific questions to find out whether they are suffering from nausea or itching and/or excessively sedated. The PONV risk score and the outline of management are given below [10, 11].

Risk factors for postoperative nausea and vomiting (PONV).

Patient Factors	Surgical Factors	Anaesthetic Factors
• Female. • History of motion sickness. • History of PONV.	• Gynaecological. • Abdominal. • Ear. • Testicular. • Laparoscopic .	• Inhalational anaesthesia. • Postoperative pain. • History of PONV. • Large doses of opioids.

There are several scales to assess the severity of nausea or sedation, one such is given below: Ask the patient to find out whether he is feeling

- No Nausea = 0.
- Nausea = 1.
- Vomiting = 2.

10.3.1 Management of Nausea and Vomiting

- Exclude hypoxia, hypovolaemia, hypotension, a full stomach.
- Ensure adequate analgesia.
- During the operation:
  - ensure that there are no contraindications to using either dexamethasone 2.5–4 mg iv and/or stemetil (prochlorperazine) 12.5 mg. IM or slow IV.
  - ensure that all suitable patients are prescribed Ondansetron PRN.
- If regular stemetil is ineffective or maximum dose is reached, add ondansetron 4-8 mg IV 8 hourly.
- Regular antiemetics may need to be given for a few days. Tolerance to nausea and vomiting caused by opioid drugs develops after 5–7 days.
- Regularly review the requirement for antiemetic therapy.

Sedation score is important as a trend towards increasing sedation may alert us to the adverse effects of opioids before respiratory depression becomes a problem. Sedation score like Pasero Opioid-induced Sedation Scale (POSS) can be used. But any standardized score which is acceptable and reproducible can be used. A simpler score is given below:

Sedation is scored as follows:

- 0 = None (alert)
- S = Sleeping normally.
- 1 = Mild (occasionally drowsy but easy to rouse)
- 2 = Moderate (frequently drowsy but easy to rouse)
- 3 = Severe (somnolent, difficult to rouse).

When the patient received a central neuraxial block it is mandatory to document the sensory and motor levels of the block. The sensory dermatomal level is often ascertained by use of ice cube in a plastic sheet or gloves. (Finding the cold response but not making the patient wet.)

Motor Block Score is assessed by the following score:

- 0 = No motor block. Free movement of legs and feet
- 1 = Unable to bend at the hip, able to bend knee, free movement of feet
- 2 = Unable to bend the knee, free movement of feet
- 3 = Unable to move legs or feet.

10.4 Review of Drugs

We will quickly review the common pain medications before we come up with management strategies. There are only 4 classes of analgesics: Paracetamol, Nonsteroidal Anti-inflammatory Drugs (NSAIDs), Opioid Medications and Anti neuropathic medications.

Paracetamol:

- Paracetamol, a centrally acting drug though the exact mechanism is not clear. It has a very good safety profile and should always be used regularly as it reduces the need for opioid and other analgesics [14].
- The maximum dose in a healthy adult weighing more than 50 kgs is 4 grams a day in divided doses. Doses should be reduced in low body weight and decompensated liver failure.
- Paracetamol can be given PO/PR/IV.
- It is difficult to estimate for how long paracetamol should be continued regularly following surgery as it depends on many variable factors including the patient's response to surgery. Consider converting from regular to 'as required' administration about 1–2 weeks after moderate surgery.

10.4.1 NSAIDs

In our unit, we extensively use NSAIDs in addition to regular paracetamol as baseline analgesia where not contraindicated. It is a very good analgesic used for short duration of action like 5–7 days. NSAIDs work by inhibition of prostaglandin synthesis at the periphery and can be broadly classified as non-selective cyclooxygenase inhibitor or relative selective cyclooxygenases type 2 inhibitors like parecoxib (iv formulation) or Celecoxib/meloxicam (oral formulation). The other group selective cyclooxygenase inhibitor like rofecoxib is withdrawn from the market due to adverse cardiovascular side effect.

Oral ibuprofen should be used where possible as it has the lowest gastrointestinal risk and relatively low cardiovascular side effects. If oral fluids are not tolerated, rectal or intravenous diclofenac may be used for short periods like 3 to 5 days. For all patients, the duration of NSAID use should be regularly reviewed as the GI risk increases significantly after 7–10 days. There are many contraindications to their use:

1. Renal dysfunction: NSAIDs may cause a deterioration in renal function and should be avoided in the presence of renal impairment (GFR < 75 mL/min/1.73 m^2).
2. Hypovolaemia and dehydration: NSAIDs should be prescribed with caution in hypovolaemic and dehydrated patients as they cause a reduction in renal blood flow and may precipitate acute renal failure.
3. Unstable asthma or asthmatic patients are known to be worsened by NSAIDs (about 10% of all asthmatic).
4. GI Risk: NSAIDs should be avoided in patients with active peptic ulceration. Gastric protective therapy (e.g., omeprazole 40 mg od) is advisable in patients at high risk of peptic ulceration and/or gastrointestinal bleeding. The r*ecognized additive GI risk factors are*:

(a) History of gastric or duodenal ulceration or gastrointestinal bleeding. (b) 65 yrs. of age (risk is highest above 75 yrs. but increases above 65 yrs). (c) Comorbidities like cardiovascular disease, renal or hepatic impairment, or diabetes. (d) Patients taking concurrent medication likely to cause GI irritation, e.g. corticosteroids, anticoagulants.
5. Coagulopathy.
6. Old age.
7. Allergy to NSAIDs.
8. Established cardiovascular disease: diclofenac 150 mg/day appears to be associated with a similar excess risk of thrombotic events (stroke and myocardial infarction) as coxibs, whereas low dose ibuprofen (<1200 mg/day) and naproxen 1000 mg/day appear to be associated with a lower risk.
9. Drug Interaction is very frequent with NSAIDs. Caution should always be exercised in patients taking drugs that interact, e.g. Lithium, methotrexate and warfarin.

OPIOID ANALGESICS (e.g.: Morphine, Fentanyl, Tramadol, Tapentadol, Buprenorphine).

These drugs are still the mainstay of acute pain relief and morphine is the opioid of choice as it is cheap, effective and side effects are easily recognizable and treatable. All opioids work by attaching to specific opioid receptors traditionally classified as mu, kappa and delta receptors.

Morphine can be given by many routes and is equally effective whatever the route, provided adequate doses are used. If the patient is nil by mouth, morphine may be given by either IM/SC injection or by IV-PCA (intravenous patient-controlled analgesia). If IV access is unavailable yet PCA remains the most appropriate method, subcutaneous PCA is equally effective [15]. When the patient is tolerating oral fluids the prescription may be changed to the oral route. A rule of thumb is 1 mg of IV morphine = 5 mg of IM/SC =10 mg of PO morphine. The figure below adapted from British National Formulary explains it well [16].

The major side effects associated with opioid use are:

1. Respiratory depression: usually of gradual onset and apparent as increasing sedation followed by a fall in respiratory rate.
2. Nausea and vomiting: should be treated without reservation.
3. Urinary retention: may necessitate bladder catheterization.
4. Constipation: may warrant regular prescription of a stimulant laxative, e.g. senna given at night.
5. Pruritus is rare but troublesome. Consider antihistamines and SC/IM naloxone 200cmg single dose. If severe with morphine convert to fentanyl IV (or patch) or buprenorphine patch. While using a patch either fentanyl or buprenorphine there should be an overlap period of 6 to 12 h, as they do not work instantly.
6. Long-term opioids (more than 3 weeks) are associated with other side effects like tolerance, dependence, addiction, suppression of immunity, suppression of pituitary adrenal axis, repeated falls and opioid induced hyperalgesia—phenomenon where increasing opioids increases the pain. So many countries have made it mandatory to reduce the use of opioids to a maximum limit for chronic patients. It is unlikely to happen in patients post operatively but many patients continue with the prescription if not discontinued at an appropriate time (https://fpm.ac.uk/opioids-aware).

All opioids should be prescribed with caution with a clear plan to deescalate and in reduced doses in presence to certain comorbidities [17].

1. Renal dysfunction.
2. Hepatic dysfunction.
3. Altered level of consciousness, e.g. Neurosurgery with a chance of raised intracranial pressure.
4. Respiratory dysfunction, e.g. chronic bronchitis leads to CO2 retention.
5. Obesity.
6. Sleep apnoea syndromes.
7. Elderly.
8. With a past history of addiction.

Oral opioids are the ‘step-down’ analgesia of choice following discontinuation of parenteral opioids. Sustained release oral morphine or codeine or tramadol can be prescribed as regular analgesics backed up by short-acting agents for

breakthrough pain depending on the intensity of pain and experience of the unit. The patients should be individualized and treated. Addition to opioids following postoperative short-term use (days to weeks) is not a concern. Problems of long-term use require sustained exposure and involve personal and social circumstances.

Tramadol is not a typical opioid. Apart from being a mu receptor agonist, it prevents the norepinephrine and serotonin uptake in the descending inhibitory fibres potentiating its effect [18]. It is used for moderate to severe pain, but not as effective in severe pain as other strong opioids. Side effects are similar to morphine except it is associated with less respiratory depression, less constipation and less addiction potential. Hallucinations and confusion are more common with its use and mostly happens with the first few doses. Concurrent use of antipsychotic and antidepressant medications especially those which prevent the reuptake of serotonin (e.g. SSRI) can cause serotonin accumulation and serotonergic syndrome in vulnerable patients.

Tapentadol is a new class of drug introduced in 2009. It can be given both orally and parenterally works via two mechanisms of action—mu-opioid receptor agonism and norepinephrine reuptake inhibition. The immediate-release formulation is approved in the US and European Union for moderate to severe pain, but it is currently unavailable in India [19]. The sustained release version which is available in India can be used in selected cases as a background analgesic where morphine is not tolerated. It has significantly less side effect profile in terms of nausea, vomiting, constipation and respiratory depression compared with stronger opioids [20–22].

Transdermal Fentanyl patches are used in some centres for the management of acute pain. It is not recommended as it is costly, not a superior method to others available, has a long latency period and cannot be titrated. It has no license to be used in acute pain.

Converting between transdermal fentanyl and fentanyl by other routes, or between transdermal fentanyl and other opioids is complex and will need expert input.

- A '25 microgram/hr' patch is approximately equivalent to 90–135 mg morphine orally in 24 h.
- If fentanyl patches are being used preoperatively, it may be appropriate to continue them perioperatively and use additional opioids (morphine, fentanyl) as required.
- The patches should be changed every 3 days.

For similar reasons, transdermal buprenorphine patches are also not recommended. But in chronic pain management, it is one of the opioids of choice being a partial agonist of mu receptors and good safety profile in the elderly population [23].

Pethidine has a short duration of action so it has a disadvantage in continuing pain. Repeated doses of pethidine increase the risk of neurological toxicity caused by the pethidine metabolite norpethidine. The use of pethidine is, therefore, not recommended.

Equivalent doses of opioid analgesics.

Drug Name	Dosage	Morphine Equivalent in 24 h
Codeine	60 mg	6 mg
Tramadol	100 mg	10 mg
Fentanyl patch	12mcg/hr	45 mg
	25mcg/hr	90 mg
	50mcg/hr	180 mg
	75mcg/hr	270 mg
Buprenorphine patch	5mcg/hr	12 mg
	10mcg/hr	24 mg
	20mcg/hr	48 mg

10.5 Local Anaesthetics

Local anaesthetics are drugs that cause a reversible loss of nerve transmission by blocking Na + channels. Local anaesthetics are formulated as hydrochloride salt so that they are water-soluble. It is used as a part of nerve blocks (e.g. Femoral nerve block), regional block (e.g. transversus abdominis plane block) or central neuraxial blocks (e.g. epidural blocks). Local Anaesthetics without preservatives and additives (apart from glucose at 80 mg/ml used in 'heavy' bupivacaine) are suitable for subarachnoid administration, as the preservatives carry the risk of producing arachnoiditis.

The commonly used local anaesthetic drugs are Lidocaine, bupivacaine, levobupivacaine and ropivacaine. The potency of the local anaesthetic is

mostly dependent on lipid solubility, but also vasodilator properties and tissue distribution of the drug. Local anaesthetics duration of action is dependent on their affinity and extent of protein binding. The drugs like prilocaine with less protein binding have a short duration of action, and, conversely, drugs like bupivacaine with more extensive protein binding have a longer duration of action.

The intrinsic vasodilator property of individual local anaesthetics influences potency and duration of action. At low concentration there is vasodilatation and the gradient is as follows: pril ocaine>lidocaine>bupivacaine>ropivacaine: and vasoconstriction at higher concentrations. Cocaineis the only local anaesthetics (rarely used now as local anaesthetics) is a vasoconstrictor. However, the total dose and concentration of administered local anaesthetic will also have a significant effect on a given clinical situation.

Local anaesthetics are generally ineffective when used to anaesthetize infected tissue due to the acidic pH of the surrounding tissues. The acidic environment polarize drug and changes it into ionic form so reducing the unionized fraction of drug available to diffuse into and block the nerve. There may also be increased local vascularity, which increases the removal of drug from the site. Intraoperative wound infiltration or regional nerve blocks or local anaesthetic infusions are preferred whenever possible to reduce the use of systemic analgesics.

Local anaesthetics have potential side effects when the recommended dose is exceeded. The management of local anaesthetic toxicity is described in the epidural section of the chapter.

10.6 Antineuropathics

These medications are also known as co-analgesics [5] and can be prescribed for nerve-related (neuropathic) pain or as a component of the multimodal approach of analgesia to reduce opioid consumption. The three types of medications most commonly prescribed for nerve pain include:

- Antidepressants or tricyclic antidepressants (TCA's), such as Amitriptyline and Nortriptyline. The newer selective serotonin reuptake inhibitors (SSRI) antidepressant medications are not considered as effective for this condition as tricyclic antidepressants. These work by preventing active reuptake of serotonin or nor adrenaline in the descending inhibitory fibres. The usual side effects are drowsiness, increase in intraocular pressure, arrhythmias, dryness of mouth and constipation.
- Anticonvulsants (also called neuroleptic medications) such as gabapentin and pregabalin. Pregabalin, a newly developed gabapentinoid is used in the perioperative period to manage pain due to its rapid onset of action, but we have to be careful about its addiction potential drowsiness which can impair recovery and recent studies suggest they are not useful in acute pain. The gabapentinoids are calcium channel blockers.
- The other group of antineuropathics which can be helpful in acute pain includes medications like ketamine, an intravenous anaesthetic and NMDA receptor agonist in low dose (0.25 mg/kg), or Clonidine, an alpha2 receptor agonist which also works on the spinal pathway or a 50% mixture of nitrous oxide and oxygen called entonox which stimulates NMDA receptors and higher centres in brain to produce analgesia.
- The list of antineuropathics can be extensive like carbamazepine, valproate, capsaicin bit these are rarely used in acute pain setting.
- So, we find we can influence the various channels which are expressed on the nerve fibres—sodium channel by local anaesthetics, calcium channels by gabapentinoids, or enhance effect by preventing active reuptake like amitriptyline.

10.7 Management of Acute Pain

The management of pain is multimodal and multidisciplinary. The most commonly prescribed medications are a combination of round the clock baseline medication and a medication to manage breakthrough pain. The breakthrough pain can be incidental like movement, or end of dose failure like just before the next dose.

Some concepts:

1. WHO Pain Ladder.

In 1986 the World Health Organization (WHO) presented the analgesic ladder as a framework that physicians could use when developing treatment plans for cancer pain. This therapeutic guideline paved the way for considerable improvements in the management of cancer pain [24, 25]. The WHO pain ladder has been modified and adapted in various forms even in the management of acute pain. Though the WHO recommendations are not evidence-based it has stood the test of time and most widely used pain tool. An outline for the use of systemic analgesics is given below:

Initial Analgesia is the responsibility of the anaesthetist. It is difficult to give an outline of what should be the ideal prescription but it depends on the patient, surgery, circumstances and familiarity of the unit.

(a) Minor Surgery:—Regular Paracetamol (PO/PR/IV) +/− Regular Ibuprofen PO for a short period like 3 to 7 days (or diclofenac PR/IV) +/− As Required Codeine/Tramadol up to 4 times a day.
(b) Intermediate Surgery:—Regular Paracetamol (PO/PR/IV) +/− Regular Ibuprofen PO for a short period like 3 to 7 days (or diclofenac PR/IV) +/− As Required Morphine (IM/PO) or Morphine IV-PCA.
(c) Major Surgery: —Regular Paracetamol (PO/PR/IV) +/− Regular Ibuprofen PO for a short period like 3 to 7 days (or diclofenac PR/IV) +/− As Required Morphine (IM/PO) or Morphine IV-PCA or Epidural or Paravertebral Infusions.

2. Step-down Analgesia.

After commencing the patients on initial analgesic, as they improve the analgesia should be optimized so the patients can be discharged home with a contingency plan. Step-down analgesia involves converting from the parenteral routes (IV, IM, SC, epidural) to the enteral routes (PO, PR). The norm is to start on regular oral paracetamol and NSAIDs (if not contraindicated) as soon the patient starts oral fluid. If the patient is on patient-controlled analgesia, oral opioids can be started when the daily consumption of morphine is less than 40 mg/day, keeping a close eye on the patient regarding his function, mobility, nausea, vomiting, drowsiness and gut mobility. Stepping down from epidural analgesia can take more time and patience. While PCAs are withdrawn in most cases by third postoperative day, (when the daily morphine requirement is less than 40 mg in 24 h) the epidural often runs till day five. The first step after starting the oral medication is to stop the epidural infusion temporarily for two to 4 hours and assess the patient in terms of pain and movement. A rough guideline can be as follows:

If oral intake of fluid has commenced and basic analgesics started, then assess the patient:

- If pain score = mild: use oral codeine 30 mg 4–6 hourly or Oral Tramadol 50 mg 6 hourly if the patient can tolerate, PRN.
- If pain score = moderate: use regular oral codeine 30 mg 4–6 hourly or Oral Tramadol 50 mg 6 hourly if the patient can tolerate and oral morphine 10–20 mg 2 hourly PRN for breakthrough pain.
- If pain score = severe: use regular oral sustained release morphine 30 mg 12 hourly or Oral Tramadol up to 100 mg 6 hourly if the patient can tolerate and oral morphine10–20 mg 2 hourly PRN for breakthrough pain.

3. Central Neuraxial Blocks like: spinal, epidural and paravertebral.

Neuraxial anaesthesia is the term for central blocks involving the spinal, epidural and caudal spaces [26]. It is a popular method of providing postoperative analgesia. It is safe, effective and frequently used technique especially in conjunction with enhanced recovery. Usually, a low concentration mixture of bupivacaine (0.1%) and fentanyl 2mcg/ml may be infused into the epidural space through an indwelling catheter. This provides excellent pain relief by interfering with the flow of 'pain signals' along nerves entering the spinal cord.

Plain bupivacaine may be infused into the paravertebral space through a paravertebral catheter (paravertebral analgesia) or through a catheter sited adjacent to a peripheral nerve to provide peripheral neural analgesia. The absence of opioid in this solution allows for additional systemic opioids to be used if required. The general term used for these techniques is 'loco-regional analgesia'.

10.7.1 Managing a Loco-regional Analgesia Patient in the Ward

- The anaesthetist is responsible for establishing the analgesic technique and also giving clear instruction about how to run the loco-regional anaesthesia. (Epidural, Paravertebral or Peripheral nerve block).
- Proper informed consent should be obtained from the patient before any loco-regional.
- The Patient must have an IV cannula in situ.
- In some hospitals for paravertebral and peripheral neural infusion bupivacaine, 0.125% is used from locked prefilled bags or syringes via infusion pumps.
- If a prefilled bag is used lines must be changed every 72 hours by the Acute Pain Team or by senior nursing staff. For epidural infusions, it can be used for up to 5 days when a 0.22-micron in-line filter is used.
- The rate of the infusions varies widely and normally ranges from 3 to 10 ml/hr. Boluses are only given if approved by senior registrars or consultant. Following a bolus patient should be observed for the effects and vitals should be monitored.
- Careful labelling of the epidural/paravertebral catheter and infusion line is essential. This is to distinguish them from intravenous lines and minimize the risk of inadvertent wrong route administration. In the UK only yellow dedicated lines with special adaptors can be used for loco-regional infusions. These must be specifically labelled as 'epidural' or 'paravertebral' or relevant to the peripheral nerve infusion, e.g. 'femoral nerve infusion'.

Documentation should involve: the timing of the procedure, any immediate complications while placing the catheter, along with the vitals, pain score, sedation score, nausea score, motor score and level of sensory analgesia. These should be recorded hourly for the first 24 hours after starting the infusion. Thereafter they should be recorded 4 hourly, or more often if either pain is poorly controlled or complications arise. While removing an epidural catheter, it is mandatory to document [27, 28])

1. The date and time of removal.
2. Condition of the catheter tip.
3. Bleeding, fluid drainage or Haematoma of the catheter site.
4. Patient tolerance.
5. Any complications and interventions.

If an epidural catheter remains in place the front of the drug chart must state 'epidural catheter in place' or have an epidural line sticker on it to alert staff to its presence. This is to minimize the risk of starting someone on oral anticoagulants before the catheter has been removed.

Managing the complications: The combination of low dose opioid and low dose local anaesthetic is given by the epidural route is safe and can provide excellent pain relief specifically targeted at the site of pain. In some patients with extensive incisions or operated on 2 different sites, for e.g., after oesophagectomy with an upper midline incision and neck incision an epidural infusion with local anaesthetic alone can be used for the upper midline incision along with a PCA morphine to manage the pain from the neck wound.

Nursing staff caring for patients with epidural/paravertebral infusions must be aware of the side effects of these procedures and their management:

1. Hypotension: Defined as systolic blood pressure is below 100 mm Hg in a normotensive adult. The blood pressure is a guide only; all patients should be assessed in terms of their preop blood pressure, current fluid status and end-organ perfusions like time and place orientation, urine output, capillary refill, etc. Management of the condition should always follow the 'SHIT' approach as outlined earlier. Also, it is prudent to use a vasoconstrictor like phenylephrine (50 to 100 mcg bolus) or ephedrine 3 to 6 mg.
2. Excessive sedation: defined as a sedation score of 2 or 3 may require intervention with naloxone apart from standard management. Naloxone (a mu receptor antagonist) is available as 1 ml ampoule containing 400 mcg to be diluted with 3 ml of sodium chloride 0.9%, making a total volume of 4 ml so each ml contains 100 mcg of naloxone. 1 ml of the above solution is given slowly through IV and repeated every 1 min until the sedation score

is 0 or 1 titrating the effect. Two important points must be stressed here. Using naloxone is an emergency and should not be delayed for authorization and the other point is naloxone is relatively short-acting. So there is a chance that the patient can be sedated after a while and should be observed closely.

3. Respiratory depression: defined as a respiratory rate of fewer than 8 breaths per minute. The management basics are again Airway, Breathing, Circulation and Naloxone administration if required.
4. Urinary retention: defined as the urinary volume of more than 500 ml with no urge to pass urine [29]. It may require a bladder catheterization. An additional dose of antibiotic covering Gram-negative organism should be used before catheterization if not contraindicated.
5. Itching: Epidural opioids may cause itching of sufficient intensity to be distressing. This is more likely to occur when the higher concentration of fentanyl is used and reversed by naloxone 25 mcg given SC or IM. If itching continues to be a problem, the epidural fentanyl/bupivacaine mixture may be changed to plain bupivacaine. In some cases, chlorpheniramine maleate or oral cetirizine can be given [30, 31].
6. Motor Block: defined a score of 2 or 3 in the absence of a recent epidural top-up with a local anaesthetic. It should be investigated as a matter of urgency. A detailed clinical examination is mandatory including signs of cauda equina syndrome. Epidural haematoma should be excluded and an urgent MRI is warranted. Early detection of epidural haematoma, within 6 h of onset, needs to be treated with emergency decompression surgery and is limb saving procedure.
7. Local anaesthetic toxicity: occurs if the epidural catheter is misplaced in an epidural vein resulting in accidental intravenous injection, or if the maximum safe dose of local anaesthetic is exceeded. Symptoms may occur sometime after the initial injection and include:
   - Tingling around the mouth—one of the earliest symptom.
   - Numb tongue.
   - Dizziness.
   - Light-headedness.
   - Twitching.
   - In severe toxicity, there will be a sudden loss of consciousness with or without tonic-clonic convulsions.
   - Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may occur.

It is a life-threatening emergency where we follow the mnemonic 'SHIT'

- S = Stop injection of local anaesthetic.
- H = Call for HELP.
- I = Intervene:

1. Maintain a clear AIRWAY.
2. initiate mouth-to-mouth, mouth-to-mask or bag and mask ventilation with 100% oxygen. Intubate if necessary.
3. Initiate CPR if necessary, following the current guidelines.
4. Control seizures: give a benzodiazepine or thiopental in small incremental doses.
5. Manage arrhythmias following the guidelines, recognizing that they may be very refractory to treatment and prolonged resuscitation may be necessary;

Consider treatment with lipid emulsion: Intralipid 20%0.1.5 ml/kg over 1 minute. Repeat the bolus dose twice at 5 min intervals if an adequate circulation has not been established.

- Continue CPR.
- Start an intravenous infusion of Intralipid 20% at 0.25 ml/kg/min.
- After another 5 min, increase the rate to 0.5 ml/kg/min if an adequate circulation has not been restored.
- Consider the use of the cardiopulmonary bypass.

T = Trace and Track to find out why the incident happened and formulate guidelines to avoid it.

10.7.2 Removal of Epidural Catheters

Most patients after major laparotomy or limb surgery receive anticoagulant to prevent venous thromboembolism right from day 0 or day 1 of surgery. The timing removal of the epidural catheter is important so the chance of occurrence of spinal haematoma is rare. Each patient should be individualized and the optimum timing is ascertained. If in doubt, discuss with an anaesthetic consultant and a consultant haematologist. In difficult cases like patients with suspected pulmonary embolism or acute coronary syndrome, further tests like platelet function assay and thromboelastography may be indicated [32, 33].

Timing of epidural catheter insertion/removal, or insertion of spinal needle, in patients given anti-thrombotic therapy

	Time to insertion of epidural catheter or spinal block	Timing of epidural catheter removal	Time to re-administering anticoagulant
Explanation: / Drug:	*Minimum* time required after last dose of anti-thrombotic therapy	*Minimum* time required after last dose of anti-thrombotic therapy	*Minimum* time required post insertion/removal before next dose of anti-thrombotic therapy
Unfractionated Heparin *Prophylaxis*	8-12 hours	8-12 hours	2 hours (delay by 24hours post insertion if traumatic insertion)
Unfractionated Heparin infusion *Treatment*	4 hours	4 hours	2 hours (delay by 24hours post insertion if traumatic insertion)
LMWH *Prophylaxis* (enoxaparin, tinzaparin or dalteparin)	12 hours	12 hours	2 hours (delay by 24hours post insertion if traumatic insertion)
LMWH *Treatment* (enoxaparin, tinzaparin or dalteparin)	24 hours	24 hours	2 hours (delay by 24hours post insertion if traumatic insertion)
Warfarin	INR<1.5	INR <1.5. Also, hold dosing for duration of epidural infusion and until 2 hours after catheter removed	Hold dosing for duration of epidural infusion and until 2 hours after catheter removed
Fondaparinux (Arixtra)	Not recommended. Use alternative anti-thrombotic agent. Discuss with Haematology		
Lepirudin infusion *Treatment*	4 hours, unless renal impairment then discuss with Haematology	4 hours, unless renal impairment then discuss with Haematology	2 hours (delay by 24hours post insertion if traumatic insertion)
Dabigatran (Pradaxa)	Contraindicated. Use alternative anti-thrombotic agent.	Contraindicated. Use alternative anti-thrombotic agent.	2 hours (delay by 24hours post insertion if traumatic insertion)
Rivaroxaban (Xarelto)	6 hours (though first dose usually post-op anyway)	18 hours	6 hours
Aspirin/NSAID Where no other anti-thrombotic agents used	No increased risk	No increased risk	2 hours (delay by 24hours post insertion if traumatic insertion)
In combination with other anti-thrombotic therapy (LMWH, clopidogrel etc)	Ideally omit for 5-7 days. As minimum, ensure LMWH timing is correct to minimise additional risk	Ideally do not restart until epidural catheter removed. As minimum, ensure LMWH timing is correct to minimise additional risk	Ideally do not restart until epidural catheter removed. If antiplatelet therapy critical, wait 2 hours after insertion (delay by 24hours post insertion if traumatic insertion)
Clopidogrel (Plavix)	7 days	7 days	Hold dosing for duration of epidural infusion and until 2 hours after catheter removed
Ticlopidine	14 days	14 days	Hold dosing for duration of epidural infusion and until 2 hours after catheter removed

4. Patient-Controlled Analgesia (PCA).

PCA is an effective and well-established method of managing postoperative pain. An IV-PCA puts the patient in charge of his/her pain control. Every time the patient presses the button a predefined small dose of opioid is injected in the bloodstream and keeps the patient pain free. The machine has also inbuilt mechanism to prevent the overdose. The advantages are:

- Gives the patient autonomy over their pain control.
- Minimizes delays in analgesia administration.
- Reduces nursing time involved in analgesia administration.
- Minimizes the side effects of the opioid.
- Improves staff and patient satisfaction.
- Minimizes the chance of overdose.

PCA consists of a syringe pump containing the desired opioid solution which is designed to deliver on-demand a pre-set amount of opioid (Bolus Dose) reliably and accurately. It is attached to the patient by a giving set with a non-return valve. The pump is activated by the patient pressing the attached dedicated handset. Each successful activation is indicated by a sound and a glowing light (depends on the make and model of the pump). The patient is told to press the handset when he/she experiences pain but the pump is activated only after a certain time set by the physician called Lock Out Time. The reasons for it are two-fold: firstly it allows time for the injected opioid to work, and secondly, it prevents the patient from inadvertently administering an overdose. The unsuccessful attempts are recorded as well as the effective boluses. This gives the clinician an indication of how well the pain is controlled and whether to increase the bolus dose. The pump has a battery facility to maintain drug administration if the pump has to be disconnected from a mains power.

There are provisions in some pump to give a background infusion or set in a 4 hourly limit for the opioid. Though age is not a contraindication to using an IV-PCA pump management of pain using PCA can be very challenging in patients with physical or mental disability. Patients need to be able to understand how to use IV-PCA effectively. The anaesthetist should explain to the patient before surgery how IV-PCA is used and is reinforced by the ward staff.

All IV-PCA pumps must be attached to the patient using a dedicated IV line or, if not possible, via a line incorporating a non-return valve. PCA can also be used via an s/c cannula if IV access is difficult [27]. The standard solution used is morphine 1 mg/ml. in a 50 ml syringe. A standard setup is 1 mg bolus dose delivered over 1 min with a lockout time of 5mins. Besides, a 40 mg 4 hourly maximum dose is incorporated in the setup.

In cases where morphine is not tolerated (for example allergic reaction) or unsuitable (for example in renal failure patients) fentanyl in a solution of 10 micrograms/ml may be used): fentanyl 500 micrograms made up to a volume of 50 ml with sodium chloride 0.9%. NSAIDs and/or paracetamol is given concurrently to decrease opioid requirements and provide good background analgesia.

10.8 Planning a Strategy for Pain Relief

The aim is to individualize patients and develop rational means to optimize drug therapy based on the patient's genotype to ensure maximum efficacy with minimum side effects. But due to limited information in this field and great inter-individual variability and magnitude of factors influencing pain perception and modulation it is not possible in the present day. The choice of analgesic depends on the patient, the type of surgery, the experience of the anaesthetist and also the infrastructure of the unit. The ability to procure opioids and other control drugs, training and expertise of the staff, the equipment and back up personnel available all are important factors.

The management starts in the preoperative period. It is important to identify the high-risk group of patients with preoperative pain, psychological vulnerability (catastrophizing), anxiety or having a history of drug misuse or on worker compensation. These patients should be preoper-

atively counselled by the anaesthetist and a detailed plan of postoperative care should be made keeping in mind the patient's wishes and requirements. The plan must be documented and made available on the day of surgery.

Patients for operations with a high incidence of nerve damage (e.g. thoracotomy) or with persistent pain or have a fast track recovery protocol should have a preoperative plan of putting a regional or neuraxial block. Proper explanation of these procedures with the risks involved must be informed at this stage. Preoperative pregabalin should be reserved for these patients [34].

Intraoperative pain management of the patient is a part of the balanced anaesthetic. Special care should be given to surgeries lasting more than 1 h [35], involving multiple dermatomes, young adults, intraoperative radiation or chemotherapy (HIPEC) or the high-risk patient group.

All plans should have a regular set of medications and an as required backup section. The regular medications must include paracetamol, NSAIDs where applicable and a sustained release opioid or epidural or PCA. The backup sections should include a quick and short-acting opioid or non-opioid which suits the patient's situation the most. The backup section will also contain an emetic and naloxone to prevent complications.

The concept of pre-emptive analgesia is now replaced by preventive analgesia which involves multiple interventions. Multiple agents have been tried to establish preventive analgesia including opioids, ketamine, dexmedetomidine, local anaesthetics and others. Epidural analgesia started before surgery has shown to have favourable outcomes in may trials [36] and probably the technique of choice in certain operations.

10.9 Some Special Problems

10.9.1 Analgesia Following Amputation

Patients with ischemic lower limbs often suffer severe, intractable and opioid insensitive pain and should be identified preoperatively.

1. The first method of choice:

   Where the placement of an epidural catheter is possible:
   - Insert an epidural catheter in the anaesthetic room preoperatively.
   - Provide *intraoperative* epidural anaesthesia using bupivacaine or levobupivacaine.
   - Maintain postoperative analgesia with an infusion of 'standard' epidural solution (bupivacaine 0.1% with fentanyl 2 micrograms/ml) for 3 days.
   - If the patient has pain preoperatively which is poorly controlled with opioids, the epidural catheter can be sited earlier, usually 1–2 days before surgery.
   - Epidural analgesia offers many advantages for these patients and should be considered for humanitarian reasons and to assist postoperative rehabilitation.
   - It is well established that epidural does not prevent or reduce stump pain or phantom limb pain[37].
2. Second method of choice.

   Where the perioperative placement of an epidural catheter is not possible:
   - Provide *intraoperative* analgesia with a peripheral nerve block (sciatic or posterior tibial) with bupivacaine or levobupivacaine [38, 39].
   - Maintain postoperative analgesia with a continuous peripheral nerve block for 3 days, using an infusion of bupivacaine 0.125%.
   - If a *continuous* peripheral nerve block is not possible postoperatively, an IV-PCA should be prescribed for postoperative analgesia. If the patient is not suitable for IV-PCA, sufficient alternative analgesia must be prescribed.
3. Third method of choice.
   - If neither an epidural nor continuous peripheral nerve block is possible, a spinal (subarachnoid) block may be used (unless contraindicated).
   - An IV-PCA should be prescribed for postoperative analgesia. If the patient is not

suitable for IV-PCA, sufficient alternative analgesia must be prescribed.
- For all cases prescribe:
- Paracetamol 1 g QDS and NSAIDs, if not contraindicated, should be prescribed as regular medications.
- Patient should also be prescribed a regular antineuropathic medication.

The treating team should have a low threshold to involve psychologist and physiotherapist early in the care pathway.

10.9.2 Analgesia for a Patient Dependent on a High Dose of Opioid

These are the patients who are on a prescribed dose of opioids. These opioid users are suffering from cancer pain, chronic non-cancer pain or patients on opioid rehabilitation or maintenance program.

The problems with these patients are [40]:

1. They are tolerant to opioids.
2. Often they under treat themselves in fear of becoming an addict.
3. They have physical dependence so will develop withdrawal symptoms when the dose is reduced or missed.
4. Some of them can exhibit drug-seeking behaviour.

The goal of managing these patients is to provide the baseline opioid requirement (even by converting to equivalent dose if not taking orally) to prevent withdrawal and treat the acute pain with short-acting opioids and adjuvants like NSAIDs and nerve blocks.

10.9.3 Analgesia for a Patient with Opioid Addiction

Before we understand the principles of managing these patients we must be familiar with certain terms:

Tolerance: Tolerance is the decreased sensitivity of patients to opioids following prolonged use. This results in less effect from the same dose and there is a need for progressively larger doses to achieve the same effect.

Physical Dependence: Physical dependence is the physiological adaptation to a drug characterized by the emergence of a 'withdrawal' syndrome if either the drug is stopped abruptly, the dose is reduced or the drug is antagonized. Physical dependence should be presumed to have occurred if repeated doses of opioids are given for 10–14 days or more.

Psychological Dependence: Psychological addiction is a pattern of substance use characterized by

- Compulsive use of a substance to experience its psychological effects or to avoid the effects of its absence (withdrawal).
- Aberrant substance-taking behaviours.
- Continued use of opioids despite the risk of physical, psychological or social harm to the user [41].

Managing these patients is often challenging requiring the need for deep involvement of carers/family and psychologists.

Problems with these patients:

1. An unknown quantity of the drug.
2. Often there is a mixture of different drugs.
3. Other factors like peer and family pressure, personality disorders, genetic predisposition, mental, physical and socio-economic context should be addressed.
4. Long-term opioid users tend to report higher pain scores, making pain scores less useful in assessing opioid requirements in these patients. High pain scores alone should not invariably prompt an increase in opioid dosage. An objective assessment of function should help to assess analgesic requirements, e.g. ability to cough, ability to ambulate.
5. Inadequate analgesia is more likely to cause anxiety, repeated demands for analgesia and reinstatement of drug-seeking behaviours.
6. Prevention of withdrawal symptoms.

10.9.4 Principles of Managing Addicted Patients in Acute Pain Include

- To provide pain relief by identifying the cause of the acute pain and treat with simple analgesics and local nerve blocks wherever possible [40].
- As far as possible, try to establish a patient's current baseline opioids requirement.
- Avoid buprenorphine, benzodiazepines and methadone for acute pain.
- To prevent and/or manage drug withdrawal syndrome to enable acute treatment.
- Start on antineuropathics like Pregabalin before the operation and continue throughout including the postoperative period up to 7 days and up to 14 days in some units.
- Use PCA Morphine is strongly recommended for most of the major procedures. In some patients, opioid-sparing agents like ketamine (1 mg/ml) can be added to the PCA solution.
- Early referral to involve specialist teams, e.g. community drug and alcohol service, psychiatric services are strongly recommended.

10.9.5 Analgesia for An Elderly Patient

Elderly people represent the fastest-growing segment of our society and undergo surgery more frequently than other age groups. Management of postoperative pain in older patients may be complicated by some factors, including a higher risk of age- and disease-related changes in physiology and disease–drug and drug–drug interactions. Physiological changes related to ageing need to be carefully considered because ageing is individualized and progressive. Assessment of pain management needs to include chronological age, biological age, about renal, liver and cardiac functions, and the individual profile of pathology and prescribed medications. Also, ways in which pain should be assessed, particularly in patients with cognitive impairment, must be considered. NRS is the most commonly used pain scales for the elderly. In older patients with mild to moderate cognitive impairment, the VRS is a better tool. For severe cognitively impaired patients, behavioural scales validated in the postoperative context, such as Doloplus-2 or Algoplus, are appropriate [42–44]. Pain treatment in the elderly is based on the principle 'start low and go slow'. Evaluation of treatment efficacy and incidence and severity of adverse events should be monitored closely.

10.9.6 Management of Patients with Acute Neuropathic Pain

Neuropathic pain is defined as 'Pain initiated or caused by a primary lesion or dysfunction in the nervous system' [2]. Management of acute neuropathic pain can be very challenging. It is an acute sharp pain that does not respond to most standard pain killers. In some operations the chance of nerve damage is high and antineuropathics should be started in the preoperative period. Examples of such operations and diseases are given below:

1. Postoperatively.
   - Post-thoracotomy.
   - Post-mastectomy.
   - Post-amputation.
2. Associated with cancer.
   - Pancreatic cancer.
   - Apical lung tumour pressing on brachial plexus.
   - Pelvic nodes pressing on sacral roots.
   - Spinal bony metastases.
3. Post-trauma.
   - Spinal cord injury.
   - Post-amputation.
   - Third-degree burns.
   - Brachial plexus avulsion.
   - Sacral root injury secondary to a fractured pelvis.
   - Major crush injuries of upper & lower limbs.
4. Medical conditions.
   - Viral infections, e.g. acute herpes zoster/postherpetic neuralgia/HIV-AIDS.
   - Trigeminal neuralgia.
   - Diabetic neuropathy.

- Alcoholic neuropathy.
- Demyelinating diseases, e.g. multiple sclerosis.

It is important to identify acute neuropathic pain early as early intensive treatment can prevent disability and improve prognosis. The salient features to be identified during careful history taking and clinical examination and sometimes investigations. The salient features of the neuropathic pain are:

- History of injury or disease-causing possible damage to peripheral nerves or spinal cord.
- Clinical evidence of damage to peripheral nerves or spinal cord: sensory loss, muscle weakness, bowel or bladder sphincter disturbance and reflex abnormalities.
- Clinical evidence of increased sympathetic activity: alterations in skin colour, temperature and texture, sweating, and nail and hair growth.
- Delayed onset of pain after an injury.
- Pain in the area of sensory loss.
- The character of pain: burning, shooting, stabbing, 'electric shocks'.
- Pain responding poorly to opioids.
- Spontaneous or paradoxical pains.
- Pain elicited to stimuli not normally painful (allodynia).
- Exaggerated pain to painful stimuli (hyperalgesia).
- Unpleasant abnormal sensations with areas of hypoesthesia where the pain is the most.

Treatment should start as soon as acute neuropathic pain is suspected. It often takes 2–3 weeks before a noticeable difference in pain score is achieved. The other problem is most of the antineuropathic drugs have multiple side effects. There is no particular drug of choice but any of the antineuropathic trials can be started if it is not contraindicated. Amitriptyline can be a first choice as the NNT (numbers needed to treat = number of patients needed to be prescribed so that one patient has a 50% reduction of pain) is around 2.3. Recently the perioperative use of pregabalin is advocated by many authors to decrease the postoperative opioid consumption and reduce the incidence of long-term neuropathic pain [34].

10.9.7 Analgesia for Patients with Renal Impairments

Renal impairments are common, especially in the elderly population. Patients with renal impairment and acute pain problems pose a clinical challenge and should be referred to the Acute pain team. Some of the drugs like NSAIDs cannot be used in chronic kidney diseases (unless they are dependent on dialysis) and the chances for opioid accumulation with subsequent respiratory depression are paramount. The protein binding of the opioids and other drugs also change in renal failure making the patient more prone for side effects.

In general, the following principles apply as a guide:

- Use non-opioid analgesics like local infiltration and paracetamol whereever possible to minimize opioid requirements.
- Start with small doses of short-acting opioids, e.g. fentanyl or alfentanil instead of morphine in these patients. Morphine is metabolized to morphine 6-glucuronide which is more potent than morphine and its accumulation in renal failure can lead to drowsiness and respiratory depression. It is often wise to confirm appropriate dosing intervals with a clinical pharmacist, particularly if renal replacement therapies are employed.
- Use as a required dosage with close monitoring in preference to regular dosing as this allows for varying effects in response to the accumulation.
- Regular dosing with longer dosing intervals (e.g. 8 hourly instead of 4 hourly) may be feasible for some patients, alongside regular sedation scoring.

As mentioned earlier it is wise to avoid opioids with active metabolites (e.g. morphine)

which has predominant renal excretion. These include morphine, diamorphine and codeine derivatives which produce toxic metabolites which accumulate in renal failure. Buprenorphine is metabolized in the liver to norbuprenorphine and buprenorphine-3-glucuronide. The parent drug is excreted unchanged via the biliary system but the metabolites are excreted by the kidneys. Although the metabolites have little analgesic action in humans, they do accumulate in renal failure and there is no robust study to recommend or reject its use [45]. In most cases buprenorphine transdermal patch up to 10 mcg/hr. is often used in these patients for chronic pain. Tramadol is successfully used in many units with increased dosing interval to 8 to 12 h. Tramadol is metabolized in the liver to one active metabolite, O-desmethyl-tramadol and 90% of the parent drug and its metabolites are excreted by the kidneys. Immediate-release tramadol would be our first choice analgesic for patients with renal failure with mild to moderate pain or as step-down analgesia.

Tapentadol is a new class of drug which has been successfully used in patients with renal failure when eGFR is more than 25 ml/min/1.73 m2. It is also recommended to be used for moderate to severe pain [46]. But most studies used the immediate-release version of tapentadol which is not available in India [47]. Using a sustained release drug in renal failure is not a good choice. More studies are required to establish the use of the drug in renal failure patients.

It has been suggested alfentanil for severe pain in renal failure [48]. Alfentanil is metabolized in the liver to non-toxic metabolites which are excreted. Only 1% of the parent drug is excreted unchanged by the kidneys. However, short bolus with titration is the safest approach. Infusion of alfentanil can increase context-sensitive half-life and accumulation. It is also not widely available in India so in Indian scenario probably fentanyl in short boluses of 10mcg iv or 25mcg subcutaneously is the only readily available drug.

10.10 Delivery of Care

Acute pain management requires a team approach involving the patient, a multidisciplinary team (consisting of pain physicians, pain nurses, junior doctors, physiotherapist, psychologist and occupational therapist) and family/careers. All these elements make up The Acute Pain Service (APS). Postoperative acute pain management starts in the preoperative period with patient preparation and managing patient expectations. It is important to stress the postoperative management during the preoperative visit. The goal of preoperative preparation is to:

1. Ascertain patient's expectation and understanding.
2. Provide patients with relevant information—an information leaflet is a good way to communicate as the patient can go back and read and refresh himself.
3. Discuss possible options with patients.
4. Identify problem patients like opioid-dependent patients.

The preoperative consultation helps the patient to make an informed choice about pain management and improve their cooperation.

The first line of the service is the recovery and the ward nurses who receive the patients from the theatre, assess their pain and provide analgesia. The job of the recovery staff can be summarized as follows:

1. Provide information and reassurance to the patient.
2. Ensure the regional block is working well.
3. All the types of equipment like PCA and Epidural infusion pumps are correctly prescribed and running. Prescriptions can be standardized across a hospital to reduce confusion among the ward staff. They can be preprinted in the sticky labels for reducing drug prescribing errors.

Types of a sticky label (covering the first-line analgesia):

- For morphine intramuscular or subcutaneous (IM/SC) prescription.
- For morphine intravenous patient-controlled analgesia (IV-PCA).
- For fentanyl intravenous patient-controlled analgesia (IV-PCA).
- For epidural analgesia: for continuous infusion bupivacaine 0.1% + fentanyl 2 microgram/ml for bolus doses ('top-ups') bupivacaine 0.1% + fentanyl 2 microgram/ml.
- For morphine IV bolus administration in critical care areas only.
- For fentanyl IV bolus administration in critical care areas only.
- For antiemetics like ondansetron.
- For Naloxone for overdose.

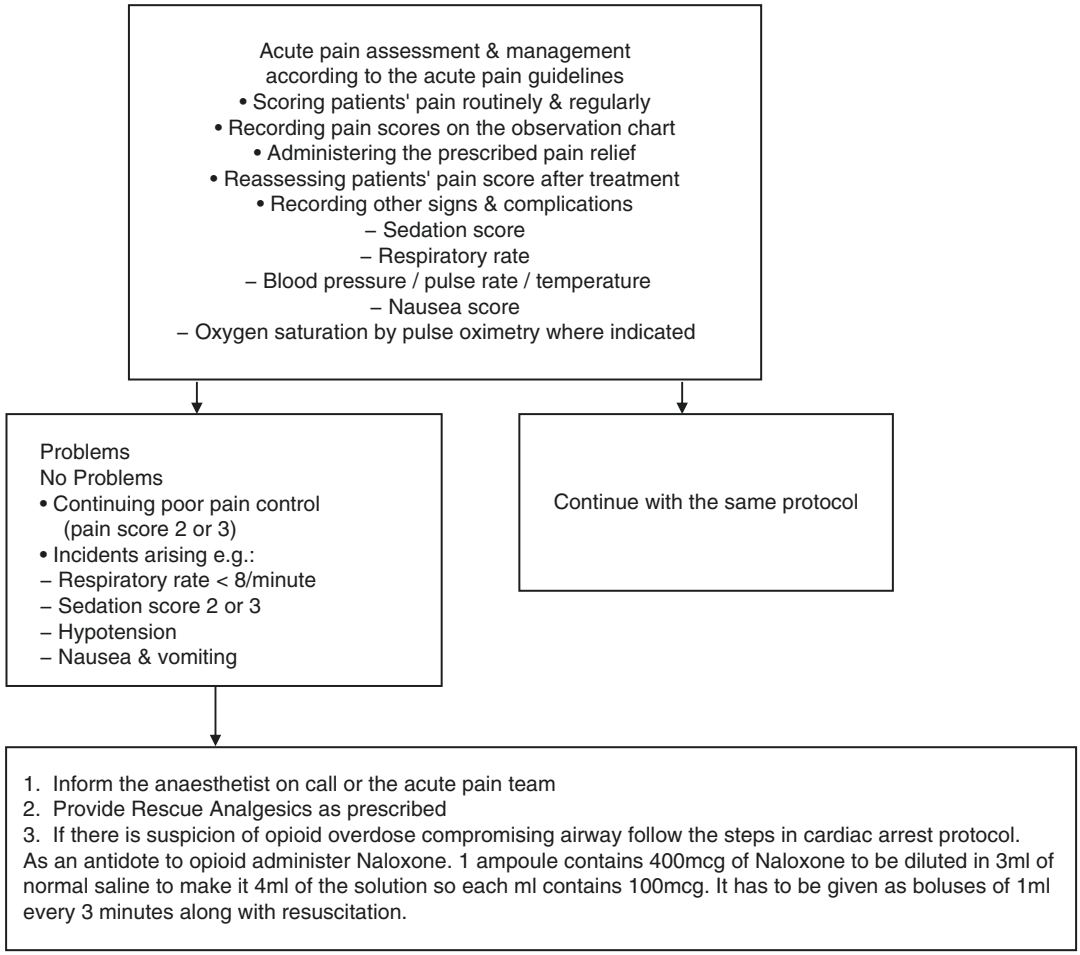
4. Liaise with the medical staff, pain team and the anaesthetist to identify and manage difficult patient.
5. Administer iv pain killers under supervision according to protocol. A commonly used protocol is to give iv morphine 1 mg every 5 minutes to a maximum of 10 mg.
6. Re-measure and record patients' pain score, sedation score, respiratory rate and nausea score along with other vital signs following specific pain relief interventions on the appropriate observation chart.
7. Ensure that no patient is discharged from the recovery ward until the following criteria are met:
   - Pain score of 1 or less at rest and 2 or less on movement (in a 4 point scale).
   - Nausea is controlled.
   - Appropriate analgesia and antiemetics are prescribed.

The second line forms the ward resident doctors who will manage most cases and identify potential difficult cases. The medical resident is the key person in delivering care. His job involves:

1. Manage and coordinate the day to day operations.
2. Be available to reassure the patient and boost the clinical staff.
3. Manage any critical incidents like drug overdose or hypotension following epidural boluses proficiently.
4. Prescribe rescue medications as appropriate for the patient.
5. Liaise with the anaesthetist or Acute pain team to manage difficult patients.
6. Maintain clinical records activity.

The acute pain team and the anaesthetic service form the third line careers who give their input in specialized situations only. The acute pain team will review all of the following patients:

- All patients with epidural infusions. This will enable the team to monitor adverse effects and change drug infusions as required.
- Patients with patient-controlled analgesia.
- Patients with pre-existing and complex pain.
- Patients on long-term opioid therapy.
- All patients awaiting limb amputation.
- Patients with renal or liver impairment.
- Patients undergoing surgery who are under the care of the haemophilia and sickle cell services.
- Patients who are under the care of the palliative care team, but who have undergone a surgical procedure.
- The anaesthetist or pain consultant also has a responsibility to assist in training new members of ward staff.
- To conduct regular ward rounds where appropriate.
- Record and investigate all incidents (critical or otherwise) relating to acute pain management.
- Audit of the service against set guidelines and come up with recommendations to improve the quality of the service.
- Train and support ward staff.



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Multimodal Analgesic Plans for Cancer Surgeries

11

Rakesh Garg and Uma Hariharan

11.1 Introduction

Pain is recognized as *fifth vital sign*. Optimal perioperative pain management not only improves overall surgical outcome but also improves patient satisfaction [1]. This requires adequate assessment preoperatively, a proper plan for pain relief and its execution during the surgical intervention which continues in the postoperative period. A prior discussion with patients allays anxiety and fear of pain for the surgical intervention. In the recent era, advancement in the surgical techniques has led to more invasive to lesser invasive like endoscope or laparoscopically assisted procedures. This has a benefit of lesser tissue trauma and thus lesser pain. On the other hand, the number of complex procedures has increased and thus need for proper planning and execution of pain management is essential. The pain management is an essential responsibility for the anesthesiologist; however, understanding the basic concepts of pain management would help the surgeons in accomplishing an effective perioperative pain management. The key to success for pain relief is to create a fine balance by judicious usage of the wide array of pain relief modalities and newer analgesic agents, thus avoiding both under- and over-treatment and creating a pain-free experience for the patient.

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11.2 Importance of Pain Management: Systemic Effects of Inadequate Pain Relief

The *IASP definition of pain* is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." [2] The term *nociception* describes neural responses to traumatic or noxious stimuli producing pain. Acute pain is caused by noxious stimulation due to injury, a disease process, or the abnormal function of muscle or viscera. Chronic pain is the one which persists beyond the usual course of an acute process or beyond a reasonable healing time (varying from 1 to 6 months). There are differences in pain perception in various patient populations. Unrelieved pain plays a major part in activation of the stress response to injury. The following are the unwanted systemic effects of inadequate pain relief [3]:

- Stimulation of sympathetic nervous system, leading to increase in heart rate, blood pressure, systemic vascular resistance, increased cardiac work load, and myocardial oxygen demand.

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- Catabolic hormone release and decrease in anabolic hormones causing greater protein breakdown, hyperglycemia, sodium and water retention.
- Impairment of immune function due to depression of the reticulo-endothelial system.
- Increased coagulability, predisposing to thromboembolism.
- Decreased regional blood flow to the skin and impaired wound healing.
- Impaired pulmonary function can occur in upper abdominal or thoracic surgeries, leading to atelectasis and hypoxemia. Other respiratory effects include increase in minute ventilation and work of breathing.
- Gastrointestinal and urinary effects include increased sphincter tone and decreased motility causing ileus and urinary retention.
- Psychological consequences can occur in the form of sleep deprivation and post-traumatic stress disorder (PTSD).
- Development of chronic pain state from prolonged or severe acute pain, known as chronic persistent post-surgical pain (PPSP).

11.3 Pain Pathways

There are four physiological processes involved in acute nociceptive pain: transduction, transmission, modulation, and perception. There are two broad types of acute (nociceptive) pain: *Somatic pain* (categorized into superficial and deep) and *Visceral pain* (categorized into true localized and referred pain) [4]. Three neural pathways transmit pain from the periphery to the cerebral cortex. First-order neurons send their axons into the spinal cord through the dorsal spinal root at each cervical, thoracic, lumbar, and sacral level. On entering the spinal cord, they segregate into large myelinated fibers medially and small, unmyelinated fibers laterally. Pain fibers travel in Lissauer's tract before synapsing with second-order neurons in ipsilateral dorsal horn. These neurons are either nociceptive-specific or wide dynamic range *(WDR) neurons*. Referred pain is because of the convergence between visceral and somatic sensory inputs in the *dorsal laminae* [5]. The spinothalamic tract running anterolaterally in the white matter is the major pain pathway. The *medial spinothalamic tract* ascends to the medial thalamus and mediates the autonomic and unpleasant emotional aspects of pain. The *lateral spinothalamic tract* ascends to ventral posterolateral thalamic nuclei and carries specific pain sensations like location, intensity, and duration. There are several alternate pain pathways, like the spinoreticular and spinocervical tracts, which are responsible for other sensations associated with pain. *Thalamus* is the site for third-order neurons. They send fibers to the *somatosensory areas I and II,* present, respectively, in postcentral gyrus and the Sylvian fissure of the brain [6]. The main chemical mediators of pain are *substance P and calcitonin* gene-related peptide. Modulation of pain (either at the peripheral or central levels) is responsible for either inhibition or facilitation of pain.

11.4 Assessment of Pain

Assessment of pain is a very important and essential. It is a prerequisite to optimal pain management. There are various scales and scores used for pain assessment both in adults and children. Since pain is a subjective experience, sociocultural background and psychological aspects of the individual patients must be considered. Both self-reporting and functional assessment of pain are vital. Uni-dimensional scales available for pain measurement include verbal (*VDS—verbal descriptor scale*), numerical (*VNRS—verbal numerical rating scale*), and visual (*VAS—visual analog scale*) [7]. VAS is the simplest scale where a 10 cm line is shown to the patient, starting from "no pain" and ending with "worst possible pain." The distance between the two marks is measured in millimeters, giving a VAS score of 1–100. VNRS uses a scale of zero to ten, where 0 signifies "no pain" and 10 reflects "worst imaginable pain." VDS is a descriptive pain scale to rate the severity of pain, in the form of "no pain," "mild pain," "moderate pain," and "severe pain." Functional assessment of pain is equally important in the current era of day care surgery. Activity

impairment due to pain can be ranked into three categories [8] by the *functional activity score (FAS)*: A—no limitation; B—mild limitation; and C—significant limitation. Pain in children has to be assessed differently and can be quite a challenging task. There are several observational scales available in infants and children [9] who are unable to self-report pain: *r-FLACC* (Revised face, legs, activity, cry, consolability) tool; *NCCPC-PV* (Non-Communicating Children's Pain Checklist-Postoperative Version); *NAPI* (Nursing Assessment of Pain Intensity); and *CRIES* scale for neonates (Crying, Requires O2 for maintaining saturation > 95%, Increased vital signs, Expression and Sleepless).

The pain assessment should be a part of vital monitoring. These pain scores should be documented in the monitoring sheets of the patient. The frequency of pain assessment needs to be individualized based on the severity of surgical intervention. These assessment tools help in titration of analgesics drugs or techniques.

11.5 Modalities of Preoperative Analgesia

Modalities of pain management can be broadly divided into *pharmacological and non-pharmacological agents.* Pharmacological modalities can be further subdivided into systemic and regional agents. Non-pharmacological techniques include alternate modes of pain management like acupuncture, *TENS* (transcutaneous electrical nerve stimulation), music therapy, cognitive therapy, behavior therapy, and physical therapies [10]. Multimodal pain management should be employed for greater benefit. Systemic analgesics can be administered intravenously, intramuscularly, transmucosal, or subcutaneous. Most post-surgical patients cannot be given oral medications and hence, systemic agents are advocated, including trans-nasal preparations. The *traditional ladder approach* can be used for most situations, starting with reassurance, mild analgesics like acetaminophen, then NSAID's, weak narcotics, and finally stronger opioids, along with adjuvants [11]. Non-opioid analgesics include paracetamol, NSAID's (non-steroidal anti-inflammatory agents), COX-2 (cyclooxygenase) inhibitors, ketamine, alpha-2 agonists, and antidepressants [12]. NSAID's exhibit their analgesic effects by inhibition of cyclooxygenase and prostaglandin synthesis. Non-selective NSAID's also have effects on platelets and gastric mucosa, making the *selective COX-2 agents* [13](Celecoxib, Rofecoxib, Valdecoxib, and Parecoxib), a safer alternative.

11.6 Regional Techniques

Regional techniques are advantageous not only in providing excellent pain relief, but also in decreasing anesthetic requirements. This leads to faster recovery and improves quality of patient care. These can be divided into the following:

1. Central neuraxial blocks.
2. Peripheral nerve plexus blocks.
3. Individual selective nerve blockade.
4. Truncal blocks.
5. Intravenous regional anesthesia.

Central neuraxial blocks can be utilized for providing anesthesia for infra-umbilical surgical interventions. These blocks, specially epidural blocks, provide effective analgesia for lower limb, abdominal, and thoracic procedures. These include: *Spinal (saddle, single shot, or continuous); Epidural (caudal, lumbar, thoracic, or cervical epidural); and Combined spinal-epidural (CSE).* They can be given either by midline or paramedian approach. Ultrasound has recently been used to improve accuracy and catheter threading can be visualized. Apart from absolute and relative contraindications to neuraxial blockade, *ASRA recommendations* for patients on anticoagulants must be strictly followed to decrease the incidence of epidural hematomas [14]. As per these guidelines, ecosprin or aspirin need not be stopped and there should be a gap of 12 h between low molecular weight (LMW) Heparin administration and insertion of block needle. For unfractionated heparin, a gap of 4 h is sufficient. For patients on oral anticoagulants (warfarin), the

coagulation profile, especially the INR (international normalized ratio) should be constantly assessed.

Spinal anesthesia can be extended in the postoperative period for providing analgesia by insertion of continuous spinal catheters [15]. The drugs used include bupivacaine and ropivacaine. Spinal opioids like morphine and fentanyl have duration of analgesia approaching 12–36 h. The main fears associated with continuous spinal include risk of infection, postdural puncture headaches and cauda equina syndrome. Combined spinal-epidural anesthesia has several advantages, including lower local anesthetic blood levels with initial spinal injection and epidural catheter used for analgesia.

The Epidural analgesic regimen could be either physician/nurse controlled or it could be patient controlled. The patient satisfaction with regard to optimal analgesia is better with patient controlled analgesia. Patient controlled epidural analgesia *(PCEA)* is now being increasingly used after insertion of epidural catheters for continued postoperative analgesia. Here patient has a control over the administration of the drugs though a dedicated infusion pump which has inbuilt safety mechanism to prevent overdoses. It has been shown that a combination of local anesthetic and opioids provides better epidural analgesia at lower doses than either drug alone. Differences in lipid solubility of opioids have minimal effects systemically, but major differences when used neuraxially. The *neuraxial opioid "Teeter-Totter,"* needs to be considered by the anesthesiologist for balancing the "pros" and "cons" of each agent used for epidural analgesia [16]. *Highly lipid soluble agents* include fentanyl and sufentanil, which are associated with narrow dermatomal spread or narrow band analgesia, rapid onset, systemic absorption, lower potency (which can be potentiated by epinephrine), and have lower incidence of pruritus/nausea. *Hydrophilic agents* include morphine and hydromorphone, which have wide band analgesia, higher potency, delayed onset, lesser systemic absorption, and are ideal for longer or multi-dermatomal incisions.

Table 11.1 Correlation of surgical site and epidural catheter insertion

S. no	Surgical site	Level of epidural catheter insertion
1.	Lower extremity	L1–L4
2.	Lower abdominal	T8–T11
3.	Middle abdominal	T7–T10
4.	Upper abdominal	T6–T8
5.	Thoracic	T4–T8

L—lumbar, T—Thoracic

The site insertion of catheter in the epidural space depends on the proposed surgical plan and surgical incision site. The insertion of epidural catheter has to be congruent as per dermatomal level of analgesia required (Table 11.1) [17].

11.7 Systemic Agents

There can be several routes of delivery of analgesic medications, depending on the type of surgery and severity of pain [18]. The oral route is simple and cost-effective, but requires a functional gastrointestinal tract. The rectal route can be specifically employed in children, but has unreliable drug absorption. The subcutaneous route can be used for opioids, but has a slow onset of action. The intramuscular route can be used for both opioid and non-opioid medications, but is painful and has unpredictable drug absorption. The most preferred route is the intravenous one. It has a fast onset and doses can be titrated. Either a single dose or continuous infusion can be utilized. Newer routes of analgesic administration include transdermal and transmucosal (sublingual, buccal, or intra-nasal) ones, especially with opioids. Systemic opioids are the agents of choice in moderate to severe acute pain. The advantage of opioids is that they do not have analgesic ceiling. The main adverse effects of opioids [19] include nausea, vomiting, sedation, pruritus, respiratory depression, and constipation. They can be given intraoperatively as I.V. bolus or by postoperative infusions for analgesia. Opioids can also be administered by the following routes: oral, subcutaneous, transcutaneous, transmucosal, intra-

Table 11.2 Various drug regimens for intravenous patient controlled analgesia

S. no.	Opioid agonist	Concentration	Bolus dose	Lockout interval (minutes)	Continuous basal infusion
1.	Morphine	1 mg/mL	0.5–2.5 mg (adult) 0.01–0.03 mg/kg (pediatric)	5–10	0.01–0.03 mg/kg/Hr
2.	Fentanyl	0.01 mg/mL	10–20 mcg (adult) 0.5–1 mcg/kg (pediatric)	4–10	0.5–1 mcg/kg/Hr
3.	Meperidine	10 mg/mL	5–25 mg	5–10	–
4.	Sufentanil	0.002 mg/mL	2–5 mcg	5–15	–

muscular, intrathecal, epidural, and intra-articular. With the advent of I.V. patient controlled analgesia (IVPCA), there is optimized delivery of analgesic opioids, thus minimizing the effects of pharmacokinetic and pharmacodynamic variability in individual patients. The various *IVPCA regimens* have been employed using the opioids (Table 11.2) [20].

The *mixed opioids or partial agonists-antagonists* include buprenorphine, nalbuphine and pentazocine [21]. These agents should be avoided in patients of opioid addicts as they may precipitate withdrawal. Buprenorphine is also available as transdermal patches. Its intravenous dose is 0.03–0.1 mg and is available as 0.03 mg/mL solution. Pentazocine is available as 10 mg/mL and can be administered in a dose of 5–30 mg intravenously.

There are several adjuvants which are used in pain management. *Adjuvants* are defined as drugs with a primary indication other than pain that have analgesic properties in painful conditions [22]. They can be classified into: multi-purpose adjuvant analgesics (antidepressants, corticosteroids, alpha-2 adrenergic agonists, neuroleptics); those specific for neuropathic pain (anticonvulsants, local anesthetics, antiarrhythmics, antihistaminics, NMDA receptor antagonists); for musculoskeletal pain (centrally acting muscle relaxants, caution: it should not be confused with neuromuscular blocking drugs used intraoperatively which are different class of drugs and not used for muscular pain); for bone pain (bisphosphonates, calcitonin and radiopharmaceuticals); and those for pain from bowel obstruction (Octreotide, anticholinergics). *Alpha-2 agonists* are the most commonly used adjuvants in acute pain management [23]. They can be administered through multiple routes (intravenous, intramuscular, intrathecal, epidural, nerve plexus and trunk blocks). Clonidine hydrochloride (an imidazoline derivative) can be administered orally, intravenously, epidurally, transdermal, and topically as well. It is metabolized in liver to inactive metabolites, with a half-life of 12–16 h. Main side effects include sedation, dry mouth, hypotension, fatigue, headache and sinus bradycardia. Its oral dose is 0.1–0.6 mg daily in divided doses. Injectable form is available as 100 mcg and 500 mcg/mL solution. Its continuous epidural dose is 30–40 mcg/h and intravenous dose is 2–3 mcg/Kg. Dexmedetomidine is a multi-purpose agent with greater alpha-2 selectivity and is given as an intravenous infusion dose of 0.4–0.5 mcg/Kg/h. Its major side effects include dry mouth, bradycardia, hypotension, heart blocks and rigidity.

There are several *additives* which can be added to local anesthetics for epidural blockade, with the benefit of making it last longer, improve quality or accelerate onset of blockade. These include epinephrine, phenylephrine and bicarbonate (carbonation).

Ketamine [24] is an intraoperative anesthetic with NMDA- antagonistic properties, important in attenuating central pain sensitization and opioid tolerance. Perioperative ketamine has been shown to reduce 24-h morphine requirements and hence, the side effects. It can be administered intramuscularly, intravenously, intrathecally, and epidurally, though the neuraxial use of racemic ketamine is not recommended in view of its neurotoxicity.

11.8 Role of Ultrasound

Ultrasound (USG) has revolutionized the field of pain management. It can be used for all peripheral nerve blocks, field blocks, neuraxial block and trunk blocks. Not only has it improved the accuracy, but also has led to decrease in the dose of local anesthetics required [25]. It can be used alone or in combination with peripheral nerve stimulator. It uses high frequency (1–20 Hz) sound waves emitted from piezoelectric crystals. These waves travel through tissues of different densities and return a signal to the transducer, which deform the *piezoelectric crystals* to create an electronic voltage that is converted into a two-dimensional gray-scale image. *Hypoechoic structures* appear black or dark (sound passes through them easily) and *hyperechoic structures* appear white or bright, as they reflect most of the sound waves. There are primarily two kinds of probes: High frequency, linear probes and Low frequency, curvilinear probes. *Linear probes* provide higher resolution images with lesser tissue penetration and therefore useful for superficial nerves. *Curvilinear probes* provide better tissue penetration, with less clear images and therefore used for deeper structures. Needle insertion can be done either parallel to *("in-plane approach*") or perpendicular to ("*out-of-plane approach*") the plane of the ultrasound waves. The path of the needle can be better visualized in the in-plane approach [26] and usually recommended for beginners. In out-of-plane approach, only the tip of the needle can be visualized. Continuous catheters can also be inserted under USG guidance for continued pain relief. Individual nerves can also be visualized and blocked for selective anesthesia of the desired part of the body. This is especially useful in day care procedures, where patient can be mobilized earlier and urinary retention avoided. USG can also be used for central neuraxial blocks in difficult spines and is particularly beneficial for caudal blocks in children (who have greater propensity for anatomical variations of caudal structures).

11.9 Patient Controlled Analgesia

Patient controlled analgesia (PCA), both mechanical and electronic, has added a major boost to pain management. Not only does it obviates "*breakthrough pain,*" but also gives the patient a sense of control over their analgesia. Intravenous PCA is commonly given with opioids (Morphine, Fentanyl, Sufentanil, Remifentanil). It is a programmed electronic device which delivers a preset basal infusion dose of the analgesic agent and an additional drug delivery pump activated by the patient to deliver a pre-determined bolus or demand dose, separated by a fixed time (called *lockout interval*) [27]. The pump does not respond to further demands during the lockout period as a safety mechanism to prevent inadvertent overdose or adverse effects. Basal and bolus rates are set according to patient characteristics and extent of surgical pain. Standardized institutional protocols must be laid out for their use to prevent incorrect prescribing or drug dilution. Proper patient education and presence of trained staff is of paramount importance. PCA pumps should be operated either by the patient, nurse or the physician. "*PCA by proxy"* (demand drug delivery by any unauthorized person, including family members) can lead to significant adverse events and must be discouraged. *Nurse controlled analgesia* can be administered by trained nurses for small children under adequate monitoring.

PCA can also be applied for regional techniques for continued postoperative analgesia. A similar electronic programmed device with pre-filled drug, preset continuous infusion and bolus rates can be attached to the epidural catheters or to *contiplex (continuous nerve/plexus) catheters*. *Mechanical or electronic PCA pumps* can be used with thoracic and lumbar epidural catheters for excellent analgesia in thoracic and abdominal surgeries. Thoracic epidural analgesia (*TEA*) is also known to be beneficial in decreasing myocardial oxygen imbalances which is important for patients sus-

ceptible to myocardial ischemia. Epidural infusions also improve gut mucosal perfusion and prevent against thromboembolism. Local anesthetics can be combined with opioids and other adjuvants for infusion. The lockout interval set is usually for 20–30 min and the demand doses can be taken by the patient for better pain relief.

Patient controlled epidural analgesia (PCEA) is the cornerstone of pain management in major abdominal, pelvic and thoracic surgeries. (Fig. 11.1) Usually dilute local anesthetic is combined with opioids for superior analgesia. Table 11.3 summarizes the various regimens commonly used in PCEA for different surgeries [28]:

11.10 Plan of Analgesic Techniques for Different Surgical Interventions

Different surgeries require different methods of pain relief and multimodal pain management must be followed for optimal analgesia. Nerve blocks and analgesic regimens vary according to the site of surgery and intensity of pain. If regional techniques are contraindicated or not instituted due to any reason, then IVPCA can be instituted with opioids, supplemented with non-opioids. The approximate 24-h morphine requirements for IVPCA in adults between 20 and 70 years can be calculated with the following formula: [29].

Average first 24 hour maintenance PCA morphine requirements in adult patients after major surgery = 100 – Age.

Fig. 11.1 Patient controlled analgesia

However, the dose and requirement of opioids need to be individualized based on adequate pain relief. The dose requirement may show inter-individual variability and also based on complexity of surgeries with regard to tissue trauma. The multimodal regimen of analgesia may be based on site of the surgery.

11.10.1 Analgesia for Head and Neck Surgical Interventions

The analgesia head and neck surgical interventions can be managed with use of nerve blocks and systemic analgesics usually. Though cervical epidurals have been described for neck procedures, however, due to risk of spinal injuries it is not a common modality for pain management. The intravenous systemic analgesics include NSAIDS and opioids (morphine and fentanyl). The nerve blocks are quite popular and are important component of multimodality pain manage-

Table 11.3 Various drug regimens for patient controlled epidural analgesia (PCEA)

Surgery	Analgesic solution	Continuous rate (mL/h)	Demand dose (mL)	Lockout interval (min)
Thoracic	0.0625–0.125% bupivacaine +5 mcg/mL fentanyl	3–4	2–3	10–15
Abdominal	0.0625% bupivacaine +5 mcg/mL; or	4–6	3–4	10–15
	0.1–0.2% Ropivacaine +0.5 mcg/mL Sufentanil	3–4	2–4	10–20
Lower extremity	0.0625%–0.125% bupivacaine +5 mcg/mL fentanyl	4–6	3–4	10–15

Table 11.4 Various nerve blocks for head and neck surgery

S. no.	Name of the block	Indications	Contraindications	Drugs	Remarks
1.	Supra and infra orbital nerve block	Eye surgeries, eye lid repairs	Local infection	0.25% bupivacaine (3–4 mL)	Caution for intraorbital injections
2.	Mental nerve block	Cleft lip repair	Local infection/ hematoma	0.25% bupivacaine (5–10 mL)	B/L submental block
3.	Cervical epidural	Thyroidectomies, neck surgeries	Coagulopathies	0.125%–0.25% bupivacaine (5–10 mL in incremental and titrated doses)	Preferably done under ultrasound or fluoroscopic guidance
4.	Superficial and deep cervical plexus block	Carotid endarterectomy, superficial neck procedures, thyroid surgeries	Caution in bilateral blocks	0.25% bupivacaine (5–10 mL) 5 ml of LA injected in a fan shaped manner for superficial	–

ment. The nerve blocks used will depend on surgical intervention (Table 11.4).

11.10.2 Analgesia for Thoracic Surgical Interventions

The thoracic procedures require a tight balance between an optimal pain relief and sedation due to opioid analgesics. The use of nerve blocks is paramount in the perioperative period and decreases the respiratory morbidity. Various regional blocks have been suggested for thoracic surgical interventions (Table 11.5).

11.10.3 Analgesia for Abdominal Surgical Interventions

The perioperative analgesia for abdominal surgeries depends on the site of surgery, i.e. upper abdominal or lower abdominal. Broadly regional anesthesia is the cornerstone for providing analgesia and it may be supplemented with systemic analgesics. The various regional techniques have been described in literature and provide optimal analgesia (Table 11.6).

Table 11.5 Various nerve blocks for thoracic surgery

S. no.	Name of the block	Indications	Contraindications	Drugs	Remarks
1.	Thoracic epidural	Thoracotomies Upper thoracic Mid thoracic Lower thoracic	Coagulopathies, local infection, anticoagulants	Dilute local anesthetics + opioids +adjuvant	Preferably done when awake. Observe hemodynamics.
2.	Paravertebral	Breast surgeries, nephrectomy	Risk of local anesthetic toxicity and require multiple injections at each vertebral level	Local anesthetics 3–5 mL for each level	Watch out for pneumothorax and hypotension. Perineural catheter insertion under USG guidance
3.	Intercostal	Supplement to thoracic epidural and reconstructive surgeries; relief of pain following rib fracture, herpes, cancer	Result in the highest blood levels of local anesthetic per volume injected; increased incidence of pneumothorax	3–5 mL of local anesthetic at each desired level	Risk of intravascular injection
4.	Interpleural/ Intrapleural	Post-thoracotomy pain	Local pathology; prevent intravascular injection	3–4 mL of local anesthetics at each level	Quality of analgesia inferior to paravertebral or thoracic epidural.

Table 11.6 Various nerve blocks for abdominal surgeries

S. no.	Name of the block	Indications	Contraindications	Drugs used	Remarks
1.	Lumbar epidural	Laparotomies	Coagulopathies	Local anesthetics + opioid + adjuvants	–
2.	Transversus abdominis plane block. Two sites: Subcostal and posterior TAP	Laparoscopic surgeries, caesarian sections. Continuous catheters can be inserted and L.A infused for postoperative pain relief.	Possibility of violation of peritoneum and bowel perforation.	15–20 mL of local anesthetic injected in the plane between internal oblique and transversus abdominis muscle	Preferably done under ultrasound guidance.
3.	Rectus sheath block	Umbilical hernias, tubal ligations	Can result in local hematoma formation.	Local anesthetics	Supra or infraumblical rectus sheath block

11.10.4 Analgesia for Inguinal and Lower Limb Surgical Interventions

The regional analgesia provides adequate pain relief for inguinal and lower limb surgeries. The various regional techniques for analgesia are well described in literature and remain the cornerstone for pain management (Table 11.7).

11.10.5 Analgesia for Upper Limb Surgical Interventions

The upper limb surgical intervention can be well managed with regional anesthesia and which may be continued in perioperative period for analgesia as well (Table 11.8). With the availability of catheters, the brachial plexus block can be used for extended purpose for providing postoperative analgesia.

Table 11.7 Various nerve blocks for inguinal and lower limb surgeries

S. no.	Name of block	Indications	Precautions	Drugs	Remarks
1.	Lumbar epidural: PCEA	Hip, pelvic, and B/L knee surgeries	Coagulopathies	Bupivacaine, Ropivacaine, Levobupivacaine with or without opioids and adjuvants	
2.	Continuous spinal catheters	Same as above	Absolute asepsis and prevention of PDPH	Bupivacaine with or without opioids	
3	Caudal blocks	Herniotomies	Coagulopathies		Can be performed under USG guidance
4	Ilio-inguinal, Ilio-hypogastric nerve block	Inguinal hernia repairs	Local pathology	Bupivacaine or Ropivacaine or Levobupivacaine.	Preferably given under USG guidance
5.	Femoral nerve block	Postoperative analgesia for hip, knee, and ankle	A 3-in-1 block is required to block femoral, lateral cutaneous and obturator nerve	Local anesthetics	Local infection or lymphadenopathy can be a deterrent Continuous femoral catheters can be inserted under USG guidance.
6.	Fascia iliaca block	Anesthetizes both femoral and lateral femoral cutaneous nerves; 2 pops are felt on piercing the fascia lata and fascia iliaca	Preferably done under USG guidance for greater accuracy	30–40 mL of local anesthetics injected after negative aspiration	
7.	Lateral femoral cutaneous nerve block	Used as a supplement to femoral nerve block or for limited anesthesia of lateral thigh.	Preferably performed under USG guidance as the feeling of pop on piercing the fascia lata near the anterior superior iliac spine may not be evident	10–15 mL of local anesthetics after negative aspiration.	
8.	Obturator nerve block	For complete anesthesia of the knee and in TURP for blunting the adductor response	Both the anterior and the posterior obturator nerves can be reliably blocked under USG guidance	Local anesthetics	Adductor canal blocks can be done separately for knee arthroplasties where a continuous catheter can be inserted under USG guidance
9.	Psoas compartment block	Useful for procedures on the hip, knee, and anterior thigh.	It can be frequently complicated by retroperitoneal hematoma, intravascular injection, local anesthetic toxicity	Local anesthetics	Currently, posterior lumbar plexus blocks deposit LA within body of psoas muscle, preferably using a curvilinear USG probe

Table 11.7 (continued)

S. no.	Name of block	Indications	Precautions	Drugs	Remarks
10.	Sciatic nerve block *posterior/ classic/Labat *anterior approach *subgluteal approach *popliteal approach	For surgeries involving the hip, thigh, knee, lower leg, foot	It is preferably done under nerve stimulation and/or USG guidance to avoid complications	Local anesthetics	Sciatic nerve can be blocked at any level from the buttocks till the thigh. With use of USG, lower LA volumes are enough as compared to the landmark technique
11.	Ankle block	Surgery of the foot	Avoid epinephrine with LA; uncomfortable for patient as it entails 5 separate injections	3–5 mL local anesthetics /nerve	The fives nerves (saphenous, deep peroneal, superficial peroneal, posterior tibial, and sural nerves) can be blocked using USG.

Table 11.8 Various nerve blocks for upper limb surgeries

S. no.	Name of block	Indications	Contraindications	Drugs	Remarks
1.	Interscalene block	Surgeries of the shoulder and upper arm	Pre-existing respiratory difficulty or phrenic nerve palsy; local pathology. Preferably done under USG guidance.	Local anesthetics	Horner's syndrome, recurrent laryngeal nerve palsy, or vertebral artery injections can occur, especially in blind technique
2.	Supraclavicular block	Surgeries at or distal to the elbow	High incidence of complications like pneumothorax	30 ml of local anesthetic after negative aspiration.	Preferably done under USG guidance
3.	Infraclavicular block	For distal arm procedures; Intercostobrachial nerve spared	Vascular puncture and pneumothorax	Local anesthetics	Preferably done under USG guidance
4.	Axillary block 3 techniques: Transarterial, nerve stimulation, and USG	For distal arm procedures	Local infection and inability to abduct the arm.	Local anesthetics	Axilla is a sub-optimal site for perineural catheter placement.
5.	Blockade of terminal nerves: Median nerve, ulnar nerve, radial nerve, musculocutaneous, intercostobrachial, and digital nerve (ring) block	Selective nerve block for sensory block of specific area of interest	Local pathology	Local anesthetics	Preferably done under USG guidance.

Intravenous Regional Anesthesia (IVRA): Also known as the Bier's block, intravenous regional anesthesia is useful for extremity procedures of intermediate duration [30]. A high volume, dilute local anesthetic is injected intravenously after limb exsanguinations and sequential inflation of two tourniquets or cuffs (proximal and distal). It is a safer alternative to standard sympathetic blocks in patients with coagulation defects. Tourniquet pain is a problem and duration of postoperative pain relief is limited. Typically 40–50 mL of 0.5% lignocaine is injected, with or without adjuvants (clonidine, dexmedetomidine, or ketorolac).

11.11 Recent Advances

The advent of ultrasound has given the most needed boost to operative and point of care pain management. Almost all blocks are now performed under ultrasound guidance resulting in greater accuracy, reduced local anesthetic volumes, and visualization of drug spread as well as catheter threading leading to increased success rate and better analgesia. Newer electronic pain pumps have been developed which are user friendly, tamper-proof, with accurate alarm systems and more portable. Iontophoretic transdermal delivery system has been recently developed for fentanyl and is as safe as intravenous morphine PCA [31]. In addition, greater availability of transdermal preparations of various analgesics like diclofenac, ketorolac, buprenorphine, and fentanyl has made pain relief reach every needy patient. Newer local anesthetic drugs and their formulations like levobupivacaine, liposomal bupivacaine, and ropivacaine have improved safety profile. Ropivacaine in a concentration of 0.5–1% is used for surgical anesthesia and 0.1–0.3% concentration for analgesia. It is the only local anesthetic that has intrinsic vasoconstrictive properties. Levobupivacaine (0.5–0.75% concentration for surgical anesthesia and 0.125%–0.25% concentration for analgesia) has lesser effect on cardiac conduction and hence, decreased frequency of arrhythmias. Several newer adjuvants have increased analgesic efficacy of pain blocks. Dexmedetomidine has been experimented to have several beneficial effects in pain management, both in systemic and regional administration [32]. It has a multi-faceted role in perioperative pain management, by acting as a perfect adjuvant in epidural, spinal, peripheral nerve blocks and IVRA. *Calcitonin,* a peptide hormone with role in calcium homeostasis, has a role in treatment of acute pain due to osteoporotic vertebral fractures and reduction of acute phantom limb pain. *Gabapentin and pregabalin* (alpha-2-delta ligands) reduce the central sensitization of pain pathways after injury and hence used as preoperative medication, to decrease opioid requirements. Alternate methods of pain relief like acupuncture or acupressure, TENS, cryoanalgesia, intra-articular injections, psychotherapy, and hypnosis can be combined with the above agents for better patient satisfaction [33].

11.12 Conclusions

Pain must be recognized as a vital parameter and treated on priority basis in every surgery. Pain management is a team-effort and all members of the surgical and anesthesia team must coordinate and commit for a pain-free perioperative period. Multimodal analgesia is the dictum, starting from mild analgesics, opioids, and regional blocks. Major scientific advancements in the field of regional anesthesia, in the form of use of ultrasound guidance, continuous plexus catheters, PCA pumps, and advent of newer agents have revolutionized pain management. Patients on chronic opioids (cancer patients) have greater analgesic requirements, both intra- and postoperatively, with the risk of development of adverse effects, tolerance, dependence, and opioid-induced hyperalgesia [34]. Special precautions, with dose adjustments need to be taken in extremes of age and pregnant women. Prompt management of acute pain is essential not only for blunting the associated sympathetic nervous system response, but also for prevention of development of chronic pain states. Continued education program and in-service training on pain management must be provided for a successful outcome, both short-term and long-term.

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12 Antiseptic Policy: What Could be Relevant Surgical Site Infection (SSI) and Abdominal Sepsis

M. D. Ray

In OPD

Advice, 4 weeks prior to surgery

1. Stop smoking or any form of tobacco intake.
2. Hygiene, Hydration, hematinics.
3. Nutrition and high protein diet.
4. Spirometry.
5. Yoga, exercise, and meditation half an hour per day.

In Ward

1. Antiseptic bath regularly with chlorhexidine/Savlon Soap, specially evening before surgery and morning at the day of surgery.
2. Shaving at the incisional site/sites only. Clipping and depilatory cream for hair removal are acceptable at the morning of the day of surgery.
3. Bowel preparation for colorectal surgery to start 48 h prior to surgery (not 24 h) Oral Tinidazole 1 gm + Erythromycin 1 gm to be given at 13:00 h (1 pm), 16:00 h (4 pm), and 23:00 h (11 pm).
4. Clean hand before touching each patient.
5. Check Hb%, Albumin, any infection at any site, TLC, Sugar level, Age, BMI, consent special consent, etc.

In OT

1. Ensure prophylactic antibiotics to be given 30 min before making incision.

   Antibiotics prophylaxis as follow, 2nd dose after 6 h and 16 h after surgery. In Clean Surgery single dose is enough.

Site	First name	Step-up
Breast	Cefazolin	Cefoperazone-sulbactam/Ceftazidime/Cefipime 1–2 gm 12 hourly
STS	Cefazolin	Cefoperazone-sulbactam/Ceftazidime/Cefipime 1–2 gm 12 hourly
RP tumor	Cefazolin	Cefoperazone-sulbactam/Ceftazidime/Cefipime 1–2 gm 12 hourly
Non-oral H&N	Cefazolin	Cefazolin/Ceftazidine
Oral	Cefuroxime+metro	Cefaperazon/Ceftadizine+Amikacin
Upper GI	Cefazolin+sulbacum	Ceftadizine /Piperacillin/Tazobactum+Metro+Amikacin
Lower GI	Cefaperazone+sulbacum+ metrogyl	Ceftadizine /Piperacillin/Tazobactum+Metro+Amikacin
Hepatobiliary	Cefaperazone+sulbacum	Piperacillin/Tazobactum +Amikacin

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Site	First name	Step-up
Thoracic	Cefuroxime	Levofloxacin/Ceftazidine/Cefipime
Genito-urinary	Cefazolin+metro	Cefaperazone + Sulbactam/Piperacillin+Tazobactum+ Amikacin

Notes: PULMONARY complications: Levofloxacin 750 mg OD (In Renal Insufficiency 250 mg OD)
LYMPHANGITIS—Roxithromycin 150 mg BD. In Renal insufficiency dose modification is not required in the following drugs—cefazolin, cefipime, piperacillin, Tazobactam, metrogyl. Only ceftazidine and Cefaperazon up to 2 gram/day is acceptable

1. Wash hand with Chlorhexidine minimum for 2–5 min
   - Soap cleaning for 2 min and Chlorhexidine washing for 3 min minimum.
   - And pay attention to other people hand washing including nursing staff.
2. Cleaning and draping
   Chlorhexidine and alcohol based antiseptics are the recommendation. Minimum contact period is 3 min.
3. Wear always double gloves
   - Change surgical gloves at 3 h if the surgery is long.
   - Torn/burnt gloves to change immediately.
4. Surgical technique:—Good wash with NS before closing. In case of Obese patients/high risk patient, use topical antibiotics Gentamycin/Amikacin/Metrogyl. Place a suction drain.

Post Op

Open sterile dressing after 48 h.

Clean hand with sterillium before touching each patient.

Send routine investigations including electrolytes on 1st POD, 3rd POD, and 6th/7th POD.

Blood Transfusion/When Hb% only <8 gm.

Early mobilization, chest physiotherapy, spirometry at the earliest

Remove drains, catheter as early as possible. Usually Breast drain < 40 ml, ICD <100 ml, Neck drain <30 ml, Abdominal drain <50 ml, Groin drain <30 ml.

Discharge certificate would be in details including Advice and Medicine and next follow-up date and time. Document SSI on follow-up pl.

1. We know commonest cause of death in a surgical patient is infection and that is 77%.
   - Among all infection SSI is around 40% and in SSI—2/3rd is superficial and 1/3rd is deep—organ/space involvement. 2nd—RTI, 3rd—UTI, 4th—Septicemia, 5th—Gastroenteritis.
   - But unfortunately, we surgeons are little bit weak in the use of Antibiotics. We like to thank to the era of broad spectrum advance antibiotics.
   - As per the history is concerned in 1860, long back, Joseph Lister proposed Antiseptic policy. At that time any post op patient had irritative fever, and there after purulent wound discharge considered as SSI.
   - And SSI is **by definition** an Infection occurs within 30 days from the day of operation broadly divided into superficial and deep.
   - SSI may lead to Sepsis—Severe sepsis → cardiogenic shock—MODS—MSOF → death Δ MCH
   - So how to **tackle this SSI** culprit?
2. **Prevention:—**we know prevention is always better than cure.

   Before that we revise the sources of SS Infection
   (a) Environmental.
   (b) Exogenous.
   (c) Endogenous.

You know when we become weak so many unwanted, unbelievable problems attack us. Like this wound is like a weaker person—surrounding commensals also take upper hand to attack the weaker area.

Every control is not directly in our hand like controlling operating room environment, ventilation system, sterilization system, HVAC (Heating

Ventilation Air conditioning System), CSSD (Central Sterile Services Dept), etc.

But what is all in our hand we have to do our best. We know outcome of a patient all most equally depends on three—pre op—30%, op—40%, post op—30%

1. **OPD Patient related**:
   We could improve (a) nutritional status, b) improve vital capacity by offering Spirometry, (c) ask to maintain hygiene.
2. **Ward**:
   (a) Admits the patients 2/3 days prior to op date.
   (b) Antiseptic bath at the day of surgery.
   (c) Part preparation not required until it is on the incision site like axillary dissection.
   But for laparotomy private part is not required to prepare.
   Best part for preparation is the morn of the day of surgery, not day before.
   (d) Bowel preparation to be done 48 hours before surgery along with oral antibiotics though the literature suggests there is no difference between mechanical and oral antibiotic bowel preparation versus no bowel preparation in terms of SSI, anastomotic leak etc. (the lancet September 2019).
3. **In OT**
   (a) Ideal temp to maintain is 20–22 °C.
   (b) Antibiotics—Prophylaxis just before or at the time of induction—as a term is called "decisive period"—the concentration of the drug will be established in serum and tissue by the time the skin incision is made.
   (c) Regarding hand wash, 2–5 min minimum.
   Proper way that reduces the infection rate But truly speaking most of the surgeons do not follow the rule. I remember a **story of Pond full of milk.**
   (d) Proper cleaning, draping—usually we do well but recommendation is to use alcohol based antiseptic and chlorhexidine.
   (e) Gloves—gloves to be changed every 3 h. Because sterile life of a glove is only 3 h. Usually we forget to change until it is torn.
   (f) During surgery—gentle tissue handling, proper homeostasis, good washing, etc.
   One Army teacher used to say complications arise during surgery only.

Post Op

- Dressing to be opened after 24–48 h.
- Hand to be washed/cleaned with sterillium before touching each patient.
- Drain, catheter to be removed timely.
- More the days we keep the catheter or drain more chance of infection.
- Mobility at the earliest.
- Incentive Spirometry, Physiotherapy, etc.
- Allow the patient to take bath after 48 h.

Now Few Lines Regarding Antibiotics

- Scientifically as per the type of wounds prophylactic antibiotics to be given.
- In—clean wound → Chance of infection (COI) 2%. so no prophylactic antibiotics required.
- So no prophylaxis is required or a single dose is enough.
- Clean contaminated—10–15% Chance of infection (COI)—prophylactic antibiotics required.
- Contaminated Chance of infection (COI) 20–40%—prophylactic antibiotics required.
- Dirty— Chance of infection (COI) 40–70%—therapeutic antibiotics are required prophylactic Antibiotics to cover gm +ve organism gm -ve- aerobes and anaerobes.
  Logical formula is

1. AAM (Augmentin, Amynoglycosides, Metorgyl) /FAM (Fluoroquinolon, Amynoglycosides, Metrogyl)

3 doses are enough
Fluoroquinolon, Amynoghycosides, Metrogyl
↓

2. CAM—Cefalosporin, Aninoglycosides, Metrogyl

Maximum up to 48 h widely used AMP
↓

3. TAM/PAM—Tazobactam/Piperacillin Amika, metrogyl

Maximum up to 48 h
↓

If any developed infection/suspected infection give full course of antibiotics

Better give antibiotics as per sensitivity

Safe antibiotics in renal insufficiencies are Augmentin, Cefazolin Cefuroxime, Cefepime, Cefixime, Salbactam, Clarythromycin, linezolide, meropenem, piperacillin tazobactam, metrgyl, tigecycline, etc.

To conclude I will say the same—better the craftsman, smarter the results. Same is very much fact for the Surgeon and his surgical art, but **there is more than what meets the eye**. Though there are lots of invisible things in the background that culminate in this craftsmanship.

"Surgery is successful but patient could not be survived" sounds very pathetic if patient dies owing to SSI.

But we all must be agreed that what is in our hand, we can do the best with that if we come forward together as we know

"Coming together is a beginning, Keeping together is progress. Working together is the success."

And when everyone moves forward together, the success takes care of itself.

I remember the nice words by Ratan Tata, "If you want to go fast, go alone, if you want to go far go together."

The perfection is a drive from inside, not outside. Excel at a task today with perfection, not necessary someone else to notice but for our SELF satisfaction.

13 Nosocomial Infections and Hospital-Acquired Illnesses: Overview

Sonu Kumari Agrawal, Naveen Kumar, and M. D. Ray

Hospital premises, nursing homes, or OPDs—are common places for acquiring infections called hospital-acquired infections (HAIs). Surgical site infection is the most common hospital-acquired infection, followed by respiratory tract infection (RTI). Other nosocomial infections are genito urinary tract infection and gastrointestinal tract infection.

The breach in the infection control practices, non-sterile surrounding, and ill employees are the important causes of nosocomial infections. We are experienced to manage the nosocomial infections at our centers. Commonly acquired hospital infections in post-surgical patients are discussed below:

13.1 Surgical Site Infections (SSIs)

Surgical site infections (SSIs) are infections of the incision, organ, or operative space that occur after surgery and are a common type of healthcare-associated infection (HAI) as defined by the Centers for Disease Control and Prevention (CDC) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). They are the most preventable HAIs, still they cause significant patient morbidity and mortality and the additional burden of costs to the health care system. Simultaneously, the prevention of SSI is also important as the number of surgery is increasing in developing countries like India. Therefore, the prevention of SSI has received considerable attention from surgeons and infection control professionals. It has been estimated that approximately half of SSIs are preventable by the application of evidence-based strategies. Managing the SSIs is important not only to improve the treatment protocols but also the preventive measures.

13.2 Risk Factors for Surgical Site Infections

The complex interaction endogenous (patient-related) factors, exogenous (procedural-related) factors, and microbial factors can lead to surgical site infection. (Table 13.1).

13.2.1 Patient Factors

Multiple patient factors may be associated with an increased risk of infection in the operative site. Hyperglycemia is one of the most important culprits promoting surgical site infection. In a study of 1000 patients with cardiothoracic surgery,

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Table 13.1 Showing factors associated with an increased risk for surgical site infection [1, 2]

Patient factors
Perioperative hyperglycemia
Tobacco
Remote infection at the time of surgery
Obesity
Malnutrition
Use of steroid
Prolonged preoperative stay
Preoperative irradiation
Staphylococcus aureus colonization
Procedural factors
Shaving at the surgical site
Use of razor
Poor preoperative part preparation
Inadequate antimicrobial prophylaxis
Failure to timely reduce antibiotics in prolonged procedures
Poor operative room ventilation
Operative room traffic
Perioperative hypothermia
Perioperative hypoxia
Surgical technique related factors
Improper sterile technique and asepsis

hyperglycemia in the 48 h of post-surgery was associated with a 102% increase in the risk for wound infections [1]. As noted earlier, colonization with *S. aureus* can also increase one's risk for SSI. Tobacco use may increase the risk for SSI, due to vasoconstriction caused by nicotine and that leads to poor wound healing [2]. Some variables are not modifiable, such as age which is a common risk factor for SSI; the Immune scene for underlying illness has been associated with increased age that may lead to increased risk of infections.

13.2.2 Procedural Factors

Breaks in the technique of sterilization during the surgical procedure, improper antiseptic precaution during cleaning and draping of skin, poor ventilation of the operation theater, and repeated use of flash sterilization of instruments during the procedure contribute to developing the SSI [3]. During part preparation, the methods used to remove hair is an important factor as using a razor blade or clipper may create micro-abrasions over the skin, which may harbor the bacteria. Failure of appropriate administration of prophylactic antibiotics is one of the major contributing factors for the development of SSI.

Several factors related to SSI infection are common and interrelated, hence a patient may have several risk factors at a time. Several methods have been devised to predict the development of an SSI in a patient.

13.3 Species and Sources of Wound Bacteria

The microbial load is an important determining factor whether or not the wound becomes infected and is relevant even in the era of the routine administration of prophylactic antibiotics for most surgical procedures [4]. Historically, the epidemiologists and surgeons have stratified the surgeries based on a load of bacteria at the operative site (Table 13.2). Several organisms have been described as wound pathogens. In general, the predominant cause of SSIs in a clean surgical surgery is endogenous skin flora such as staphylococcal species. In recent years, the pathogenesis of SSIs is evolving because of the emergence of new multidrug-resistant organisms such as MRSA and multidrug-resistant gram-negative pathogens. Colonization of *S. aureus* in the nostrils is the most important risk factor for developing the SSI particularly in a selected group of patients like diabetic and kidney failure patients who are on dialysis. Atypical organisms such as non-tuberculous mycobacteria, *Nocardia* spp., *Legionella* spp., *Mycoplasma hominis*, and *Propionibacterium acnes* have rarely caused surgical site infections as well. Approximately 20% of skin bacteria present in the skin appendages like the sebaceous gland and hair follicles, so the currently used antiseptic methods can decrease the chance of infection but do not eliminate the pathogenic skin flora. The incision on the skin during surgery migrates these bacteria in the wound and causes wound infection. For contaminated and complex procedures, SSI occurs due to the normal gut flora which migrates during the

Table 13.2 Interventional maneuvers in diminishing the risk of surgical site infection

Operative factors
Avoid unnecessary preoperative antibiotic use
Shorter preoperative hospitalization
Control of remote infections before surgery
Avoid preoperative shaving or razor used at the operative site
Delay hair removal at the operative site until time of surgery and remove hair (only if necessary) with electric clippers or depilatories
Ensure timely administration (including appropriate dose) of prophylactic antibiotics
Consider elimination of *Staphylococcus aureus* nasal carriage via decolonization techniques
Intraoperative and postoperative factors
Carefully prepare patient's skin with antiseptic
Rigorously adhere to aseptic techniques
Isolate clean from contaminated surgical fields (e.g., reglove and change instruments used to harvest saphenous vein before working in the intrathoracic field)
Maintain a high flow of filtered air
Redose prophylactic antibiotics in prolonged procedures
Minimize operative personnel traffic
Minimize immediate use steam sterilization of surgical instruments
Minimize the use of drains
Bring drains, if used, through a separate stab wound
Maneuvers to improve host containment of contaminating
Bacteria
Preoperative factors
Resolve malnutrition or obesity
Discontinue tobacco use for at least 30 days preoperatively
Maximize diabetes control
Intraoperative and postoperative factors
Minimize dead space, devitalized tissue, and hematomas
Consider the use of supplemental oxygen therapy
Maintain perioperative normothermia (core temperature at or above 36.0 ° C)
Maintain adequate hydration and nutrition
Identify and minimize hyperglycemia (through 48 h postprocedure)

procedure. For example, after the colonic surgeries, the gram-negative and anaerobic bacteria are common pathogens for SSI. Contaminated surgical instruments or material, preexisting infection, and already contaminated skin, mucous membranes, and dress of OR staff are the potential sources of microbial infection.

13.4 Prevention of Surgical Site Infection

The goal is to eliminate all potentially preventable infections through the use of evidence-based processes. CDC Guidelines recently of SSI focused on for the Prevention and select the areas which were considered important by clinical experts and the HICPAC. The core sections have given the recommendations based on the available data to many surgical specialties. Several interventions have been tried previously to reduce the risk of SSI. Here, we described the current recommendations found in the CDC, and these interventions are grouped into two main categories (Table 13.3). The first major class of prevention measures is directed to reduce the inoculation of bacteria into the wound. Preoperative bathing with a chlorhexidine solution suppresses the colonization of bacterial on the skin at the site of the incision. Clippers or depilatory cream are preferred methods for the removal of hair [5] and recommendation by several randomized trials in patients of SSIs [5]. Although there are recommendations not to remove hair preoperatively.

Table 13.3 Classification of operative wounds by level of bacterial contamination

Class I: Clean wound
Where no viscera (respiratory tract, alimentary tract, genital, and uninfected urinary tract) is opened and no inflammation has occurred is called a clean wound. Also, the stab wound or blunt trauma where the no viscera is entered or opened is included in the clean wound.
Class II: Clean-contaminated wound
Here, the viscera are opened in a controlled fashion without any contamination in the cavity. Examples are bowel procedures, the opening of the vagina, or biliary tract with any spillage of content in the cavity.
Class III: Contaminated wound
Contaminated wound includes open, fresh, or accidental wounds where major breaks have occurred in the sterile technique or gross spillage of content (perforation, or urinary leak).
Class IV: Dirty-infected wound
Old wound with devitalized tissue that has been occurred because of previous perforation or preexisting infections. This means that the organism responsible for postoperative infection is already there in the wound beforehand.

There are pieces of literature that support the view that the use of clippers and depilators for hair removal may increase the risk of infection [5]. Other sources of infection are cavity drains and catheters. These should be removed in the postoperative period as early as possible. The second class of preventive measure is an improvement in the host containment and microbial elimination that have been inoculated into the wound. To prevent SSI prophylactic antibiotic plays a vital role. Other factors that reduce the infection rate in the postoperative period include gentle tissue handling, removal of clots, dead space obliteration, the proper approximation of skin.

13.5 Perioperative Antimicrobial Prophylaxis

The guiding principle of prophylactic antimicrobials that the antimicrobials in the host tissues increase the immune defense system which helps to kill bacteria in the wound. To prevent the infection, it is always ensured to maintain antibiotic levels above the minimal inhibitory concentration (MIC) throughout the procedure. The role of preoperative antimicrobial prophylaxis is always unquestionable and it is proven by numerous both randomized and nonrandomized trials. The choice of antibiotics, timing, and duration are still not very clear. As per the recommendation given by CDC both clean and clean-contaminated procedures require antibiotic prophylaxis [4]. However, in dirty or contaminated procedures the antibiotics are usually started before the procedures and other prophylaxis can be added based on the coverage of antibiotics. Selecting appropriate antibiotic prophylaxis depends on several key factors such as allergic status, penetration power of antibiotics, local availability of the drugs, and susceptibility to the common flora (Table 13.4). Several prospective studies for antibiotic prophylaxis have given the various antibiotics for different surgical procedures. The American Society of Health-System Pharmacists (ASHP), Surgical Infection Society (SIS), Society for Healthcare Epidemiology of America (SHEA), and Infectious Diseases Society of America (IDSA) published a consensus guideline on surgical antimicrobial prophylaxis in 2013. This will help to further harmonize recommended practices (Table 13.4) [6]. The cephalosporins are commonly used prophylactic antibiotics because of their low incidence of side effects, allergic reactions, and wide-spectrum nature. In particular, the emergence of CA-MRSA as vancomycin can be considered for the treatment of staphylococcal prophylaxis as well as for treatment where the prevalence of MRSA is high. Vancomycin should not be used routinely [6].

The exact timing for prophylaxis is ranged from half an hour to 2 hours before the incision. However, the recent guidelines have suggested the appropriate timing 1 h before the incision except for vancomycin and fluoroquinolones

Table 13.4 Antimicrobial prophylaxis according to the site of surgery

Microbial flora	Surgical procedure	Recommended antimicrobials
Staphylococcus aureus, CoNS (GNR less common)	Cardiac surgery	Cefazolin, cefuroxime
S. aureus, CoNS	Thoracic surgery	Cefazolin, ampicillin-sulbactam
GNR (less commonly, anaerobes and enterococci)	Biliary surgery	Cefazolin, cefoxitin, cefotetan, ceftriaxone, ampicillin-sulbactam
GNR, anaerobes	Appendectomy	Cefoxitin, cefotetan, cefazolin+ metronidazole
GNR, anaerobes (especially *Bacteroides fragilis* and *Escherichia coli*)	Colorectal	Cefazolin+ metronidazole, cefoxitin, cefotetan, ampicillin-sulbactam, ceftriaxone + metronidazole, ertapenem
S. aureus, CoNS	Neurosurgery	Cefazolin
S. aureus, CoNS, streptococci, GNR (*Propionibacterium* spp. in shoulder procedures)	Orthopedic surgery	Cefazolin
GNR *(E. coli),* rarely enterococci	Urological procedure	Fluoroquinolone, trimethoprim-sulfamethoxazole, cefazolin

and they should be given within 2 h before incision [6].

Most guidelines for surgical prophylaxis recommend discontinuation of prophylactic antibiotics within 24 h, however, for cardiac surgery, some groups recommend continuing prophylaxis for 48 h, based on concerns that more data are needed before uniformly recommending a shorter duration in this population [7]. The new guideline challenges this recommendation, stating prophylaxis for the procedure's duration, and at most, 24 h is appropriate for cardiothoracic procedures [6]. Prompt discontinuation of prophylaxis does not impact the risk of developing SSI but failure to do so contributes to unnecessary antimicrobial use with increased risk of acquiring an antibiotic-resistant pathogen [8].

13.6 Surgical Site Infection Surveillance

A key component in the prevention of SSIs is the establishment of surveillance infrastructure to regularly detect and monitor rates of procedure specific infections, to define the changing ecology of resistant microbes that cause surgical infections, and to provide accurate analysis of the pervading antimicrobial sensitivity patterns in each specific institution to allow for tailoring of prophylactic regimens. Such surveillance must use standardized infection definitions, such as those used by the CDC's, National Healthcare Safety Network (Table 13.5). Surveillance systems should also utilize the input of representatives with surgical, infectious diseases, and hospital epidemiology expertise in the analysis and evaluation of data. Any method of surveillance must address these concerns and accommodate the unique attributes of each specific hospital and patient population.

Table 13.5 Definition of surgical site infection proposed by the National Healthcare Safety Network (NHSN)

Superficial
Infections involving only skin and subcutaneous tissue of the incision occurring within 30 days after the procedure with one or more of the following:
• Purulent drainage from the superficial incision
• Fluid or tissue collected from superficial wound become positive on culture.
• Deliberately opened surgical wound associated with swelling, redness, warmth, and tenderness. *or*
• Diagnosis made by a treating surgeon or physician
Deep
Involvement of deep soft tissue (fascia muscle layers) by infective organisms occuring within 30 or 90 days (dependent on the procedure type) after the procedure with one of the following:
• Purulent discharge from deep incision not other than organ space
• Spontaneous wound dehiscence or wound opened by a surgeon with culture-positive discharge from the wound or not being cultured but has fever, pain, or tenderness
• Abscess involving a deep incision found by direct examination, during an invasive procedure, or by histopathological examination or imaging test; *or* diagnosis by a surgeon or attending physician
Organ/space infections
Involvement of part of the body that opened or created during the surgical procedure, excluding skin incision/fascia/muscle layers, within 30 or 90 days (dependent on the procedure type) with one of the following:
• Drainage of pus from the drain that is placing in organ space
• Positive culture growth of a specimen of tissue or fluid aseptically obtained
• Evidence of infection by clinical examination, during invasive intervention or by histopathological examination or imaging test; *or* diagnosis by a surgeon or attending physician

13.7 Nosocomial Urinary Tract Infection

A urinary tract infection belongs in the category of nosocomial infection (NUTI or NAUTI). There are major differences in the epidemiology, pathogenesis, treatment, and prevention of nosocomial UTI and uncomplicated UTI, which are shown in Table 13.6. UTI is a nonspecific term that generally refers to bacterial or fungal infection of the bladder or kidney, or both, in a patient, without regard to the presence or absence of urinary symptoms. Catheter-associated (CA) bacteriuria, asymptomatic bacteriuria, and UTI are defined in Table 13.7. Instrumentation of the urinary tract is the important cause of nosocomial UTI, use of a catheter is the most common cause among them, also known as catheter-induced urinary tract infection (CAUTI).

Table 13.6 Comparison of uncomplicated urinary tract infection and nosocomial urinary

Factors	Uncomplicated	Nosocomial
Age	Younger	Older
Sex	Female, rare in males	Male and female, female
Main risk factor	Intercourse	Predominance Urinary catheter
Microbiology	The single pathogen, usually *E. coli;* yeast rare	Single to multiple organisms; diverse flora with gram-negatives, gram positives, *Candida* sp.
Clinical	Cystitis: Dysuria, frequency, or urgency	CA-UTI: Fever, altered mental status, other nonspecific signs/symptoms, usually no lower tract symptoms
Diagnosis	Pyelonephritis: Fever, back pain/ tenderness ASB: $\geq 10^5$ CFU/mL Cystitis/pyelonephritis: $\geq 10^3$ CFU/mL	CA-ASB: $\geq 10^5$ CFU/mL CA-UTI: $\geq 10^3$ CFU/mL
Treatment	Short-course (single-dose to 5-day regimen, depending on the drug)	5 to 14 day regimen, depending on the severity

Table 13.7 Definitions for urinary tract infection

Terms	Definition
UTI	Nonspecific term that generally refers to bacterial or fungal infection of the urinary tract
Catheter-associated Bacteriuria (CA-bacteriuria)	Presence of significant bacterial count in a catheterized or recently catheterized patient without regard to the presence or absence of urinary symptoms
Catheter-associated UTI (CA-UTI)	Presence of significant bacteriuria in a catheterized or recently catheterized patient with symptoms or signs referable to the urinary tract
Catheter-associated asymptomatic bacteriuria (CA-ASB)	Presence of significant bacteriuria in a catheterized or recently catheterized patient without symptoms referable to the urinary tract

13.8 Epidemiology

Instrumentations of the urinary tract like Foley's catheter insertion are the most common cause of hospital-acquired UTI. Worldwide UTI is the most common cause of hospital-acquired infection, the majority of them are associated with urological procedures (10–20%), prolonged urethral catheterization (80%), or both (uti-22). 3% to 8% per day incidence of bacteriuria is associated with closed urethral catheterization [9, 10]. As compared to other HAIs, CAUTI related morbidity and mortality are considered to be low. Based on American data, the majority of the CAUTI are preventable. Recommended infection control measures (17% to 69%) (uti-23).

13.9 Risk Factors

The development of UTI is directly related to the duration of catheterization, and it is the major risk factor [11, 12]. There are some patient-related risk factors which may precipitate UTI like diabetes mellitus, female sex, history of chronic kidney disease. Other factors that may play a vital role in UTI are bacterial colonization in urine bag, breach in the aseptic precaution during catheter insertion, and lack of antibiotic therapy [13–16].

13.10 Pathogenesis

The main factor for nosocomial UTI is the urinary catheterization; it provides direct access to the urinary tract. Sometimes the urinary catheter bypasses the protective mechanism and it prevents the formation of biofilm and decreases the chance of bacteria and epithelial interaction. The CAUTI may be developed from both exogenous and endogenous sources. Bacterial colonization in the urethral meatus, rectum, and vagina are the endogenous sources, whereas contaminated instruments and the hand of the healthcare workers are the exogenous sources. The catheter in situ transmits the bacterial inoculum in the urinary bladder through the surface of the retrograde migration from the urinary bag.

13.11 Etiology

A broad range of bacteria are the causative factors of nosocomial UTI, and some of them are resistant to several antimicrobial agents [17]. Bacteriuria in short-term catheterized patients is mainly caused by single organisms, mostly gram-negative bacilli and enterococci [18]. Other organisms are *Klebsiella*, *Serratia*, *Citrobacter*, *Enterobacter.* Nonfermenters (*Pseudomonas aeruginosa),* gram-positive cocci (coagulase-negative staphylococci), and *Enterococcus* are the other causative organism [18]. Fungal infection, mainly caused by candida species found in 3% to 32% of patients with short-term catheterization [17, 18]. The bacteriuria in long catheterization is more likely polymicrobial. The organism responsible for bacteriuria in short-term catheterization along with other less common species like *P. mirabilis, Providencia* spp., and *Morganella morganii* are responsible for infection in long-term catheterization [18].

13.12 Signs and Symptoms

Clinical presentation of CA-UTI is fever with chills and rigors, altered mental status, malaise, flank pain, tenderness at the costovertebral angle, sudden hematuria, urgent or frequent urination, dysuria or suprapubic pain or tenderness.

13.13 Diagnosis

Clinical signs and symptoms and the presence of a significant count of bacteria in urine examination are the mainstays of diagnosis of CAUTI. The ideal method of collection of the urine sample by puncturing the catheter directly using a syringe [18]. If a patient is catheterized for a long duration, the collected sample may be contaminated, in such scenario, urine should be collected after insertion of a new catheter [19, 20]. The chance of contamination is less if urine is collected from a catheter, and a count more than or equal to 10^2 CFU/ml is considered to be significant in both male and female [21]. Definitions for significant bacteriuria are summarized in Table 13.8.

Table 13.8 Definitions for significant bacteriuria

Noncatheterized, clean-catch voided specimen
Symptomatic female or male
$\geq 10^3$ CFU/mL (based on data with coliforms; sparse data on gram-positive organisms)
Asymptomatic
Female: $\geq 10^5$ CFU/mL of same species in two consecutive voided specimens
Male: $\geq 10^5$ CFU/mL in a single voided specimen
Catheterized: Urine from freshly placed catheter preferable
Symptomatic female or male
$\geq 10^3$ CFU/mL
Asymptomatic female or male
$\geq 10^5$ CFU/m

It is practical to use a quantitative count more than or equal to 10^2 CFU/ml in symptomatic person, rather than 10^2 CFU/mL, as most of the laboratories do not quantify the urine culture to 10^2 CFU/mL routinely. Presence of pyuria is not always diagnostic of CAUTI or catheter-associated bacteriuria. To differentiate between CA-ASB and CA-UTI pyuria should not be a differential factor. Pyuria associated with CA-ASB is not an indication of antimicrobial therapy. In a symptomatic patient without pyuria, a diagnosis other than CA-UTI should be considered.

13.14 Prevention

For the prevention of CAUTI, a guideline had been published by the Centers for Disease Control and Prevention (CDC) in 1981, and it was updated in 2009. These guidelines mentioned how to use catheters and how to take care of them. The summary of the guidelines is enumerated in Table 13.9.

13.15 Management of Nosocomial Urinary Tract Infection

Bacteriuria in a catheterized person with symptoms or signs compatible with a UTI (usually fever) in the absence of another obvious cause of

Table 13.9 Catheter-associated urinary tract infection (CA-UTI) prevention

• Develop and implement written guidelines for use of urinary catheters
• To ensure the supplies of the aseptic-technique catheter
• Implement a medical record documentation system for catheter use
• Sufficient trained persons and resources are required for surveillance of catheter use.
• Perform surveillance of CA-UTI in high-risk groups or units
• Educate health care personnel about CA-UTI prevention techniques
• Insert urinary catheters only when necessary and remove them when appropriate
• Condom catheter and in-and-out catheter should be considered when appropriate
• During insertion and manipulation of catheter hand hygiene should be maintained.
• Insert catheters using aseptic technique and sterile equipment
• Urethral meatus should be cleaned with an antiseptic solution using gloves, drape, and sponges.
• Properly secure catheter to prevent movement
• Sterile and continuously closed drainage system should be maintained
• The catheter and drainage tubes should not be disconnected unless the catheter must be irrigated
• To examine urine, aspirate a small sample from the sampling port with a sterile syringe
• Collect larger volumes of urine for special analyses aseptically from the drainage bag
• Unobstructed urine flow should be maintained
• Urine bag should be emptied regularly. A separate container should be used for each patient.
• Urine tube and bag should be at a lower level than the urinary bladder all the time.
• During cleaning the meatal area, hygiene should be maintained

the symptoms or signs should be treated with antimicrobial therapy. It is difficult to generalize antimicrobial therapy in CA-UTI, due to the presence of a variety of underlying conditions, a wide variety of etiological agents, and a lack of proper RCTs. Unless and until underlying metabolic, anatomic, and functional defects are corrected antibiotics may not be effective. However, urinary catheterization itself should not complicate the eradication of bacteriuria, although it predisposes to early recurrence. The antibiotic agents should be chosen as per specific organisms found on sensitivity testing. Empirical treatment regimens for CA-UTI are shown in Table 13.10.

Table 13.10 Empirical management of catheter-associated urinary tract infection

Mild to moderate, afebrile (dosage duration: 5–7 days)
Ciprofloxacin 500 mg PO twice daily or 1 g (extended-release) PO once daily
Levofloxacin 750 mg PO once daily
Severe illness or febrile, or both (dosage duration: 5–14 days)
Ciprofloxacin 400 mg IV twice daily
Levofloxacin 500–750 mg IV once daily
Ceftriaxone 1–2 g IV once daily
Cefepime 1 g IV twice daily
Piperacillin-tazobactam 3.375 g IV q6h
Meropenem 500 mg–1 g IV q8h
Imipenem-cilastatin 500 mg IV q6-8h
Doripenem 500 mg IV q8h
Ertapenem 1 g IV once daily
Gentamicin 5–7 mg/kg IV once daily
Ampicillin 1–2 g IV q6h
In choosing an empirical agent, consider the following
Severity of illness and comorbidities
Antimicrobial susceptibility of prior urinary tract infection strains
Local resistance data
Exposure to the same class in past 3–6 months choose alternative agent
Consider adding vancomycin if gram stain shows gram-positive cocci
Use a carbapenem (meropenem, imipenem, doripenem, or ertapenem) if an Extended-spectrum β-lactamase strain is known or suspected

13.16 Summary

Nosocomial UTI is one of the most common hospital-acquired infections. Urinary catheterization is the main risk factor for the development of UTI. Removal of the catheter is key to avoid the nosocomial urinary tract infections. All symptomatic patients should be given antibiotic therapy. However, resistance to common antibiotics is a major concern.

13.17 Nosocomial Pneumonia

Nosocomial pneumonia is defined as pneumonia acquired during hospital stay. It can be divided into two categories. Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the two spectrum of nosocomial pneumonia. In most of the studies on nosocomial

pneumonia the focus is on VAP, so this chapter also focuses primarily on VAP.

13.18 Health Care Associated Pneumonia

HAP: antimicrobial therapy within the preceding 90 days; hospitalization for 2 or more days within the preceding 90 days; residence in a nursing home or extended care facility; chronic hemodialysis; home infusions of antibiotics or chemotherapy; immunosuppressive disease, treatment, or both; home wound care; a family member with a multidrug-resistant pathogen; and a recent visit to a hospital or hemodialysis clinic [22]. The local prevalence of drug-resistant pathogens, recent broad-spectrum antibiotics, hemodialysis, poor functional status, and severity of illness appear to be better predictors of drug-resistant pathogens and morbidity than patients'outpatient exposure histories.

13.19 Epidemiology

Second most common nosocomial infection is ventilator-associated pneumonia (VAPs) and is the major cause of mortality in ICU patients. Several factors determine the incidence rate (5 to 67%) of VAPs, such as the immune-compromised state, surgical, and elderly patients [23]. The infection rate of VAPs is 1.5% per day. After 14 days of mechanical ventilation, the infection rate decreased to 0.5% per day [24]. The duration of mechanical ventilation and intensive care is extended by 4 to 6 days due to VAPs [25]. Crude mortality rates for VAP range between 16% and 78%.Crude mortality rates for non-ICU nosocomial pneumonia range from 26% to 53% [13].

The microbiology of nosocomial pneumonia varies considerably depending on the duration of hospitalization before pneumonia, the severity of illness, comorbid conditions, the reason for admission, and prior antibiotic exposures. *Streptococcus pneumonia,* beta-hemolytic streptococci, and *Haemophilus influenzae* are the most frequent organisms in patients just admitted to the hospital (≤2 days) [14]. Thereafter, *S. aureus, Pseudomonas aeruginosa,* Enterobacteriaceae, and *Acinetobacter* species begin to predominate. The risk of *S. aureus* being methicillin resistant rises progressively with duration of hospitalization [14]. Patients hospitalized for extended periods or exposed to prolonged courses of antibiotics, or both, are also susceptible to *Stenotrophomonas maltophilia, Burkholderia cepacia,* and other difficult-to-treat organisms.

A substantial proportion of VAP cases are polymicrobial, especially in aspiration pneumonia and ARDS [15, 16]. *Candida* species, enterococci, and coagulase-negative staphylococci are almost always colonizers rather than invaders. Viruses can account for up to one third of severe pneumonias, including healthcare-associated pneumonias, particularly in immunocompromised.

hosts [26, 27].

The organisms responsible for VAPs are as follows [28]—

(a) Aerobic *Enterobacteriaceae* (25%).
(b) *Staphylococcus aureus* (20%).
(c) *Pseudomonas aeruginosa* (20%).
(d) *Haemophilus influenza* (10%).
(e) Streptococci.

There are several independent risk factors for the emergence of multidrug-resistant pathogens, include late-onset of disease, use of broad-spectrum antibiotics before mechanical ventilation, and duration of mechanical ventilation more than 7 days [29].

13.20 Ventilator-associated Pneumonia: The Risk Factors

The pathogenesis of VAP is microbial invades the normal sterile lower respiratory and establishes infection in an immune-compromised state. There are two groups of risk factors are identified for VAP: ventilation-related factors and patient-related factors (Table 13.11). Unlike other nosocomial infections, VAP is difficult to prevent [30].

Table 13.11 Ventilator-associated pneumonia—Empirical treatment. IV = Intravenous, OD = Once daily, BD = Twice daily, TDS = Thrice daily, QID = four times daily

No high-risk factor and low risk of mortality:	**Risk of gram-negative bacterial infection and the mortality rate is moderate**	**Mortality risk is high**
(a) IV Cefepime 2 g BD or TDS (b) IV Levofloxacin 500 mg OD (in case of compromised renal function dose to be reduced) **OR** (c) IV Piperacillin-tazobactam 4.5 g TDS	(a) IV Cefepime or ceftazidime 2 g BD or TDS **OR** (b) IV Piperacillin-tazobactam 4.5 TDS or QID **OR** (c) IV Levofloxacin 500 mg OD IV Ciprofloxacin 400 mg BD **OR** (d) IV Imipenem/Meropenem 1 g TDS IV Vancomycin 15 mg/kg BD **OR** (e) IV Linezolid 600 mg BD	(a) IV Cefepime or ceftazidime 2 g BD or TDS **OR** (b) IV Piperacillin-tazobactam 4.5gm TDS or QID **OR** (c) IV Levofloxacin 500 mg OD IV Ciprofloxacin 400 mg BD **OR** (d) IV Imipenem/Meropenem 1 g TDS **AND** IV Amikacin 25 -30 mg/kg OD **OR** (e) IV Vancomycin 15 mg/kg BD **OR** (f) IV Linezolid 600 mg BD Combinations of the drugs may be offered as per the culture and sensitivity report

13.21 Diagnosis

Diagnosis of HAP and VAP is challenging because the cardinal clinical signs are not sensitive and specific in hospitalized patients. VAPs can be diagnosed clinically and radiologically. However, it has been seen that these criteria are not accurate [31, 32]. Sputum or BAL specimens can help to make a diagnosis. The absence of organisms on Gram stain or less than 50% neutrophils in BAL fluid helps exclude the diagnosis [33, 34]. The absence of new infiltrates makes pneumonia unlikely, but their presence is not specific. But no findings are specific to establish the diagnosis and to start the treatment.

13.22 Microbiologic Evaluation

It is important to try to establish a microbiologic diagnosis to ensure coverage of the active pathogen(s) and minimize exposure to unnecessary agents. Inappropriate or delayed therapy increases mortality risk [35]. Blood and respiratory cultures are indicated in all patients. Pneumococcal and *Legionella* urine antigen testing increase diagnostic yield compared with respiratory sampling alone. Viruses can account for up to a third of severe pneumonia cases and can be transmitted in hospitals [36]. Viral studies are, therefore, indicated during periods of endemicity, in immunocompromised patients, and patients with diffuse ground-glass opacities on CT [36]. Several options for respiratory tract sampling are available, including endotracheal aspirates, BAL, and protected specimen brush. These in turn can be analyzed qualitatively or quantitatively. There has been a great deal of controversy over whether clinicians should routinely acquire specimens by using invasive techniques (BAL or protected.

specimen brushes) or noninvasive techniques (endotracheal aspirates).

13.23 Treatment and Prevention

The VAP is managed with the empirical treatment; however, an inappropriate selection of antibiotic is associated with high mortality [37, 38]. The selection of proper antibiotics is the main challenge in the treatment of VAPs. Proposed North American regimens are listed in Table 13.11. Preventive measures of ventilator-associated pneumonia are shown in Fig. 13.1.

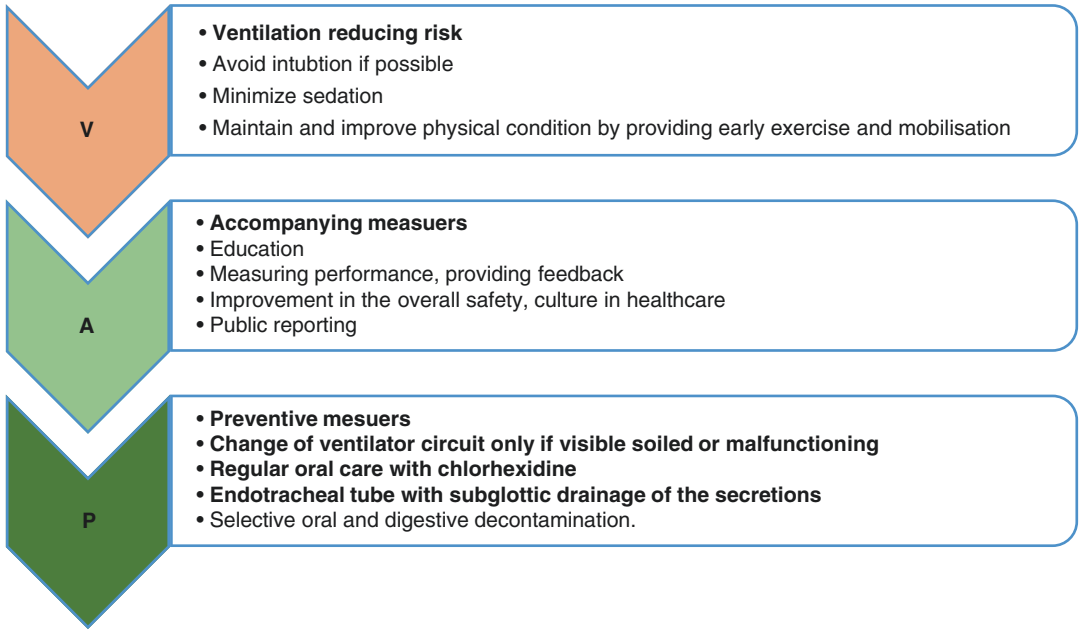

Fig. 13.1 Preventive measures of ventilator-associated pneumonia

Conclusion: The major cause of nosocomial infection is the breach in hospital infection control policy, like non-sterile environment, lack of proper disposal of hospital waste, lack of awareness among health care workers regarding cleanliness and sterility. Maintaining personal hygiene, hand washing at regular intervals, proper disposal of hospital waste, proper and timely sterilization of medical equipment are essential components to reduce the rate of nosocomial infection as well as mortality.

Patient-related risk factors are as follows

(a) History of an underlying illness.
(b) Male sex.
(c) Extreme of age.
(d) Previous history of central nervous system disorder.
(e) History of emergent surgery.
(f) Re-intervention.
(g) Acute underlying diseases.
(h) Immunocompromised state.
(i) Acute respiratory distress syndrome (AIDS).
(j) Acute renal failure (ARF).
(k) Ulcerative disease.

Intervention-related risk factors

(a) Transfusion of blood products in the perioperative period.
(b) Duration of the mechanical ventilation.
(c) Supine position of patients during enteral nutrition.
(d) Use of enteral nutrition.
(e) Use of antibiotics.
(f) Interdepartmental transport.
(g) Requirement of continuous sedation.
(h) Paralytic agents use.
(i) Need for reintubation.
(j) Need of tracheostomy.
(k) Use of nasogastric tubes.
(l) Change in the ventilator circuit frequently.
(m) Intracuff pressure < 20 cm H_2O.

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DVT: Prophylaxis and Management

14

M. D. Ray

Learning Objectives
Introduction, Review of literature, Pathophysiology of venous thromboembolism (VTE) with cancer and Incidence of VTE in malignancy, Diagnosis of VTE, Diagnostic value, Clinical features of VTE, Cancer surgical risk groups, Caprini Score Model, and Preventive measures.

14.1 Introduction

To tell the truth that relationship between malignancy and thromboembolism has been a well-established fact but unfortunately pathophysiology is still not fully cleared. Trousseau is the person who reported migratory thrombophlebitis in gastric cancer patients in 1865 [1]. Since then a large number of evidence has been identified to showing the relationship between venous thromboembolism (VTE) and cancer. Despite significant advancement in the prevention of VTE, however it remains the most common preventable cause of hospital death in surgical patients [2]. It is well-known that Asian population is genetically quite different from US and European group. A large number of trails supports that Asians have low risk for DVT [3]. There is no Indian data from any major cancer centre reporting the incidence of post-operative cancer patients; hence there is no uniform policy to practice thromboprophylaxis in onco-surgery patients.

The very few literature available in India only two RCTs showed very low incidence of DVT after major abdominal surgeries [4, 5]. A prospective observational study conducted in 250 patients at Surgical Oncology Department at IRCH, AIIMS from 2013 to 2016 showed none of the patients who underwent complete resection (RO) for various cancers showed any evidence of VTE both clinically and radiologically. Post operatively patients were monitored closely for any signs of DVT. Bilateral Colour Doppler should be done by using all modes, on the post op day 7, 28 and earlier if VTE is suspected clinically. But without any doubt VTE is the captain of post-surgical death worldwide. Effective and newer prophylactic methods are now available for high-risks patients [6, 7] and different evidence based guidelines have been showing the way of preventing VTE [8, 9]. But most audits demonstrated that appropriate thromboprophylaxis is not being offered to large number of cancer surgical patients [10, 11].

14.2 Review of Literature

The complications of deep vein thrombosis (DVT), pulmonary embolism (PE), i.e. VTE and the post-thrombotic syndrome are important not

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only as the most common preventable cause of post-operative death in hospital but also important cause for long-term morbidity [12]. Proper understanding of underlying epidemiology, pathophysiology, and natural history of VTE is important in guiding appropriate prophylaxis for cancer surgery patients. National Comprehensive Cancer Network (NCCN) guidelines divided venous thromboembolism (VTE) broadly into deep vein thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis (SVT), and thrombosis in other vascular territories (portal vein, mesenteric vein, inferior vena cava, and superior vena cava) [13].

A thrombus is a semisolid mass formed from the components of fibrin and red blood cells with a variable platelet and leukocyte component. A clot is nothing but blood which has coagulated in vitro (i.e. in a test tube). A DVT is a thrombus, which has formed in the deep veins beneath the deep fascia of the lower limb. Thrombus within the pelvic or abdominal veins that carry blood from the legs is also commonly classified as "deep vein thrombosis" and some would include thrombus in the communicating veins of the lower limb within the definition [12].

14.3 Pathophysiology of DVT

Over a period of time it has been realized that the formation of DVT is multifactorial, with components of Virchow's triad as depicted below.

Virchow's triad is well-known for this regard. It consists of (i) Stasis—abnormalities in blood flow such as immobilization, obesity, pregnancy, malignancies, paralysed patients (ii) Vessel wall injury—vascular endothelial injury due to surgery or venepuncture, hypertension, atherosclerosis, chronic inflammation, infection, etc., and (iii) Hypercoagulability—post-operative period, malignancies,pregnancy, etc.

14.4 Pathophysiology of VTE and Cancer

Various studies suggest the prothrombotic pathways of cancer molecular biology [14].

The thrombus formation in cancer is involving of multiple complicated pathways [15].

The association between cancer and thrombosis is well-known but pathophysiology remains poorly understood. Trousseau was first to recognize the association between thrombosis and malignancy and later his work was supported by Sack [14]. The genesis of thrombosis in oncosurgery is critical and reflects of multiple pathways including activation of procoagulants, inhibition of anticoagulant or fibrinolytic pathways and cytokine release [15].

14.5 Cell–Cell Interactions and Procoagulants

It is known that cancer cells express important factors for platelet adhesion. Studies have shown that tumour cells express glycoprotein Ib and glycoprotein IIb/IIIa (GP IIb/IIIa), which are key platelet adhesions molecules likewise, cancer has been associated with high levels of von Willebrand factor. Platelet adhesion to tumour cells via GP IIb/IIIa could play a key function in tumour spread. The main pathway for activation of the coagulation involves exposure of the tissue factor (TF) and endothelium. TF subsequently activates coagulation factor VIIa, which leads to conversion of prothrombin to thrombin.

It has been defined that tumour cells not only express TF, but also express normal cells, such as vascular endothelial cells, monocyte, and macrophages. Tumour cells also express a cysteine protease, cancer procoagulants that directly split factor X to Xa. Studies that used enzyme linked immunoabsorbent assay have shown increased cancer procoagulants levels in 81% of malignant patients. Accordingly, cancer procoagulant has been identified as a potential tumour marker.

Adhesions of platelet to tumour cells play an important role in tumour spreading. The main pathway for activation of coagulation pathway involves exposure of sub-endothelium and tissue factor (TF). Ultimately VIIa activated by this tissue factor which is responsible for the conversion of prothrombin to thrombin. Normal cells also can express TF. Tumour cells also express cancer

procoagulants, cysteine protease which directly convert factor X to Xa (34,35). As per the literature around 81% of malignant patients having increased level of procoagulant in their blood and thus procoagulants have been acting as tumour markers.

14.6 Fibrinolysis

Fibrinolytic pathway playing the most important part in maintaining hemostatic balance. Tissue plasminogen activities and urokinase type plasminogen (UPA) activities converting plasminogen to plasmin. High levels of UPA (Urokinase type Plasminogen Activities) and its corresponding receptors (UPAR) and PAI are associated with malignancies. When the normal coagulation fibrinolytic balance in malignancy are affeted, bleeding in leukaemia patients and VTE episode occur in solid organ tumours.

14.7 Cytokines and Angiogenesis

The role of cytokines in tumour genesis is well-known. It is also established, angiogenesis plays very important role in tumour growth. These cytokines predispose to develop thrombosis.

VEGF, TNFα, IL_1 all stimulate the expression of tissue factor on vascular endothelium leading to formation of thrombosis. Both TNFα and IL_1 down regulate the expression of thrombomodulin. The thrombin and thrombomodulin complexes lead to activation of protein c, a strong anticoagulation!

Thus both the upregulation and downregulation of tissue factor produce a prothrombotic effect. On the other hand, IL_1 and TNFα produce PAI by stimulating vascular endothelium, thereby there is increase propensity to form the clots.

14.8 Incidence of VTE in Malignancy

To tell the truth true incidence of VTE in cancer patients is not well understood still.

Silvertein et al. estimated a yearly incidence of VTE of 117 per 100,000 population but as far as cancer patients are concerned VTE rate increased 1 in 200 per year. It is more than 4 folds compared to non malignant patients [16]. Stein et al. showed that incidence of VTE is doubled in cancer patient (2% versus 1%) [17].

A study in Netherlands of 66,329 patients showed the cumulative incidence of DVT is 12.3 per 1000 population in initial 6 months [18].

Certain tumours like haematological and metastatic diseases are more prone to develop VTE [19]. Mucin producing cancers like ovarian carcinoma, colorectal cancers, and lung cancers are likely to be associated with VTE than other solid tumours [15].

Levitan et al. reported systematically the incidence of VTE with different cancers, e.g.—Ovarian ca (12 per 1000 patients), lymphoma (9.8 per 1000), pancreatic ca (11 per 1000 pts), brain tumour (11.7 per 1000 patients). They described lowest rates of VTE in Ca breast (2.2 per 1000 pts), Ca bladder (2.2 per 1000 pts), and in head and neck malignancy (1.6 per 1000 pts).

14.9 Diagnosis of DVT

Only 25% of patients of DVT present with compatible symptoms. Maximum patients may have minimal or atypical symptoms and clinical features.

Harmon's test itself 30% sensitive only. So, a proper clinical assessment, history of varieties of risk factors, and sensitive diagnostic tests may confirm the diagnosis of DVT.

14.9.1 Symptoms

The symptoms that are commonly produced by deep vein thrombosis are pain, swelling, and a faint red blue discoloration of the skin. Profound cyanotic discoloration (phlegmasia cerulea dolens), or pallor (phlegmasia alba dolens) and frank venous gangrene are much less common. The more proximal and occlusive thrombus leads to more marked symptoms and physical signs.

Deep vein thrombosis may also present as pyrexia of unknown origin or with the symptoms of pulmonary embolism without any leg symptoms.

14.9.2 Signs

The physical signs of a deep vein thrombosis may be as ephemeral as the symptoms, and often there are none. Diagnostic values of clinical features have been summarized in Table 14.1 and show that the clinical evaluation may imply the need for further evaluation but cannot, by itself, be relied on to confirm or exclude the diagnosis of DVT.

14.10 Diagnostic Value of Clinical Features of VTE

Clinical feature	Sensitivity (%)	Specificity (%)
Calf pain	66–91	3–87
Calf tenderness	56–82	26–74
Homans' sign	13–48	39–84
Swelling of calf or leg	35–97	8–88

Table 14.1 Wells clinical probability score

Clinical features	Score
Active malignancy (on treatment, < six months, or on palliative care)	1
Paralysis, paresis, or recent plaster immobilization of the lower limbs	1
Recently bedridden more than three days or major surgery <12 weeks need general or regional anaesthesia	1
Localized tenderness along the deep venous system	1
Swelling of entire lower limb	1
Leg swelling >3 cm compared to contralateral side (measured 10 cm below the tibial tuberosity)	−2
Pitting oedema of involving symptomatic leg	
Collateral superficial veins (non-varicose)	
Previous H/O DVT	
Alternative diagnosis likely as DVT	

14.11 Wells Clinical Probability Score (Table 14.1)

This is a scoring method that categorizes patients into high, intermediate, and low risk of DVT according to numerous defined criteria (outlined below). A score of ≥3 indicates high probability of DVT, 1 or 2 a moderate probability, and ≤ 0 indicates low probability.

Diagnostic Tests for DVT

1. Non-invasive diagnostic tests include Duplex Ultrasound, Impedance Plethysmography, CT venography, MRI/MR venography.
2. Invasive diagnostic tests: Contrast venography.
3. Fibrinogen uptake test.

14.12 Biomarkers for the Diagnosis of Deep Vein Thrombosis

Gold standard for DVT diagnosis is compression ultrasound. Biomarkers and making a serological diagnosis are desirable. D-dimer, a highly sensitive biomarker, is very useful to exclude VTE. But it lacks of specificity.

The upcoming plasma biomarkers in the diagnosis of VTE are selectins, microparticles, IL 10, and other inflammatory markers. These inflammatory markers may also predict recurrence rate, thrombi which resolve spontaneously, and determine the therapy either standard anticoagulation or aggressive therapies.

14.13 Risk Factors for DVT

DVT occurring in the setting of a known risk factor is defined as secondary, whereas that occurring in the absence of risk factors is defined as primary or idiopathic. Risk factors can be further classified into acquired or congenital risk factors. (Table 14.2).

Cancer Surgical risk groups are:

1. Increasing age.
2. Past history of VTE.
3. Family h/o VTE.
4. H/o inherited or acquired hyper coagulable state.
5. Obese patient.

6. History of Chemotherapy 6.5 fold, Presence of mucin secreting cancer like ovary, colorectal, lung other like brain, pancreatic ca, pelvic malignancies 3–5 fold.
7. More co-morbidities (like heart disease, infection, sepsis, chronic inflammatory disease, recent stroke, etc., more prone to develop VTE).

Table 14.2 Acquired and congenital risk factors for DVT

Acquired risk factors for DVT
Acute spinal cord injury laparoscopic surgery
Age major surgery
Central venous access malignancy
Congestive heart failure minor surgery
Elective major lower extremity arthroplasty multiple trauma
Heparin-induced thrombocytopenia myocardial infarction
Hip, pelvic, or proximal femur fracture obesity
History of DVT or PE Oral contraceptives
Hormone replacement therapy pregnancy
Homocysteinemia Sepsis
Immobilizing plaster casts stroke
Inflammatory bowel disease patient confined to bed 0.72 h
Varicose veins
Congenital risk factors for DVT
Antiphospholipid antibody syndrome
Hyperviscosity syndromes
Antithrombin III deficiency
Lupus anticoagulant
Disorders of plasminogen and plasmin activation
Myeloproliferative disorders
Dysfibrinogenemia
Protein C deficiency
Homocysteinemia
Protein S deficiency
Prothrombin 20210A allele

The risk of developing post-operative VTE also depends upon degree of invasiveness type and duration of surgery, Anaesthesia and requirement for immobilization [20]. As per world literature, in the absence of appropriate prophylaxis incidence of asymptomatic DVT is widely varied from 10–80% and total pulmonary embolism is 0.1 to 0.8 percent after effective general surgery [21]. In high-risk patient with Caprini score 5 or more and undergoing abdomino-pelvic surgery without prophylaxis, chance of VTE is approximately 6%.

14.14 Caprini Risk Scoring Method for the Risk Assessment (Table 14.3)

The Caprini score is calculated by adding the scores of all risk factors. The Caprini score is calculated in the following method:

- **Score 0–1**: Low risk.
- **Score 2**: Moderate.
- **Score 3–4**: High risk.
- **Score ≥ 5**: Highest risk.

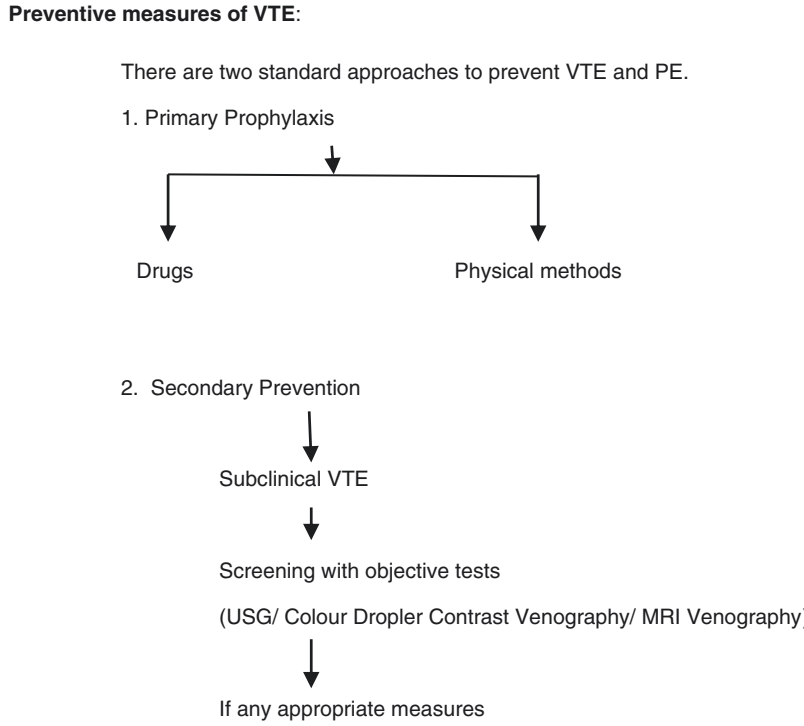
Table 14.3 Caprini score model. The different scores for the factors included in the Caprini score depicted in this table

Five points	Three points	Two points	One point
• Stroke (previous month) • Fracture of the hip, pelvis, or leg • Elective hip replacement surgery • Recent spinal cord injury (in the previous month)	• Age≥ 75 yrs.Previous H/O VTE • Positive F/H/O VTE • Prothrombin A • Factor V Leiden • Lupus anticoagulants • Anticardiolipin antibodies • Increased homocysteine in the blood • HIT • Other congenital or acquired thrombophilia	• Age: 61–74 yrs. • THR surgery • Lap surgery lasting >45 min • General surgery lasting >45 min • Malignancy • Plaster cast • Bedridden for >72 h • Central venous catheter	• Age 41–60 yrs. • BMI > 25 kg/m^2 • Minor procedures • Oedema in the lower limb • Varicose veins • Pregnancy • Post-partum • OCP • HRT • Unexplained or recurrent abortion • Recent H/O Sepsis • H/O pneumonia in previous month • Abnormal PFT • Acute MI • Congestive heart failure (in the previous month) • IBD

• **Score 0–1**: Low risk, **Score 2**: Moderate, **Score 3–4**: High risk, **Score ≥ 5**: Highest risk

14.15 Preventive Measures of VTE

There are two standard approaches to prevent VTE and PE.



Primary prophylaxis is a preferred method as it is safe, effective, and no need or limited need for laboratory monitoring.

And the secondary prevention is advised for patients in whom primary prophylaxis is either contraindicated or ineffective.

14.16 Primary Prophylaxis

1. Early and frequent ambulation for all patients, maintenance of hydration, and prevention of sepsis.
2. Mechanical methods are preferred in low-risk group (Caprini score 1 to 2) and patients with a contraindication to pharmacologic prophylaxis.
3. Pharmacologic prophylaxis is preferred in surgical patients at moderate- and high-risk patients (Caprini score ≥ 3).
4. Combined pharmacologic and mechanical methods (usually intermittent pneumatic compression) are considered for very high-risk patients (Caprini score ≥ 5).

Pharmacologic Agents for VTE Prevention Various drugs are now available for VTE prevention, including unfractionated heparin, the LMW heparins, fondaparinux, the vitamin K antagonists, and the newer antithrombotic agents rivaroxaban, dabigatran, and apixaban. These will be discussed below. When available, meta-analyses of the comparative effectiveness among these various agents will also be discussed.

Pharmacological agents usually used:

1. **UFH:** LMW (Low Molecular Weight) heparins, Daltaparin and Fondaparinux, are preferred than UFH**.** UFH is safe in renal function derangement and cost is Rs 100–150/dose (5000 IU).

(a) **Daltaparin** (Fragmin) in moderate- to high-risk cancer patients—2500 IU subcutaneously 1–2 hr. before surgery followed by 2500 IU 8–12 h later and then.

Once daily post-operative dose of 5000 IU subcutaneously for 5–10 days or till the time of discharge depending upon the risk score. Contraindication: Renal insufficiency.

Coagulation profiles like PT and APTT are relatively insensitive measures of Daltaparin, therefore, unsuitable for monitoring the anticoagulant effect. Creatinine clearance should be monitored and the cost for single dose (5000 IU) is Rs 400–600/– in Indian currency.

(b) **Fondaparinux**: Prophylactic dose 2.5 mg s/c to be started 6–8 h after surgery. Once daily for 5–10 days or till discharge of the patient. Cost Rs 1050–1300/dose (2.5 mg s/c).

(c) **Enoxparin:** 30–40 mg s/c once daily starting 12 h after surgery. Next time Low dose unfractionated Heparin (UFH) is used where LMW is contraindicated, i.e. in renal insufficiency and where cost is an issue. Cost 175–250/dose (40 mg).

Thrombocytopenia to be monitored routinely.

(d) **Warferin** may be advised as an alternative to LMWH and UFH when delayed prophylaxis is planned.

14.17 Comparison among all Type of Heparins (Table 14.3)

Comparison of Agents To compare the agents across studies of hip or knee surgery have been difficult, since the drugs under investigation and the dosing schedules have varied between trials. Even in the similar clinical trial there can be considerable variability. In addition, bleeding rates have varied across the trails, at least in part because different definitions for bleeding have been used.

A number of randomized trials have compared LMW heparin with UFH, *warfarin* or acenocoumarol, or *fondaparinux* in patients undergoing total hip replacement (THR), and to a lesser extent total knee replacement (TKR). A meta-analysis compared vitamin K antagonists versus LMW heparin for the prevention of VTE in orthopaedic surgery revealed that the vitamin K antagonists are less effective than LMW heparin, without any remarkable difference in bleeding risk (Table 14.4).

Table 14.4 Comparison

Warfarin	Heparin: UFH	Heparin: Low molecular weight heparin
Limitations: Dosing difficult Slow onset (the anticoagulant effect may not reach its peak until after 72–96 h) Slow clearance (Duration of action, 25 days). Recent guidelines recommend effectiveness of therapy titrated to a target INR 2 -3—Requires frequent blood sampling Cost: Vol. 1 mg (10 tabs)—Rs. 95 Vol. 2 mg (10 tabs)—Rs. 115 Vol. 5 mg (10 tabs)—Rs. 200	Mechanism of action—Pentasaccharide sequence binding to antithrombin which enhances its ability to inhibit both thrombin and factor Xa Route—S.c or Iv Antidote—Protamine sulphate Complication—HIT Cost: Rs. 100–150/dose (5000 IU)	Compared with UFH, LMWHs have more predictable pharmacokinetics and greater bioavailability. Weight adjusted dose once or twice daily Recommended for: Thromboprophylaxis in moderate- and high-risk surgical patients, For post-discharge thromboprophylaxis in high-risk surgical patients Initial short- term treatment of DVT in general population First three to six months for long-term treatment of DVT and cancer Cost: Daltaparin cost Rs 400–600/dose (5000 IU) Fondaparinox Rs1050–1300/dose (2.5 mg) Enoxaparin cost 175–250/dose (40 mg)

In general, LMW heparin has been shown to be superior to UFH or *warfarin*, but inferior to *fondaparinux* in terms of efficacy, with similar bleeding rates in patients undergoing THR OR TKR surgeries.

The use of LMW heparin *enoxaparin* differs between regions. Thus:

- In North America, *enoxaparin* at a dose of 30 mg twice daily started after 12 to 24 h after surgery.
- In Europe, *enoxaparin* at a dose of 40 mg is started 12 h after surgery and is then given once daily.
- Other LMW heparin preparations have usually been given in a once daily dose, started after surgical procedure.

A meta-analysis in patients underwent surgery for cancer concluded that there was no difference between LMWH and UFH in terms of efficacy, DVT location, or bleeding complications.

A Cochrane review of the use of LMW heparin to prevent VTE in surgical patients with lower immobilization concluded that LMW heparin in outpatients effectively reduced the VTE incidence. A further meta-analysis reviewed the use of intermittent pneumatic compression (IPC) with or without pharmacologic prophylaxis. It was shown that, compared with IPC alone, combined prophylactic methods reduced the VTE incidence.

In neurosurgical procedures, LMW heparin was shown to be effective then IPC. In major trauma management, LMW heparin was effective than UFH in the prevention of DVTs.

Timing of Prophylaxis Recommended either before or immediately after surgical procedure and continued until the patient is mobile.

In moderate- and high-risk patients LMWH started either 12 h before surgery or 18 to 24 h after surgery.

The term extended prophylaxis is used by ACCP & NCCN and ASCO—for a very high-risk patients (Caprini score > 5) where prophylaxis may be extended 10–35 days. It is recommended for a period of four weeks.

Other drugs used are—direct thrombin & Xa inhibitor, Rivaroxaban, DabigationXilate, Apixaban, Endoxaban, etc.

Mechanical Methods

1. Intermittent pneumatic compression (IPC)—It enhances blood flow in the deep veins in the leg, thereby preventing venous stasis.

   It reduces plasminogen activator inhibitor-1 (PAI-1) thereby increasing endogenous fibrinolytic activity [22].

Among all mechanical devices, efficacy of IPC appears best [23].

2. A graded compression stocking (GCS)—GCS when combined with other prophylactic modalities appears to improve rate of DVT prevention.
3. Venous foot pump (VFP)—Like GCS, it is used combined with other prophylactic methods.

   Inferior vena cava (IVC) filters: In general IVC filters should be avoided as primary prophylaxis. The indication for filter placement as a therapy for DVT. (Figs. 14.1 and 14.2).

14.18 Summary and Recommendations

Every hospital may develop a formal strategy for the prevention of VTE for their surgical patients. Strategies should be developed with proper thromboprophylaxis recommendations, including authorized order sets, periodic audit, follow-up with feedback.

The article "Prevention of venous Thromboembolism" ACCP evidenced based clinical practice guidelines (eighth Edition) is a recommended guideline for the prevention of VTE which may be useful in formulating these policies [8].

Number of attempt has been made to develop risk assessment models for VTE in individual patients. At this time, none of the risk stratification models has been validated in prospective trials, although this subject is under active study.

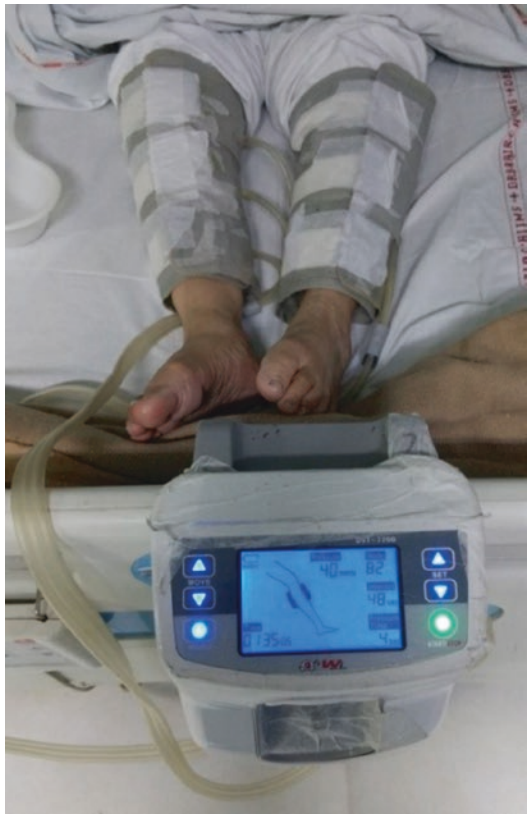


Fig. 14.1 DVT Pump used for DVT Prophylaxis

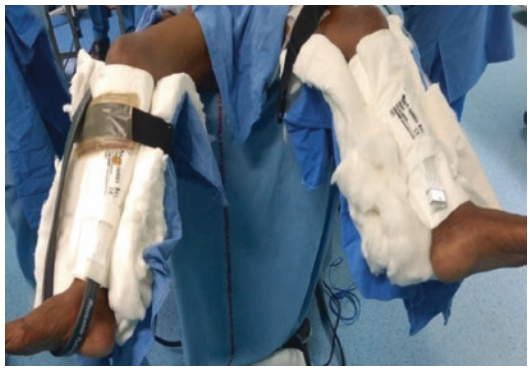


Fig. 14.2 DVT pump used intra operatively in Post-operative period in ICU

In patients with additional risk factors (e.g. previous H/O VTE, advanced age particularly >75 years, active cancer or a history of cancer, a more extensive surgical procedure) consideration should be given to more aggressive prophylaxis in the form of increased intensity or duration of a pharmacologic agent, or the addition of intermittent pneumatic compression (IPC) [8].

In patients from specific ethnic groups in which the incidence of post-surgical venous thromboembolism is low (e.g. Asian populations), consideration may be given to **less** aggressive prophylaxis.

Assignment of surgical risk groups: The risk of post-operative VTE depends upon the surgical procedure (e.g. type and duration of anaesthesia and surgery, requirement for post-operative immobilization), as well as patient-related factors (e.g. increasing age, prior VTE, presence of cancer or obesity, presence of an inherited or acquired hypercoagulable state). Patients have been generally divided into low-, moderate-, and high-risk categories.

Low-risk general and abdominal-pelvic surgery: For low-risk surgery (Caprini score 1 to 2) the use of mechanical prophylaxis is preferred, over no prophylaxis or prophylactic anticoagulation.

Moderate-risk general and abdominal-pelvic surgeries: For moderate-risk general and abdominal-pelvic surgery (Caprini score 3 to 4) the recommend method is the use of prophylactic anticoagulation over no prophylaxis.

*High-risk general and abdominal-pelvic surgery***:** For high-risk general and oncologic abdominal-pelvic surgery (Caprini score 5 or more) the use of prophylactic anticoagulation is recommended. Reasonable choices include LMW heparin, UFH in renal insufficiency, or Fondaparinux.

Length of treatment: For moderate-risk patients undergoing major general and abdominal-pelvic surgeries, the recommendation is that continue thromboprophylaxis until hospital discharge, rather than for a shorter or longer period.

14.19 Timing of Regional Anaesthesia/Analgesia: (Cork University Hospital, Version 1 Guideline 2015)

UFC (subcutaneous)

- Should wait minimum four hours after a dose prior to block or catheter removal.
- Should wait minimum one hour prior to dosing after procedure (catheter insertion or withdrawal).

UFH (intravenous)

- Infusion should be stopped 2–4 h prior to block.
- Start infusion > one hr. after block.
- Remove epidural catheter not before 2–4 h after discontinuation of infusion.

LMWH

- Should wait minimum twelve hours after a prophylaxis dose before block.
- Should wait minimum 24 h after a therapeutic dose before block.
- Should wait minimum ten hours after dose before removing catheter.
- After catheter removal wait 2–4 h before next dose.

Conclusion For selected high-risk general and abdominal-pelvic surgery patients, the suggestion that continuing thromboprophylaxis after hospitalization with LMW heparin for up to 4 weeks be considered, minimum till the patient discharges from the hospital and ask the patient to keep on moving at home, not to be at bed always.

Further trails involving various regional cancer centres with huge sample size may provide further epidemiological data related to VTE in onco-surgery patients. So continue efforts to be made to find the most effective and safest method to prevent and manage VTE.

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15 Research and Publication: Importance in the 21st Century

Amar Ranjan, Arshi Rizwan, Lawanya Ranjan, Harshita Dubey, and M. D. Ray

15.1 Introduction

Barack Obama once said "Science is more essential for our prosperity, our health, our environment and our quality of life than it has ever been before." According to Collins "Biomedical research has generally been looked at for its health benefits, but the case for it Generating economic growth is pretty compelling" [1].

The driving force for promoting sustainable growth in any field is new knowledge, which is possible by scientific discovery, technological breakthroughs and innovation. May it be health, economy, industry, clean energy, global climate changes, or our national security? [2]

After a research, documentation of results in scientific ways and to publish it in a scientific journal provides the recognition to that research. Ultimately researches are linked to innovation [3].

15.2 Definition of Research [4]

Definition of research includes following components:

- Creation of new knowledge and/or
- Use of existing knowledge in a new way to create new concepts, methodologies, and understandings.
- It may include analysis of previous research that leads to new outcomes [4].

Research includes experimental development to give a novel creative outcome that aids in existing stock of knowledge. The knowledge may be in terms of humanity, culture, and society. This new knowledge is utilized in novel applications in different disciplines.

Research is an integral part of the development, so it is commonly used as Research & Development (R & D).

R & D has been classified in to four categories [5]:

- Pure basic research
- Strategic basic research
- Applied research
- Experimental development

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Pure basic research: It is a theoretical cum experimental work. It is done to acquire new knowledge. Any long-term benefit is not expected from such activities.

Strategic basic research: This is theoretical cum experimental work aiming to have new knowledge in any specified area. It provides the necessary solutions of a recognized practical problem.

Applied research: An original work is undertaken to acquire new knowledge with a specific application in mind. It aims at using the findings of basic research. It may explore some novel technique to solve any specific objective.

Experimental development: The existing knowledge is used in systematic ways. It is implemented in practice. This practical experience is aimed at producing new materials, products, or devices, which are installed in new processes, systems, and services.

15.3 Requirements to Conduct Research [4]

- Professional, technical, administrative, or clerical support staff directly engaged in activities essential to the conduct of research.
- The activities and training of staffs involved in research.
- Research and experimental development into applications software, new program.

The aim of educational innovations is having knowledge of theory and it should be utilized in practice like spreading the knowledge to beginners, parents, community, and society. The technology in spreading knowledge needs a well-conceptualized theory, which must fulfill the requirement and it should have an excellent pedagogy. A technology must be cost effective and time efficient [6].

Education serves the requirements of a society. It is an indispensable requirement for a society for their growth and development. Education must be comprehensive and sustainable. It needs modifications times to times to justify the changes occurring in the society in a changing world. Evolution in technology would be consistent and systemic. This requires teachers or educators and policy makers to keep them updated on the knowledge of novel innovation and any modification in the existing theory [6].

Innovation is similar to mutation in biology. Mutations keep on any species evolving to let them survive in a continuously changing environment (Hoffman and Holzhuter 2012).

Innovative Creation is an instrument to bring a necessary and positive change. Any discipline associated with human activity like industry, business, or education needs constant modification (innovation) to remain viable.

Social and economic well-being of a community depends upon their education and mode of spread of information (media).

The requirement of innovation originates from demographic, political, economic, and technological needs [6].

Conceptual paper Necessity is the mother of invention (Plato).

Publishing is the only way scientists communicate with each other and gives the authors credit for the work they have done. Publishing provides an authenticity of the work that has been done. In recent times, publishing has become vitally important even for clinicians for a variety of reasons, including career advancement, mandatory government regulations, and greater opportunity for International collaborations as well as monetary incentives in the form of grants. Government is striving to provide adequate resources and training, sought and attained with collaborations and short-term courses. Recently Govt launched an incentive program for acquiring higher degree which is research based, during service.

However following queries has been generated

1. If there is any way to create an arrangement in which the outcomes of scientific research can be described?
2. If yes, what shall be the inputs, outputs, and structure of the arrangement?
3. Which disciplines of science should inform the making of such an arrangement?

So, considering all above points, a system should be formed which enables the effects of

research be viewed as an ongoing basis, this will ensure less burden on principal investigators and Institutions.

"Publish or Perish" is like a fated maxim among academics [7]. Publication of thesis, articles, reviews, dissertation, (not common) is an inevitable part of research & development. Trusted information about the work of academics can only be gathered by a series of planned experiments and proofs about the research being carried out. Various interactive sessions like timely presentations amongst their close groups, attending and participating in conferences, are ways in which they exchange their scientific ideas; also share ideas, but again only publications in peer reviewed journals can authenticate the importance and originality of the work.

15.4 Research and Publication in Indian Academic Curriculum

Most of the authors of Research papers we see today are owned by faculty members of prestigious institutes as Research and publication are an integral part of the professional activities But Times are changing and encouragement to young minds is the new academic shift. Originally Doctor of Philosophy (PhD) was the first step of research in the lives of young researchers, however, now the idea of inculcating the charm and hands on experience of Research has been started in forms of thesis and dissertation in Masters course. It is now the first step of learning research under expert guidance. This indeed provides in a way to more man power to the research being carried out Under the Faculty of the particular Subject in a particular Institute [8].

In India, there are more than 300 universities and institutions of higher learning and hundreds of research laboratories; both in the government sector and to private sector, but there are only 178 open access journals and 33 registered archives. The National donor agencies such as the Department of Science and Technology, The Department of Biotechnology, and heads of major @search councils such as the CSIR, ICMR (in the field of medicine), AGC are yet to decide if the results of all publicly funded research should be made available through self-archiving and encourage open access journal publishing initiatives to achieve high impact on research and publications.

15.5 Process of Getting Research Grant, Medical Writing, and Publications

The process of getting Research grant starts as early as for PhD students. PhD programs are equipped with a rainbow of curriculum, along with their own thesis and exams, they also get involved into teaching academia to undergraduates. Publishing articles of their research being the most valuable part of their curriculum out of all.

To start a research, Grant is required for chemicals, equipment, sometimes even study material grant.

The procedure of getting a research grant involves the following steps:

- Writing a Research project along with the help of chief guide at the host institute.
- Approval of Ethics Committee to carry out the research. Ethical Committee will vary depending upon the type of research carried out, for e.g., there are different approvals for different research work done on humans, animals, drug-based study, treatment-based study, etc.
- After approval, the project is sent to a funding agency.
- The funding (COMMA NITY MEDICINE 326 Indian Journal of Clinical Practice, Vol. 28, No. 4, September 2017) agencies have an interview of the Principal Investigator before a scientific committee. And depending on the relevance and quality of protocol submitted it decides whether the protocol suits fit for the grant.
- With successful interview grants are provided.
- If the grant is provided, timely monitoring of the ongoing research is done, periodic reports are asked for, and meetings are held.

Since India is a huge country, competition of getting research grant is really high. One really has to bring quality work in order to receive a grant. Also, now there are various agenda and schemes to encourage the research of young minds. Individual fellowship is also available under schemes like Women Scientist, Young Scientist provided by ICMR, DST, DBT, etc.

There are various National & International funding agencies that provide grant. One can decide depending upon the subject of the project, which agency will best fit for the grant; as each agency has different rules. Government funding agencies in India are Dept. Of Science and Technology (DST), Dept. of Biotechnology (DBT), University Grants Commission (UGC), Indian Council of Medical research (ICMR), etc. Details of the proposed projects can be sent to these agencies online.

There are certain International funding agencies, which might also provide opportunity to work at International level too. On completion of a research project, students present their work in National and International conferences.

After successful completion of project, the article can then get published in a peer reviewed journal. The common forms of publications in a journal include original article, review article, case reports, letter to the editor, etc. This may also be in the form of monograph, chapter in a book, conference paper, research report, etc.

This serves as a go getter in the academic career of a PhD student. As a rule of completion of degree, one article from the relevant research work done in the field should be published in an authentic journal. A research grant aids in the smooth running of research and completion of the degree.

15.6 Relevance of Research and Publication in Today's World

Quality Research is the true Research. To assess the quality of Research Publications are important. Research is the only way of evolving and getting better than yesterday. Most of the developed countries in the world today are actively involved in Research works; like Europe, USA, Australia. They not only encourage citizen of their country to participate in research but also encourage scientist, doctors, nurses, academics community from all around the world to actively share their ideas on a world level basis (II).

In a number of countries, research funding bodies have initiated efforts to assess research impact, including United Kingdom, The United States of America, Netherlands, and Australia [9, 10].

The impact of research can be assessed qualitatively or quantitatively. Qualitative approaches, such as the one recently trialled by the UK government's Higher Education Funding Council, involve expert panels evaluating impact, for example, as high, medium, or low, based on written descriptions of impact [9]. Quantitative approaches can involve numerical indicators derived from scoring systems or questionnaires focused on the various possible impacts of a research program or project. An approach developed by Wording rr *ul.* in the UK for the Arthritis Research Campaign rr *ul.* [11, 12] is largely quantitative, and measures the impact of a funding body's research portfolio based on self-reported impacts. The STAR METRICS system in the United States [10] aims to capture data on scientific outputs and activities linked to research investments systematically. This will enable quantitative assessment and analysis of the impacts of research. On an average research is expected to take at least five years.

15.7 Relevance in Medical Field

Research and publication comprise an integral component especially in medical science. This is because human body is a much more complicated structure than any artificial machine on which we work. Due to generation of novel diseases due to environmental changes, we need to keep us updated regarding novel causative agent and the mode of management required for novel agent. Clinical trials for novel therapeutic agents are a continuous process, which is a component of research.

Genetic alterations have been studied a number of pathologic processes in human being. It may be associated with disease process, which may be benign or malignant. Carcinogenesis is an excellent example to understand the importance of research. Genetic studies have altered the pathogenesis and therapeutic plans in a number of malignancies nowadays.

Altered human behaviors have also been implicated with genetic abnormalities [13]. Research and development constitute an integral part of any Government. A significant amount of budget is allocated for this work, which employ clinical and basic scientists. Clinical scientists are qualified doctors who take interest in research activities. Good correlation between clinicians and scientists is required for a productive outcome in medical research [14].

Developing countries like India lack a lot in clinical research, as most of doctors are engaged in providing clinical services and managing their livelihood. They do not have time for research activities. On the other hand, basic scientists have limited opportunities. After completion of master degree, they do not get fund for implementing research activity. Those who get fund do not find proper infrastructure to work or even support from their guides, although Government of India has started a number of schemes for medical research. Organizations like Indian Council of Medical Research are leading this initiative. Other associated organizations are Department of Science and Technology, Department of Biotechnology are also actively involved in promoting research activities. University Grant Commission and Indian Council of Agriculture Research are two other bigger agencies which promote research activities apart from regulating different teaching organizations.

When we analyze the features of single disease in different individuals, it varies from initial presentation to final outcome. This may be due to difference of immune status of individual. Secondly it may vary due to the virulence of invading organism or changes in genetic structure.

Outcome of disease also varies according to the institution involved in the management of that case. This may also be influenced by social factors like educational and economic status of the patients especially in the countries like India, where most of the people are not having coverage of health Insurance scheme.

Poor patients residing in rural areas present to the tertiary care centers in late stages when we consider any chronic diseases like malignancies.

A disease outcome is monitored by certain statistical data like disease free survival, overall survival, or progression free survival. It indicates quality of life a patient during or after therapy. Economic status is also an important factor in development of disease and therapeutic outcome especially in countries like India.

15.8 Scenario in India

When we compare the health facilities in India in relation to developed countries, we stand nowhere. In western world, people are covered with Health Insurance schemes. They have far better infrastructure for health facilities even in Government setup. Whereas in India there is a clear-cut difference between Government and private setup in term of health facilities. India Government has far less budget for health infrastructure. Most of budget here are being provided in clinical management. A small fraction of total health budget is being spent on research & development activities. Certain private Institutions are also engaged in research promotion activities in India mostly drug companies. They are interested more on marketing their drugs than promotion of research.

Medical Council of India (MCI) is the governing body for medical institutions in our country. During the process of recruitment for faculties, research & publications remain an important indicator for the competency of a candidate. This employs more in their promotion. Because once individuals become faculty, they get better opportunity to have fun for research activities. They have an opportunity of enrolling PhD students, who are the backbone for research & development activities. But unfortunately, limited medical institutions are engaged in research activities

in our country. Most of the Institutions have "Doctor of Medicine" or "Master of Surgery" students who are engaged in research works during their thesis preparation, which constitutes essential criteria for having the two degrees. A number of medical institutions in our country are lacking Institute Ethics Committee, which is an essential requirement to have research work on human samples.

Recently new course, MD–PhD, is being introduced in certain Medical Institutions to incline clinicians towards research activities. But it is in nascent phase, prediction of its outcome is difficult till date.

In western countries research and development activities get priority over clinical activities. They have mandatory requirement of research activity while having recruitment for medical faculty.

In India two research projects is mandatory for post-doctoral medical courses (DM/much/DNB), during due course of three years. Research methodology and critical analysis constitute an important input in their thesis. They need data analysis to be done by any qualified Biostatistician. In present scenario, Medical researchers in India have no much opportunity as a clinical medical professional. They have no placement for their bright career. This results in to poor quality of research outcome [15]. There is no significant reward for professional who have published their works in high impact factor journal. Reward for students either under or post graduates will result in to a better outcome in research activities.

15.9 Importance of Research and Publication

Initially related to Master degree and PhD course only but nowadays it has become a part of our academic life! Scientists, throughout the globe, can communicate only through Research & Publication. Prof Sugarbaker sibling in Washington DC, Oliver Glehen in France, M. Hoobnev in Switzerland, we know them because of their research & publication.

As a super specialist, if you appear in any interview starting from Faculty interview to promotion board, the experts like to ask on your Research & publication only. So, for the cancer progression it is an integral part!

Government is trying to promote research by providing some extra incentive, for instance, being a Faculty y, if you do a research related course, you will get 30,000/- for 3 years course, 20,000/- for 2 years course, 10,000/- for I year course, etc.

15.10 Research Methodology

1. Title of the study.
2. Rationale/Relevance of the study/Hypothesis.
3. Review of literature.
4. Objectives.
5. Research methodology.
   (a) Ethical committee clearance.
   (b) Nature of the study—basic, clinical, or translational.
   (c) Sample size.
   (d) Study designs.
   (e) Outcome measures
6. Performa of data selection.
7. Data analysis limitation of the study.
8. Presentation of results.
9. References

15.11 How to Improve Scientific Research and Publication Quality?

1. Strong review process is essential for grant proposal in funding agencies.
2. Requirement of more funds from funding agencies.
3. Collaborative research at national and international level.
4. Self-internal committee review board for better output for each institute.
5. A researcher or scientist must have good command over English language to publication or in grant proposal writing.

6. Government and industry should support for product-based funding.
7. Last but not the least. Make a habit then the habit makes you.

15.12 Conclusion

Research and publications are an essential tool for progression of mankind. The developments we have achieved in medical, scientific, and technological fields have been possible by only and only research and development. If we as a society fail to publish all competent research, we have committed irreparable world-scale malpractice. The moral imperative of "publish or perish" is now broad and urgent with the advent of easy and prompt publication. If we fail to publish data, the data perish; with data's demise, people (whose clinicians should have had the advantage of knowledge in the literature) suffer and perish, along with the public investment we have made as taxpayers, donors to, participants in and fundraisers for research.

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16 Critical Care of Postoperative Patient after Major Onco-Surgery: Overview

Nishkarsh Gupta, Saurabh Vig, and Anju Gupta

16.1 Introduction

Postoperative management of major surgical oncology patients is always challenging in view of patient status and complex surgical interventions. Preoperative clinical status may be affected due to chemotherapy, radiotherapy and impact due to cancer per se. This is compounded by complex, long duration, and extensive surgical interventions. Thus, patients require utmost care for an uneventful outcome after successful surgical interventions. Patients may require intensive monitoring in dedicated unit like intensive care unit (ICU) for optimization of various systems functions affected intraoperatively. Usually in cases of uneventful surgery and airway integrity being maintained, trachea is extubated soon after completion of surgery and requires routine postoperative observation in addition to optimal analgesia. However, a group of patients would require intensive monitoring or postoperative mechanical ventilation support in view of compromised systemic function including airway. Due to limited availability of beds in ICU and limited resources, triage should be done for making decision of shifting the patient to ICU. Although ICU constitutes less than 10% of total hospital beds but more than 20% of hospital expenditure is contributed by ICU. Usually ICU stay is 3–5 times more expensive than general surgical wards.

16.2 Need of Surgical ICU

The various issues that mandate transfer to critical care unit after surgery are varied and would depend on many pre- and intra-operative factors. The usual factors include patient hemodynamic instability or requiring mechanical ventilation either due to airway compromise or till optimization of systemic factors. It has been reported that diabetes and old age are risk factor for ICU admission after elective craniotomy. Mostly, patients posted for thoracic or abdominal surgeries are shifted to ICU due to an increased propensity of developing complications. ICU admission facilitates monitoring of oxygenation, bleeding, acidosis, consciousness, vitals, hemodynamics, respiration, pain, sedation, airway, urine output, and perfusion of vital organs. APACHE and SOFA are commonly used scoring system to assess for risk and mortality in postoperative surgical patients. Age, comorbidities, and emergency surgeries are associated with increased mortality risk (Table 16.1).

It is pertinent that certain details need to be communicated to critical care specialist prior to shifting to the ICU. This would help in proper

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Table 16.1 Factors for ICU admission in postoperative surgical oncology patients

• Elective mechanical ventilation in head and neck surgery due to anticipated airway compromise
• Excessive blood loss and associated hemodynamic instability and requirement of inotropes/ vasopressors
• Sepsis and septic shock
• Acute respiratory failure
• Inadequate neuromuscular blockade reversal
• Elective procedures like tracheostomy
• MODS (Multiorgan Dysfunction Syndrome)
• Patients requiring non-invasive mechanical ventilation support for respiratory insufficiency or increased oxygen demand
• Advanced age with associated comorbidities
• Prolonged duration of surgery
• Associated comorbidities like coronary artery disease (CAD), neurological diseases, etc.

Table 16.2 Consideration of patient at shifting to the ICU

• Detailed medical and surgical history: for planning management strategies in ICU
• Indication for ICU admission:
• Comorbidities
• Age
• Nutritional and functional status
• Elective or emergency surgery
• Hemodynamic
• Medication history
• Ventilator settings and special need for some specific ventilator modes
• Complications of surgery or anesthesia intraoperatively
• Number and type of drains and drain output
• Fluid input and urine output status
• Metabolic and respiratory status—arterial blood gas analysis (ABG)
• Blood loss and requirement of blood products as per coagulation and blood investigation values
• Requirement of sedatives, neuromuscular blocking agents or opioids
• Laboratory investigations as per need of the patient
• Admission chest X-ray for the evaluation of central line, endotracheal, nasogastric, and thoracostomy tube
• ECG in patients with new arrhythmia
• Body temperature
• Glasgow Coma Scale/Score (GCS)
• Pain scores, sedation scores assessment like visual analog scale, Ramsay sedation scale, etc.

planning and arranging the necessary monitoring, equipment, drugs, infusions ready prior to shifting of the patient to maintain continuity of care. The issues that require assessment at shifting of postoperative surgical oncology patients are varied (Table 16.2).

Once the patient is received in the ICU, the continuity of care should be continued as per management in the operating room like continuation of drugs (vasopressors, inotropes, and sedation). Transfer of critically ill patient is very challenging. All preparations should be done before shifting the patient to ICU. The initial management needs to include all critical steps that may affect various systemic functions of the patient. Once critical steps have been managed, then routine assessment and planning strategies for further management may be reviewed again. This is followed by initiation of other monitoring and interventions with regular reassessment (Table 16.3).

16.3 Taking Care of Lines, Tubes, and Catheters

Endotracheal tubes must be properly fixed and its position should be checked. Position of oral or nasal gastric tube should be confirmed on chest X-ray. All the drainage tubes should be properly labelled and the drainage output should be continuously monitored. Hemorrhagic drain may suggest surgical bleeding or coagulopathy. All intravascular catheters should be looked and any unnecessary catheter should be removed. Position of central line should be confirmed on X-ray. Arterial line should be properly labelled and continuously flushed with heparinized saline.

16.4 Clinical and Biochemical Monitoring and Other Specific Monitoring as per Need Based on Assessment like Cardiac Output Monitor

Patient needs to be monitored by electrocardiogram, blood pressure, pulse rate, oxygen saturation, and other specific monitors as per patient need. Perfusion of end organs can be clinically monitored by urine output, mean arterial pressure, lactic acid levels, pulse volume, heart rate,

Table 16.3 Various aspects of ICU Care of postoperative surgical oncology patients

1. Care of lines, tubes, and catheters
2. Clinical and biochemical monitoring
3. Other specific monitoring as per need based on assessment like cardiac output monitor
4. Systemic examination: head to toe and also include other system examination
5. Temperature monitoring
6. Nursing care
7. Glucose control
8. Antibiotics to prevent and treat infection as per institutional protocol
9. Ventilator mode, settings, and parameters
10. Weaning from mechanical ventilation and extubation
11. Preventing ventilator-associated pneumonia (VAP)
12. Sedation and Analgesia
13. Deep vein thrombosis (DVT) Prophylaxis
14. Stress ulcer prophylaxis
15. ICU agitation and delirium
16. Nutrition
17. Physiotherapy
18. Prognostication

skin color, and capillary refill time. Biochemical monitoring needs to be done as per assessment outcome. Goal directed fluid therapy should be practiced. Based on clinical signs aided by monitoring would guide the need of fluid and drugs.

16.5 Systemic Examination: Head to Toe and also Include Other System Examination

Patient needs to be examined from head to toe and systemic examination for assessment of various body systems like cardiovascular, respiratory system, etc. The assessment needs to be repeated for any change as per need of the patient and specific time frame cannot be suggested. It is prudent to assess after any intervention is done to check for the response and further planning.

16.6 Abdominal Examination in Abdominal Surgery

After abdominal surgery, abdominal girth should be monitored regularly. Abdominal pain, distension, firmness, and abdominal drain output can guide regarding abdominal complications. It may affect not only perfusion of bowel but also may compromise the renal function.

16.7 Temperature

Usually, patients are shifted after surgery in hypothermic state. Heat is lost due to vasodilatation, infusion of cold fluids or blood products, surgical site loss, and low operating room temperature. Hypothermia is associated with an increased risk of coagulopathy, arrhythmia, and other metabolic abnormalities in the form of acid base imbalance. All patients with hypothermia of less than 36 °C should be kept well covered and actively warmed using forced air blankets and fluid warming devices.

16.8 Nursing Care

Nursing care is paramount for an optimal outcome in critically ill patient. The ratio of 1:1 nurse to patient ratio should be there to manage patients on mechanical ventilation in ICU for monitoring and pharmacological support. Nurses need to provide general care, oral care, beddings, monitoring, informing doctors about alarms or investigations as a team member, caring of tubes, lines or catheters, blood transfusion and providing pharmacological support. Patients' position should be changed every 1–2 hourly to prevent development of pressure sores.

16.9 Glucose Control

Hyperglycemia is very common in postoperative period due to stress induced release of counter regulatory hormones like glucagon and epinephrine. Hyperglycemia may also occur due to use of corticosteroids and diuretics. It is associated with increased morbidity, increased risk of infection, polyneuropathy, and delayed wound healing. Target blood glucose levels in ICU should be less than 180 mg/dL. Other measures preventing hyperglycemia should be instituted like avoiding unnecessary dextrose infusion and overfeeding.

Insulin is the most effective way to control blood glucose by sliding scale or continuous infusion.

16.10 Antibiotics in ICU

Sepsis in ICU is a major challenge for an intensivist and requires prompt action to deal with it. Septic shock is a common cause of death in ICU set up in surgical patients. Appropriate antibiotics in post-operative patients are started based on the site of surgery and probable pathogens suspected. The choice of antibiotics should be decided based on institutional policies and as per antibiogram. Antimicrobial prophylaxis is started based on evidence based guidelines. Suitable antibiotics should be started early and de-escalation should be considered each day depending on the condition of the patient. The intensivist should always consider the dose, dose adjustment depending on the comorbidities, drug interactions, antibiotic resistance and its side effects. In ICU, intravenous route is the preferred route. In case of suspected infection, cultures should be sent as soon as possible before the start of antibiotics and antibiotics to be modified based on the culture reports. In mechanically ventilated patients, Gram negative organisms and *Staphylococcus aureus* are the commonest cause of VAP. Intra-abdominal infection requires immediate consultation with the surgeons. At times, focal source of infective pathology should be ascertained specifically when occurs after some delay of the surgical intervention. If present, then appropriate measures for its drainage needs to be considered. Antifungals can be started if fungal infection is anticipated as in cancer, neutropenia, burns, organ transplantation, and parenteral nutrition.

16.11 Ventilator Settings and Parameters

Mechanical ventilation supports oxygenation and reduces the work of breathing. If the patient requires mechanical ventilation, ventilator parameters like tidal volume, fraction of inspired oxygen (FiO2), modes of mechanical ventilation, airway pressures, end-tidal carbon dioxide, respiratory rate, minute ventilation, positive end-expiratory pressure (PEEP), and auto-PEEP should be monitored at constant intervals. The mode of ventilator is based on patient need and plan for weaning. Fully controlled mode is required for patient who are hemodynamically unstable and need controlled mode of ventilation. However, controlled mode may be shifted to supported mode at the earliest and when weaning is planned. ABG may be required in selected cases as it provides information on oxygenation, ventilation, and acid base balance. Pulse oximeter and end-tidal capnometer should be continuously used to monitor such patients. Patient ventilator interaction can be assessed by observing the patient directly and by vital signs. Ventilator alarms should be set to monitor for ventilator parameters and detect any adverse events. Patients on mechanical ventilation are at risk of developing venous thromboembolism, VAP and gastric stress ulcer and appropriate measures should be taken to prevent them.

16.12 Weaning from Mechanical Ventilation

Weaning in ICU should be attempted after hemodynamic stability, normalization of gas exchange abnormalities, resolving acidosis, return of consciousness, return of airway reflexes, and attainment of adequate tidal volume. Patients should be daily assessed clinical readiness for weaning. Spontaneous breathing trial should be done daily to promote early weaning.

16.13 Preventing Ventilator-Associated Pneumonia (VAP)

Ventilator bundle should be followed to prevent VAP in mechanically ventilated patients. Health care personnel should be educated regarding VAP bundle and regular surveillance for its compliance should be done. Patients in the postoperative period should be encouraged to cough, practice deep breathing, early ambulation, and start of

incentive spirometry. Patients should be kept in semirecumbent position by elevating the head of bed by more than 30°. Elevating head prevents gastro esophageal reflux and there is thus less risk of aspiration and VAP. Hand washing should be encouraged in ICU by both doctors and paramedics. Any procedure in ICU should be performed with full barrier protection. Prevention and management of septic patients may be as per the surviving sepsis guidelines.

Endotracheal tube with additional drainage tube from the subglottic area above the cuff has been proven to decrease the risk of VAP. Orotracheal intubation is preferred over nasotracheal intubation. Oral hygiene should be maintained by daily rinsing mouth of the patients with chlorhexidine. Daily evaluation should be done for weaning from mechanical ventilation. Use of non-invasive ventilation should be encouraged. Gastric over distension should be avoided. Any condensate collecting in the ventilator tubing system should be discarded periodically.

16.14 Sedation

Patients requiring postoperative mechanical ventilation require adequate sedation to tolerate endotracheal tube. This improve endotracheal tube tolerance, prevent patient ventilator asynchrony, prevent accidental endotracheal extubation, better compliance with invasive procedures, tracheal suctioning, cough suppression, physiotherapy, chest X-rays, dressings, positioning, and nursing care. It also prevents psychological complications and post-traumatic stress disorder. In addition, good sedation also prevents hemodynamic changes, decreases anxiety and irritation, and improves metabolic and stress responses.

The deep sedation prolongs weaning, increases the length of hospital stay, increased risk of ventilator-associated pneumonia (VAP), the risk of neuromuscular alterations, increased cost and morbidity. Also, inadequate sedation increased stress, discomfort, anxiety, agitation, increased catabolism, immune suppression, increased sympathetic outflow, and hypercoagulability affecting patients morbidity. Agents like midazolam, propofol, opioids, and dexmedetomidine are often used alone or in combination to achieve this goal. Choice of sedative agents depends upon the indication, sedative goals, pharmacology of drugs, and total cost. Daily interruption of ICU sedation should be done preferably in the morning and daily assessment should be done for readiness to wean from mechanical ventilation. This practice decreases the duration on ventilator and length of hospital stay. Sedation scales, such as the Ramsay and Richmond Agitation Sedation Scale can be used in ICU to monitor sedation and to promote early recovery from mechanical ventilation.

16.15 Analgesia

Pain assessment in ICU is a difficult task due to sedation or mechanical ventilation. Analgesia in ICU is provided by combination of acetaminophen, NSAIDS, and opioids. Opioids can be given by various routes like intrathecal, epidural, oral, IV bolus, continuous infusion or patient controlled analgesia (PCA). Side effects of opioids should be simultaneously monitored. Adequate analgesia facilitates cough and deep breathing and prevents sympathetic response. Pain should be regularly assessed and documented. Pain in mechanically ventilated patients can be assessed by hemodynamics and grimacing. Various pain scales in ICU like critical care pain observation tool (CPOT) and behavioral pain scale (BPS) have been used to assess pain in patients who cannot report their pain themselves in addition to unidimensional pain measurement tools like visual analog scale or numerical rating scale.

16.16 Prevention of Venous Thromboembolism and Deep Venous Thrombosis

All patients after surgery should be considered for mechanical or anticoagulant based DVT prophylaxis. Risk of postoperative thromboembo-

Table 16.4 Drugs used for venous thromboembolism and deep venous thrombosis

Drugs for DVT Prophylaxis	Dose
Unfractionated heparin	5000 U sc BD
Enoxaparin	40 mg sc OD or 30 mg sc BD
Dalteparin	5000 U OD
Fondaparinux	2.5 mg sc OD

lism is increased in patients with cancer, prior history of thromboembolism, obesity, advanced age, immobilization, and hypercoagulability. DVT prophylaxis is usually provided with low molecular weight (LMW) heparin, unfractionated heparin, and fondaparinux (Table 16.4). Anticoagulant should be used with caution in patients having epidural catheters in situ. Mechanical DVT prophylaxis should be considered in patients with increased risk of bleeding and neurosurgical patients. Patients should be monitored for heparin induced thrombocytopenia which can occur 5–7 days after initiating heparin.

16.17 Stress Ulcer Prophylaxis

All patients in ICU are provided with stress ulcer prophylaxis to prevent gastrointestinal bleeding. Patients at increased risk of stress ulcers are patients on mechanical ventilation, sepsis, steroids, burns, coagulopathy, and increased length of ICU stay. Proton pump inhibitors and histamine 2 receptor antagonists provide mucosal protection by decreasing gastric acid secretion. Commonly used proton pump inhibitors are pantoprazole and lansoprazole and commonly used histamine blockers are ranitidine and famotidine.

16.18 Dealing with ICU Agitation and Delirium

Critical illness is associated with delirium and is a major problem in ICU patients after the surgery. It is associated with increased ICU stay, increased morbidity, and postoperative cognitive dysfunction (POCD). It occurs in 70–80% of ICU patients and is often undiagnosed. It occurs due to an increase stimulatory neurotransmitters like dopamine and decrease in GABA and cholinergic activity. Old age, sepsis, metabolic disturbances, pain, hypoxemia, hypoglycemia, hypotension, use of benzodiazepines, opioids, antipsychotics, and anticholinergics are associated with an increased risk of delirium. It can be prevented by adequate pain control, maintenance of oxygenation and sleep wake cycle, correcting metabolic abnormalities, meeting time with family members, and early ambulation. Treatment includes use of haloperidol and antipsychotics like olanzapine and risperidone.

Nutrition In postoperative patients, nutrition plays an important role because of increased demand by wound healing and anastomotic function. Nutrition provides energy for metabolic processes and prevents further protein catabolism. Nutritionist should be involved in calculating the total energy requirement of such patients. Feeding should be started within 24–48 hours of surgery. Patients usually require 25–35 mg/kg/day of calories. Oral route is preferred over enteral and enteral nutrition is preferred over parenteral nutrition. Enteral nutrition is associated with decreased risk of infections, decreased length of hospital stay and cost effective as compared to parenteral nutrition. Enteral nutrition preserves the gut function by reducing gut mucosal atrophy and thus improves gut immunity. Sometimes, enteral nutrition is not feasible due to the site of surgery and risk of anastomotic leak.

Parenteral nutrition is started if the patient is malnourished and is not able to tolerate enteral nutrition for 7 days or enteral nutrition is not able to provide more than 60% of daily nutritional requirement. Total 1.5 g/kg/day of protein intake should be supplemented daily. Nutrition can be started orally and via Ryles tube or feeding jejunostomy. After giving the test dose, enteral nutrition is started and gradually increased to meet the nutritional requirement. If residual gastric volume remains more than 250 ml on more than two

occasions 6 hours apart, enteral feeding should be temporary stopped and measures should be taken to improve gastric motility. Gastroparesis is a common problem postoperatively and can be improved with metoclopramide.

Summary ICU care involves multidisciplinary teams including intensivist, nurses, physiotherapist, ICU technician, and dietician. Once ICU care is no longer required, patients should be transferred to a step down unit. ICU care allows better patient and family satisfaction, decreased complication, and decreased length of hospital stay providing morbidity benefit. The FAST HUG mnemonic (**F**eeding, **A**nalgesia, **S**edation, **T**hrombo-prophylaxis, **H**ead-of-bed angle, **U**lcer prophylaxis and **G**lucose control) was proposed as checklist to be considered at least daily for all ICU patients.

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17 ICU Care of Surgical Oncology Patients

Rakesh Garg

17.1 Introduction

Intensive care unit (ICU) care for a patient in the post-operative patient may be required electively or due to unexpected complications in the perioperative period. Critically ill surgical patient is at risk of developing a variety of complications, in addition the physiologic response to surgery which may alter tissue homeostasis and body function in the post-operative period. Thus a patient undergoing a major surgical procedure warrants special care in the post-operative period to optimize body functions, minimize hemodynamic alterations, and manage complications if any. Such patients may require elective ICU stay in the post-operative period.

As perioperative physicians, it is required to be well versed with changes in physiology after a surgical insult which may warrant ICU admission. Also one must be familiar with other aspects of care of a patient in ICU like feeding, thromboprophylaxis, fluid, electrolyte management, ventilator management, etc.

We aim to discuss the major aspects of managing a surgical patient in ICU starting from the basic understanding of the physiologic response to surgical insult, indications of ICU stay in a surgical patient, and the various important aspects of managing a surgical patient in ICU.

17.2 Physiological Response to Surgical Stress

Body's response to surgery leads to specific fluid, electrolyte, hormonal changes, and other system related alterations that must be considered for management of a patient in the ICU. The duration and magnitude of the surgical procedure are directly proportional to the intensity of endocrine and metabolic response [1].

17.2.1 Endocrine Response

Surgical stress leads to the release of cortisol, catecholamines, glucagon, antidiuretic hormone (ADH), aldosterone, inflammatory cytokines and decrease in insulin release. These lead to proinflammatory catabolic state leading to negative nitrogen balance, altered glucose metabolism with insulin resistance, and hyperglycaemia or unmasking of a latent diabetic state. Also acute fluid and electrolyte shifts may occur with altered renal response to fluid infusion.

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17.2.2 Third Space Fluid Sequestration and Altered Fluid Homeostasis

Occult fluid loss may occur following surgical resection in the interstitial and extra vascular spaces. In addition surgeries involving manipulation of gastrointestinal tract have additional fluid losses in the gut lumen, gut wall and in the area of peritoneal resection. These losses are not measurable by clinical methods and may lead to depletion of circulatory reserve. Body releases ADH and aldosterone to counteract these insensible losses. Thus close titration of fluid balance is a crucial component of post-operative ICU care.

17.2.3 Hypercoagulable State

Surgical trauma, proinflammatory state, and post-operative immobilization leading to vascular stasis promote a prothrombotic state in the post-operative period. Every post-operative patient is at risk of thromboembolic complications with some surgical populations like ovarian tumours for resection at particularly high risk.

17.2.4 Respiratory Changes

A number of physiological and pathological changes occur in the post-operative period. Increased metabolic rate due to surgical stress increases the oxygen consumption by the body and leads to increased oxygen requirement. These increased demands may not be met in a nutritionally depleted or a patient with compromised cardiovascular function and may lead to overt respiratory failure.

Other factors which may lead to post-operative respiratory failure are—post-operative pulmonary oedema, atelectasis, diaphragm dysfunction, and hypoventilation. Various factors predispose the patient to post-operative atelectasis and diaphragmatic dysfunction (Table 17.1).

Efforts must be taken to promote chest physiotherapy, spirometry and minimize the factors promoting respiratory dysfunction to prevent respiratory complications in the post-operative period. The spirometry should be done as per the convenience of the patient during his awake time.

Table 17.1 Perioperative atelectasis and diaphragm dysfunction

Predisposing factors	Preventing factors
Old age	Non-modifiable
History of smoking	Smoking cessation
Obesity	Positive end expiratory pressure
Supine position	45 degree upright position in post op period
Airway secretions	Cough, suction, deep breathing
Pulmonary oedema	Prevent over hydration
Bronchospasm	Bronchodilator therapy
Ascites	Drainage of ascites in the preoperative/intraoperative period
Peritonitis	Treatment with antibiotics
Upper abdominal incision	Adequate analgesia

17.3 Indications for Post-Operative ICU Admission

Patient undergoing surgery may need post-operative ICU care for a number of reasons like [2]**:**

(A) Elective or planned admission in view of:

- As a part of surgical and anaesthetic plan:
  - (a) Overnight ventilation (prolonged surgery, surgery handling the airway).
  - (b) Maintenance of post-operative hemodynamic targets (persistent hypotension, excessive blood loss, persistent arrhythmias).
  - (c) As a special surgical precaution for grafts requiring restricted movements.
  - (d) Post-operative analgesic management.
  - (e) Post-operative blood gas, electrolyte, glycaemic control.
- Optimization of preoperative comorbid conditions requiring special care, e.g. cardiac disease, patient on anti-coagulants, etc.

(B) Unplanned or emergency admission in view of:

- Unanticipated intraoperative complications: Various surgical related massive haemorrhage leading to hemodynamic instability. Injury to vital structures during resection, unanticipated difficult airway leading to airway injury, hypoxia, laryngeal oedema, etc.
- Exacerbation of preoperative lung pathology leading to intraoperative hypoxia, retained secretions, atelectasis, etc. necessitating post-operative respiratory monitoring or ventilation.
- Delayed post-operative complications like anastomotic leak, suture dehiscence, wound infection and sepsis, etc.

17.4 Triage and Predictors of Post-Operative ICU Admission

With increasing load of surgical patients the need of beds for post-operative ICU care is ever increasing. Scarcity of ICU beds is the most important limiting factor worldwide limiting admission of an eligible patient to the ICU. It is a known fact that optimum post-operative care plays a major role in positively influencing surgical outcome [2, 3]. It is thus essential to know factors that correlate with increased post-operative morbidity and mortality. Such factors can be used to predict the need of post-operative ICU care in a select group of patients for optimum utilization of scarce resources. We describe the various predictors in the following section [2, 3]*:*

17.4.1 Predictors of Post-Operative Outcomes

(a) Patient factors: The predictors of the post-operative outcome may be related to patients' preoperative comorbidities. The preoperative scoring systems like American Society of Anaesthesiologists' (ASA) physical status, Charlson's comorbidity index, revised cardiac risk index (RCRI) have been validated for predicting post-operative morbidity. None of these scoring systems is complete in it nor has been used as a sole guide for post-operative ICU admission. Individual patient factors like extremes of age, poor functional and nutritional status have been found as independent predictors of increased post-operative mortality and morbidity.

(b) Surgical factors: These are related to surgery specific factors for outcome. Surgical duration and urgency are independent factors associated with poor post-operative outcomes. Intraoperative factors like uncontrolled tachycardia, extremes of blood pressure are associated with poor post-operative outcomes.

Perioperative scoring systems like P-possum score predict the post-operative mortality and morbidity, scoring systems like Acute Physiology and Chronic Health Evaluation (APACHE) score, the Simplified Acute Physiology Score (SAPS), and the Mortality Probability Model (MPM) are being used for predicting morbidities in critically ill patients requiring ICU care. ICU. The Simplified Acute Physiology Score (SAPS- 3) scoring system has been used to predict the need of post-operative ICU stay in a small subset of patients [4]. SAPS-3 score is calculated as arithmetic mean of three sub scores [5]. These sub scores are based on patient characteristics, prior admission in critical care set up (length of stay in hospital prior to being shifted, location in hospital and comorbidities), circumstances for admission (planned vs unplanned admission, primary reason, any therapeutic intervention, infection), and physiological derangements at admission (GCS, blood counts, haemodynamics, temperature, and oxygenation).

Majority of components of the SOFA 3 can be scored at the end of surgery, thus it may serve as a triage tool to guide ICU admission of a surgical patient. Studies in surgical population have shown that higher SOFA 3 scores serve as independent predictors of post-operative ICU admission [5]. None of these scoring systems is comprehensive and have not been validated as a sole criterion to predict need of post-operative ICU care.

Presently, the American College of Critical Care Medicine has presented document for criteria for ICU admission of critically ill patients [3]. Thee guidelines has prioritized the patient in different categories for ICU admission. These categories are primarily based on judicious use of available resources and resources required for patient management ranging from intensive invasive support to just supportive care.

In an earlier guideline by the American Thoracic Society stated triage of patients to the ICU on the basis of a first come first serve policy or to patient most likely to benefit. However, none of the consensus guidelines addresses the issue of severity of the surgical procedure performed when considering triage for ICU admission. It has been observed in literature that admission criteria for post-operative critical care are highly inconsistent [6].

17.5 Management of Post-Operative Patient in ICU

Duration of stay in the ICU for a surgical patient is usually shorter than a non-surgical case. Care of a post-operative patient in ICU includes:

- General care: the "FAST HUG BIDS" algorithm.
- Acute post-operative pain management.
- Post-operative elective ventilation, weaning, and extubation.
- Management of specific complications, e.g. haemorrhage, sepsis, wound site infections, etc.

17.5.1 General Care

"FAST HUGS BID" pneumonic (feeding, analgesia, sensorium, thromboprophylaxis, haemodynamics, ulcer prophylaxis/urine measurement, glycaemic management, oxygen supplementation, bowel status, indwelling catheters, drugs therapy) to identify key aspects of critical care was first described by Vincet and Hatton [7]. Following this pneumonic twice a day for general aspects of patient care in the ICU has been shown to improve survival (Table 17.4). This pneumonic has been modified for a surgical patient [8]. In addition to this assessment, the surgical patients needs additional assessment related to surgical factors like surgical bleed, anastomotic leak, postoperative surgical pain, etc. is required. The patients should also be assessed for focus of infection and its appropriate management including antibiogram based antibiotics admministration [8].

17.5.2 Acute Post-Operative Pain Management

The acute post-operative pain may be major reason for elective admission of a patient to the ICU after major surgery and thus needs to be actively managed [9]. Post-operative pain may be managed on the basis of guidelines given by the American Pain Society. These can be summarized as thorough assessment of pain using various approved pain measurement scales, accurate description of pain and treatment of pain tailored to type of surgery, and individual response using multimodal analgesic techniques (Table 17.2). Accurate description of pain may be done by taking various elements into consideration, like onset and pattern of pain, location, quality, intensity, aggravating and relieving factors, and response to previous treatment (if any). It is suggested that multimodal analgesia using a combination of regional anaesthetic techniques and various pharmacological agents needs to be used as per site and extent of surgery (Table 17.2).

17.5.3 General Recommendations

- The dosage of the various analgesics needs to be appropriately used as suboptimal dose may not relieve pain and over dosages may have side effects (Table 17.3). Wherever possible prefer oral route over intravenous route for administration of opioids for post-operative analgesia.
- Avoid using intramuscular and subcutaneous routes for administration of analgesics especially in post-operative period because of erratic absorption.

Table 17.2 Analgesic regime according to site and extent of surgery

Type of surgery	Systemic pharmacology	Regional anaesthesia	Neuraxial anaesthesia
Thoracotomy	• Opioids • NSAIDs • Paracetamol • Adjuvants- gabapentinoids, ketamine	Paravertebral block, fascial plane blocks	Central neuraxial block- spinal/epidural/ combined; using local anaesthetic with adjuvant like opioids
Open laparotomy	• Opioids • NSAIDs • Paracetamol • Adjuvants- gabapentinoids, ketamine	Transverse abdominis plane block	Central neuraxial block- spinal/epidural/ combined; using local anaesthetic with adjuvant like opioids
Cardiac surgeries	• Opioids • NSAIDs • Paracetamol • Adjuvants- gabapentinoids, ketamine	–	–
Head &neck surgeries	• Opioids • NSAIDs • Paracetamol • Adjuvants- gabapentinoids, ketamine	Superficial and deep cervical plexus blocks	Nerve blocks

Table 17.3 Characteristics of commonly used analgesics in the ICU

Drug	Dose (mg)	Onset of action	Elimination half-life
Paracetamol	15 mg/kg iv at 6–8 h	5–10 min	2 h
Fentanyl	0.35–0.5 mcg/ kg IV	1–2 min	2–4 h
Morphine	0.1 mg/kg IV	5–10 min	3–4 h
Ketamine	0.5 mg/kg IV	30-40 s	2–3 h
Gabapentin	900–3600 mg/ day in three divided doses, starting from lower doses (300 mg at night) and titrate accordingly	1–2 h	5–7 h
Pregabalin	300–900 mg/ day in three divided doses, starting from lower doses (75 mg at night) and titrate	15–30 min	8–12 h

- For patient requiring intravenous opioids one should prefer patent controlled analgesia (PCA) if available.
- In opioid naïve patients routine use of basal opioid infusions with PCA should be used cautiously.
- In patients receiving opioids in the post-operative period appropriate measures (clinical assessment, pulse oximetry, capnography, etc.) to monitor respiration and respiratory status should be taken.
- Acetaminophen and/or NSAID's (if no contraindication) should be routinely used as part of multimodal analgesia to manage post-operative pain.
- Consider gabapentin/pregabalin as component of multimodal analgesia.

17.5.4 Post-Operative Elective Ventilation and Extubation

Post-operative patient admitted may be ventilated due to prolonged duration of surgery, inad-

equate or partial recovery from muscle relaxants or residual effects of narcotics leading to respiratory depression [10]. Surgical causes of post-operative ventilation include hemodynamic instability, head and neck surgeries involving manipulation of airway, etc. Ventilation in a post-operative patient is usually of short duration and patients are usually ready for extubation after the surgical insult has settled or the residual effects of anaesthetics have worn off. Extubating a ventilated patient can be divided into 4 steps: plan, prepare, extubate, post-extubation care and observation.

- Plan: Planning for extubation includes assessment of general and airway specific risk factors that may prevent successful extubation (Table 17.4).
- Prepare: The preparation for extubation includes optimization of general and airway specific risk factors listed in Table 17.4.
- Extubation: The patient can be classified as "low risk" or "at risk" on the basis of risk factors listed above. "Low risk" patients can be minimal risk and may not need prolonged postextubation monitoring. "At Risk" patients require special care and precautions during extubation such as extubation over an airway exchange catheter or a backup plan for re intubation or emergency surgical airway access in case of failed extubation.
- Post extubation care: It includes monitoring oxygen saturation, providing supplemental oxygen, measures to prevent atelectasis and encourage lung recruitment to prevent respiratory complications. Incentive spirometry, nebulization, steam inhalation and chest physiotherapy should be done regularly to clear chest secretions even after extubation and thus prevent respiratory complications.

Table 17.4 Risk factors for failed extubation

General risk factors	Airway specific risk factors
Cardiovascular (hemodynamic instability, high dose vasopressor support)	Known difficult airway
Respiratory (poor respiratory drive)	Deterioration of airway (active bleeding, trauma, oedema)
Neurologic (poor GCS, depressed consciousness)	Restricted airway access (head and neck, ENT procedures)
Metabolic (acid base imbalance)	Obesity/OSA
Special medical conditions. (motor neuron disorder, GBS, etc.)	Aspiration risk. (depressed consciousness)

17.5.5 Post-Operative Fever and Sepsis

Transient self-limiting episode of fever is common in the post-operative period; it is a manifestation of inflammatory response to the surgery [11]. However, persistent post-operative fever is a cause of concern and should be thoroughly evaluated and treated. The aetiology for post-operative fever may be infectious or non-infectious. The assessment should be aimed to look for these factors including surgical site infection, lung infection, urinary infection or due to body inflammatory response to surgical insult.

The post-operative sepsis is a major concern and has systemic effects even leading to multiorgan failure [11–13]. Its prevention and timely management is key to an optimal outcome. Sepsis may be result of surgical site infection or a systemic infectious complication. Certain surgical intervention like involving pancreas, oesophagus, and stomach has been found to have more risk of surgical infection. In addition, emergency surgical interventions have increased risk of post-operative infection.

17.5.6 Management of Post-Operative Sepsis

The most important concern in managing a case of post-operative infection is locating the source of infection. Surgical causes like surgical site

infection, intraabdominal collection or abscess formation may be difficult to pinpoint on clinical examination alone. Ultrasound and CT scan are useful diagnostic tests which may help pinpoint the localized source of infection. Surgical exploration or damage control surgery of the infected part or wound is an important component of treatment of surgical causes of sepsis in addition to standard antibiotic regimes as for other non-surgical source of infections.

17.5.6.1 Discharge from the ICU

Minimizing mortality by prevention and early diagnosis and treatment of post-operative complications is the key component of post-operative critical care. Patient may require post-surgical ICU care for a number of reasons as described above. The duration of ICU stay will vary with the indication of admission, e.g. a post-operative patient for monitoring of vitals will have a short transient stay when compared to a patient in sepsis due infection of the surgical wound. No set timeline or discharge guidelines are available for discharge of a post-operative patient from ICU. Surgical team along with the critical care physician should take a combined decision for the optimal time needed for each patient in the ICU. Teamwork between the surgeons and the intensivist is a necessity to minimize morbidity and mortality in the acute post-operative phase in the ICU and to ensure optimum utilization of resources to ensure maximum patient benefit.

17.6 Conclusion

Surgery represents an acute state of physiological derangement. Adequate post-operative care is crucial for the success of surgery. Patient undergoing surgery may require ICU care as a planned post-operative admission or unplanned/emergency admission. A comprehensive plan for shifting the patients to ICU and their management needs to be formulated as per local protocols for successful outcomes.

Key Points

1. Patient undergoing a major surgical procedure warrants special care in the post-operative period to optimize body functions, minimize hemodynamic alterations, and manage complications if any.
2. Scores like SAPS 3 can be used for triage of surgical patient for ICU admission.
3. An admission policy should be made considering local facilities and availability of resources.
4. Care of a postoperative patient in ICU can be summarized as general care, management of post-operative pain, management of ventilation, and management of post-operative complications.
5. Sepsis and multiorgan dysfunction is a dreaded post-operative complication and should be promptly diagnosed and treated.
6. Surgical exploration or damage control surgery of the infected part or wound is an important component of treatment of surgical causes of sepsis in addition to standard antibiotic regimes as for other non-surgical source of infections.

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18 Blood and Blood Transfusion in Surgical Oncology Patients: Importance and Relevance

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Blood is an integral part of our body. It is composed of three living cells red blood cells (RBC), white blood cells (WBC) and platelets. RBCs contain haemoglobin and carry oxygen from lungs to the rest of our body. WBCs defend against infection while platelets help in clotting of blood when injury occurs. Blood transports gases (oxygen and carbon dioxide), nutrients, waste, cells and hormones throughout the body. It helps in regulation of pH, temperature, and water content of cells. Blood products are usually required to improve oxygen delivery and to correct coagulopathy.

Oxygen delivery is a product of cardiac output and arterial oxygen content. Oxygen content is dependent upon haemoglobin concentration. If patient is anaemic, oxygen delivery can be maintained either by increasing cardiac output or oxygen extraction at tissue level. This result in rapid pulse rate or symptoms related to tissue hypoxia.

18.1 Blood Grouping

There are approximately 33 blood group systems. ABO system is used for transfusion. So, an individual may have group like A, B, AB, and O depending upon which antigen he /she have. Second most important blood grouping system is Rhesus system. So, the above group can be either RhD positive or RhD negative. So there are total eight blood groups. Cross matching is done to confirm ABO compatibility between donor and recipient. Ideally blood of the same group should be transfused but if it is not available, then next compatible blood group should be transfused. O negative (universal donor) can donate blood to all patients, while AB positive (universal recipient) can receive from all patients.

Patient's blood group	Could receive from
1. O	O
2. A	A, O
3. B	B, O
4. AB	AB, A, B, O

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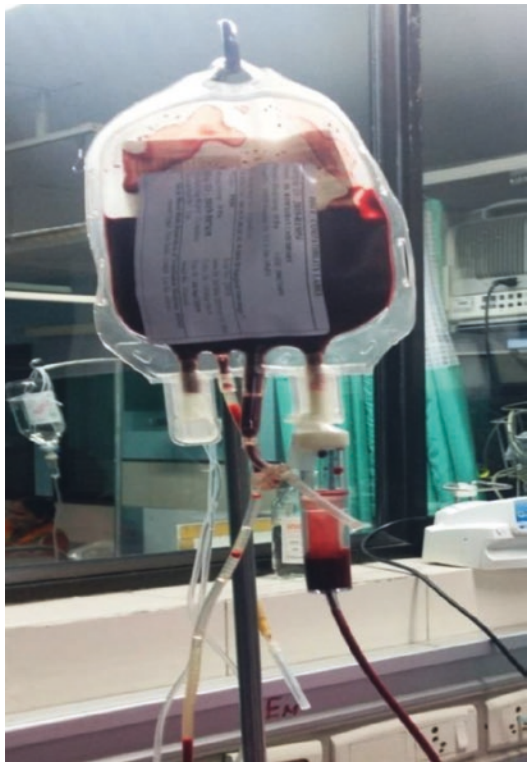

18.2 Why Blood Is Important in Surgical Oncology Patients

Blood and blood products replacement remains a major issue for any surgical procedures. Patient undergoing major oncosurgery may require blood in perioperative period. The need for blood replacement is primarily due to preoperative anaemia, bleeding, and coagulopathy during surgery. Cancer patient may bleed due to tumour biology and stage, preoperative cancer therapies (chemotherapy, radiation therapy, and immunetherapies) leading to thrombocytopenia and coagulopathy, vascular proximity to surgical area, complexity of the resection, and perioperative factors (haemodilution, hypothermia, and metabolic derangements).

Cancer patients usually have anaemia due to the following reasons:

- Cancer causes anaemia of chronic disease.
- Nutritional deficiency, malnutrition.
- Neoadjuvant chemotherapy and radiotherapy leading to bone marrow suppression.
- Bleeding tumours like gastric and colorectal cancer.
- Operative blood loss in complex, long duration surgery can cause anaemia.

18.3 Measurement of Blood Loss

Blood loss is monitored by visualizing the collection of blood under surgical drapes, oozing in the surgical field and collection in suction canister. For better estimates, gravimetric method is used which calculates weight difference between dry and blood-soaked gauze pads. One ml of blood weighs approximately 1gm.

Sponge
Well soaked sponge contains approx ~200 ml of blood volume

Gauze piece contains ~50 ml

Swab
- Small 10x10cm ~ 60 ml
- Medium 3x30cm ~140 ml
- Large 45x45cm ~ 350 ml

These methods of measurement should be supplemented with laboratory investigations and assess for signs of tissue hypoxia like capillary fill time (Fig. 18.1).

Maximum allowable blood loss (MABL) during surgery is calculated based on estimated blood volume (EBV) and target haematocrit.

Estimated blood volume is 65–70 ml/kg in adult male, while target haematocrit is 25%.

$$\text{MABL} = \text{EBV} \times \frac{\text{Initial haematocrit} - \text{Target haematocrit}}{\text{Initial haematocrit}}$$

Fig. 18.1 Blood loss measurement by sponge count

MABL marks the amount after which haemorrhagic complications start occurring.

1 ml of blood loss is replaced with 3 ml of crystalloid/1 ml of colloid/ 1 ml of whole blood.

18.4 Maximum Surgical Blood Ordering Schedule (MSBOS)

MSBOS helps in efficient use of blood in elective surgery. Blood loss also depends upon surgical skill of operating team. Instead of blanket order of 2–4 units of blood for all major surgical oncology procedures, proper assessment of blood loss from historical records should be made and then blood should be ordered. This way, it is enough for 85–90% of patients for each surgical procedure. This reduces unnecessary cross-match for blood transfusion, stress, and cost.

Concerns related to blood transfusion: It may be associated with acute and delayed complication.

18.4.1 Acute Complications

- Transfusion associated circulatory overload (TACO) especially in patient having cardiac disease or extremes of age.
- Transfusion related acute lung injury (TRALI).
- Febrile non-haemolytic transfusion reaction (FNHTR).
- Infectious disease transmission.
- RBC alloimmunization.
- Haemolytic transfusion reaction.
- Metabolic derangements.
- Mistransfusion (incorrect blood product and/or patient).
- Allergy/anaphylaxis.

18.4.2 Delayed Complications

- Delayed haemolytic transfusion reaction.
- Iron overload, especially in repeated transfusion.
- Microchimerism- presence of genetically distinct cells.
- Post-transfusion purpura.
- Transfusion related immunomodulation (TRIM).
- Transfusion associated graft versus host disease.

18.5 Preoperative Assessment for Blood Replacement Related Issues

All patients must be assessed for real need of blood or blood products transfusion in perioperative period. Patient should be reviewed for associated comorbidities, previous blood transfusion, and recent treatments with chemotherapy, radiotherapy or anticoagulant drugs. History of herbal supplements like ginger, ginkgo biloba which may affect coagulation should be elicited. Risk factors for organ ischemia (e.g. cardiorespiratory disease) need to be assessed as these will influence the need of blood transfusion. These patients should be examined for clinical signs like ecchymosis, petechiae, pallor. Laboratory investigation like complete blood count, coagulation profile, and serum iron should be ordered preferably 6 weeks before surgery.

18.6 Preoperative Optimization

Supplementation of iron along with erythropoietin should be done for correction of preoperative anaemia, especially in patient with chronic disease. Drugs like vitamin K, low molecular weight heparin, antiplatelet drugs, aspirin, and NSAIDs which causes coagulation abnormalities should be discontinued. Antiplatelet drug given for cardiac stent should be discontinued and bridged with unfractionated heparin in perioperative period. In case of emergency surgery, rapid reversal of anticoagulation with prothrombin complex concentrate, vitamin K, fresh frozen plasma, and antifibrinolytics should be done.

To avoid allogenic transfusion, autologus donation should be done if patient is fit to donate. It should preferably be done 6 weeks before surgery and haematinic supplement with or without erythropoietin should be given.

18.7 Intraoperative Strategies

18.7.1 Surgical Technique

1. Minimally invasive surgical technique like laparoscopy, video assisted thoracoscopic surgery should be used to reduce blood loss.
2. Complex cases should be done as staged operation to minimize blood loss.
3. Big surgical team to reduce duration of surgery like in case of head and neck tumours where one team will do resection of tumour and other team will prepare muscle pedicle graft for reconstruction.
4. Use of electrocautery, harmonic scalpel, surgical adhesive, tissue sealant, and haemostatic agents (fibrin, glue, and thrombin gel).
5. Tourniquet with proper exsanguinations during amputation.
6. Wherever applicable preoperative neoadjuvant chemotherapy and radiotherapy should be administered to shrink/reduce the tumour size.
7. In highly vascular tumour, tumour vessel embolization helps in reducing blood loss.
8. Local vasoconstrictor should be injected at the site of surgical resection.

If moderate to high blood loss is anticipated in surgical procedure, preoperative autologous donation and acute normovolaemic haemodilution may be done.

18.7.2 Anaesthesia Techniques

1. Intravascular volume: maintain optimal intravascular volume for adequate tissue perfusion.
2. Regional anaesthesia: Regional anaesthesia causes sympathetic block and hypotension. This will lead to 20–25% less blood loss in perioperative period.
3. Positioning: elevating surgical site above the level of right atrium facilitates venous drainage and reduces local venous pressure.
4. Ventilation: Positive pressure ventilation decreases venous return and may lead to more blood loss. By reducing positive end expiratory pressure and using low tidal volume, venous return could be improved.
5. Controlled hypotension: mean arterial pressure should be maintained around 50–75 mmHg.
6. Antifibrinolytics: use of ethamsylate, tranexamic acid, and epsilon amino caproic acid in major surgical resection.
7. Hypothermia: Intraoperative hypothermia causes coagulation derangement and should be avoided.

18.8 Postoperative Strategies

1. Drain management: Drains are used to diminish haematoma and compression of vital structures. Drain blood can be reperfused within 6 hours if it is less than 1000 ml with or without processing.
2. Cell salvage: Perioperative cell salvage and reinfusion with or without washing reduces transfusion requirement especially in orthopaedic surgery.
3. Stop unnecessary anticoagulation and antiplatelet agents.

4. Avoid unnecessary postoperative blood sampling as it is a significant cause of blood loss.
5. Proton pump inhibitor prophylaxis reduces incidence of upper gastrointestinal bleed.
6. Withhold anticoagulant and use mechanical devices (graduated compression stockings, pneumatic compression device) for deep vein thrombosis prophylaxis if drain output is high.

18.9 Indications of PRBC Transfusion

1. Haemorrhagic shock with hemodynamic instability.
2. Acute anaemia with poor perfusion pressure leading to tissue hypoxia (oliguria or anuria, lactic acidosis, restlessness).
3. Serum Hb <7 to 8 g/dL depending on patient characteristics.

18.10 Restrictive vs. Liberal Strategy of Blood Transfusion

Restrictive strategy: Blood is transfused when patient's haemoglobin fall between 6 and 8 g/dL. It can be tolerated by healthy, young patients and not having cardiac disease. This strategy allows less allogenic transfusion and its associated complication.

Liberal strategy: Here blood is transfused at higher haemoglobin level of 9–10 gm/dL. This is followed in old, critically ill patients having poor cardiorespiratory reserve.

Restrictive strategy has no advantage over liberal strategy in terms of 30 days mortality in sepsis or septic shock. Restrictive strategy is as safe as liberal strategy in cardiac surgery and overall hospital stay is similar in both groups. In high risk patients undergoing major surgical resection, restrictive strategy should be used with caution. Liberal transfusion may be better in geriatric population. Thus overall condition of patient should be considered for transfusion strategy decision.

18.11 Blood Storage and its Effects

Blood is stored with citrate phosphate dextrose adenine. Some biochemical changes occur in stored blood over time. Anaerobic glycolysis and lactate production occurs in RBC resulting in acidosis. There is also reduction in 2, 3-diphosphoglycerate. This along with rising lactate causes cell membrane rigidity and predisposes RBC to haemolysis. Intracellular potassium got released in plasma. One unit of packed RBC usually raises serum haemoglobin by 1gm/dL in an average adult. When older blood is transfused, patient will not have incremental rise in haemoglobin. Old stored blood has detrimental effect on coagulation. This causes transfusion related morbidity, prolonged hospital stay and mortality.

18.12 Platelet Transfusion

Indications:

- Thrombocytopenia (<10,000/microlitre) even without bleeding.
- Thrombocytopenia <50,000/microlitre if actively bleeding.
- <100,000/microlitre if patient has CNS bleeding or polytrauma.

Platelet transfusions are contraindicated in setting of haemolytic uremic syndrome; heparin induced thrombocytopenia, thrombotic thrombocytopenia purpura, and disseminated intravascular coagulation unless life threatening bleeding is present.

18.13 Plasma Component Transfusion

18.13.1 Fresh Frozen Plasma (FFP)

- Given in bleeding patients due to coagulation disorder.
- In non-bleeding patient even with abnormal coagulation tests, FFP is not transfused prophylactically.

18.13.2 Cryoprecipitate

When FFP is thawed at 4 °C, insoluble material which is rich in plasma proteins factor VIII and fibrinogen comes out and called as cryoprecipitate. Cryoprecipitate may be given to replace factor VIII, von Willebrand factor, and fibrinogen. It is indicated mainly for bleeding patient with specific coagulation factor deficiency.

18.13.3 Transfusion Reaction

Transfusion reaction occurs most commonly due to clerical error leading to transfusion of blood to wrong patient. This could lead to ABO-incompatibility.

Before transfusing, properly check the blood bag and match the details of patient. For first 15 min, transfusion should be done slowly and monitor vitals, if there is no reaction, then transfusion should be completed within 4 hours of starting transfusion.

If a serious transfusion reaction is suspected (chest tightness, brownish urine, and hemodynamic instability), then immediately stop the transfusion and start resuscitation if needed. Send the remaining blood bag to transfusion laboratory for further management.

18.13.4 Summary

Surgical oncology procedures are time sensitive and preoperative optimization like correction of anaemia may not be feasible. Blood and blood products are life-saving when administered with due considerations and precautions. Allogenic blood transfusion is associated with morbidity and prolonged hospital stay and even linked with cancer recurrence in recent studies. So a balance approach needs to be taken for blood loss and its replacement in perioperative period of surgical oncology interventions.

Principles of Blood Products Management in Onco-surgeries

19

M. D. Ray

19.1 Introduction

Patients undergoing major onco-surgery may require blood and blood products in the perioperative period. The need for its replacement is primarily due to preoperative anemia which is common in cancer patients and due to bleeding and coagulopathy during surgery. Optimal blood and blood product replacement is paramount for an optimal perioperative outcome. The bleeding may be related to tumor biology, site, extent, preoperative cancer therapies (chemotherapy, radiation therapy, and immune-therapies), the extent of surgical dissection, perioperative metabolic, and homeostasis disturbances.

Anesthesiologists, surgeons, and critical care physicians have to coordinate to decide the need to administer blood products to patients undergoing onco-surgery. Despite a substantial amount of research on the biological consequences, and clinical impact of perioperative blood product transfusions in patients undergoing major onco-surgeries, no concrete indications or consensus guidelines exist. It has been acceptable conventionally to transfuse blood if hemoglobin <10.0 g/dL or the hematocrit <30% in elective surgeries. In 1942 this RBC transfusion trigger was proposed by Adams and Lundy. However, several pieces of evidence following that do not support a single transfusion trigger. Presently, the individualized need for blood transfusion remains an important concept rather than a single transfusion trigger especially in cancer patients, and may range 6.0 and 10.0 g/dL.

19.2 Why Blood in Onco-surgeries?

In oncology set up, the prevalence of anemia is seen in almost 30% to 90% of patients. Perioperative cancer-related anemia can result from diminished production, increased destruction, or loss of RBCs. Their production may be reduced due to chemotherapeutic agents, radiation therapies, chronic renal disease, iron deficiency, and myelodysplasia or bone metastasis. On cancer surgery, blood loss remains an important reason for anemia in the perioperative period.

The hemostatic function may be deranged in cancer patients because the tumor itself can induce activation of the coagulation system resulting in a chronic hypercoagulable state, a thrombolytic state, or a condition of chronic Disseminated Intravascular Coagulation (DIC). Thrombocytopenia due to treatment-related myelosuppression may be seen and associated with increased blood loss in the perioperative period. Other mechanisms of thrombocytopenia in this population include increased destruction

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(immune and non-immune), decrease production, sequestration, and dilutional. Dilutional thrombocytopenia (infusion of crystalloids and blood products) and DIC are the most common causes of a low count of platelets during and after cancer surgery.

19.3 Concerns Related to Blood Transfusion

Blood products are administered perioperatively to improve oxygen delivery (red blood cells [RBCs]) and/or to manage coagulopathies [fresh-frozen plasma (FFP), platelets, cryoprecipitate). Usually, allogenic blood transfusion remains the modality for transfusion. The blood transfusion may be associated with certain adverse events like febrile reactions, transfusion-related acute lung injury (TRALI), immunomodulation, etc. The transfusion-related infective concerns like hepatitis B, hepatitis C, human immunodeficiency virus (HIV) are also of concern. At times, life-threatening reactions do occur, and it has been estimated to occur in 1 in 1.5 lac patients transfused. The biological consequences of the administration of packed RBCs, FFP, and/or platelets are immune suppression due to transfusion-related immune modulation [TRIM] and can impact the patient in the short and long term. Blood transfusion is also expensive and related to multiple steps of its collection, testing, and then transfusion. The cost factors in limited sources should also be considered in addition to other infective and non-infective concerns.

19.4 Preoperative Assessment for Blood Replacement Related Issues

All patients must be assessed for the real need of blood or blood product transfusion in the perioperative period. A conscious decision should be based on a holistic assessment. Patients should be reviewed for the medical records for associated medical comorbidities, previous blood transfusion, recent treatments including medical therapy and drugs used. The history should include:

- Intake of the drug affecting coagulation – aspirin, warfarin, heparin, etc.
- Herbal supplements.
- History of congenital disorders related to coagulopathy.
- History of any bleeding or thrombotic disorders.

History evaluation should also be accompanied by physical examination and clinical signs like ecchymosis, petechiae, pallor. Based on history, specific laboratory investigations may be sought. Preferably, preoperative evaluation should be performed weeks before the procedure so that patients can be prepared properly before the procedure.

19.4.1 Onco-surgeries and Hemoglobin

Although healthy subjects can tolerate hemoglobin (Hb) values below 6 g/dL, older patients and those with significant comorbidities like cardiac diseases need to have Hb of 8 g/dL or greater. So these limits may be the deciding factor of preoperative optimization and the need for blood transfusion. Also, other factors like the urgency of surgery, the type and extent of surgery also need to be considered before the decision of blood transfusion are considered.

19.4.2 Onco-surgeries and Platelet

The indications for platelet administration to patients undergoing oncological procedures depend on the number of circulating platelet and the clinical judgment of perioperative physicians. In patients with hematologic malignancies, the trigger threshold for prophylactic transfusion is 20,000 platelets/μL; however, it has been indicated that in patients not taking an aspirin a count of 10,000 platelets/μL could also be used as a trigger. It is commonly accepted that patients with 50,000 platelets/μL or more could have surgery “safely”; unless other disorders in the coagulation system exist including the presence of platelet inhibitors or consumption coagulopathy (DIC) and do not involve

high-risk surgery for closed cavity bleeding (i.e., neurosurgery).

19.4.3 Onco-surgeries and Fresh-frozen Plasma (FFP)/ Cryoprecipitate

Coagulation disorders can be found in patients who undergo cancer-related surgery. Blood products such as FFP and cryoprecipitate are commonly administered to cancer patients to prevent bleeding and correct abnormal coagulation in those acutely bleeding. In the preoperative period, patients may present with abnormalities in the hemostasis due to any drug intake which affects coagulation or may be related to cancer therapy which causes myelosuppression. Also, cancer therapy causes immunosuppression with the risk of sepsis, which in turn affects coagulation. Consensus on the trigger "threshold" to start the administration of products like FFP or cryoprecipitate is still lacking in the surgical oncology literature; however, it is worth remembering that clinical studies demonstrate that the expected correction (per unit of FFP administered) in the international normalized ratio is minimal when pre-transfusion values are minimally elevated. This suggests that patients who benefit from the administration of FFP are those who present serious coagulation abnormalities.

19.5 Preoperative Optimization

Preoperative hematological optimization improves the overall outcome of the patient in the perioperative period. Various options include:

19.5.1 Therapeutic Interventions for Anemia

Anemia is defined as a hemoglobin level below:

- Children below 5 year—11.0 g/dL.
- Children aged 5–12 years—11.5 g/dL.
- Children aged 12–15 years—12.0 g/dL.
- Nonpregnant women—12.0 g/dL.
- Pregnant women—11.0 g/dL.
- Men- 13.0 g/dL.

Anemia affects the overall outcome in the perioperative period with increased length of hospital stay, infection rate, and even mortality. But as the onco-surgery is time-sensitive surgery, the surgery in patients with reduced hemoglobin levels than normal has to be undertaken. Erythropoietin injection and iron supplementation are very effective in reducing allogeneic blood transfusions. Administration of iron preparation should be considered to improve hemoglobin levels as iron deficiency is quite common in cancer patients especially in developing countries.

19.5.2 Advice Regarding Ongoing Anticoagulants and Antiplatelet Agents

Patients with ongoing treatments with drugs affecting coagulation should be assessed for thrombosis vs. bleeding before blood product transfusion. Patients may be categorized for risk of thrombosis if they had venous thromboembolism in the last 3 months or the presence of a prosthetic heart valve. These patients would require bridge anticoagulation and heparin may be required as the bridging therapy. Usually, the low molecular weight heparin (LMWH) remains one of the options for such therapy. INR is the monitoring tool and the target INR remains to be 2–2.5 when warfarin is being used in at-risk patients. When the patient receives warfarin for management of atrial, then during surgery use of bridging anticoagulation with LMWH is not routinely recommended. In surgical emergencies, where sufficient time for withdrawal of warfarin is not possible, then reversal of warfarin may be done by administration of prothrombin complex concentrate (PCC) 50 IU/kg or by fresh-frozen plasma. Another option includes the administration of intravenous vitamin K (10 mg).

Antiplatelet drugs inhibit the platelet function for its lifetime irreversibly. The functional platelets are replenished slowly and at the rate of around 10% per day and depend on the type and

dose of the individual antiplatelet drug. Aspirin acts by inhibiting platelet function by blocking thromboxane and may be continued till the surgery except in some surgical intervention with the risk of bled like intracranial surgery. In these situations, it may be stopped for 5 days before surgery. Clopidogrel is a longer-acting agent from the thienopyridine class of antiplatelet agents. It should be stopped 7 days before surgery. The appropriate timing, now a day, may also be assessed using point-of-care testing for platelet function. A similar principle is applicable for newer agents like prasugrel and ticlopidine.

Patients with cardiac stenting and on antiplatelet drugs need to be assessed for coronary thrombosis and weighed against the risk of bleeding during surgery. After a bare-metal stent placement elective surgery should be avoided for 4–6 weeks and after the drug-eluting stent (DES), it should be avoided for 6 months. But a time-sensitive surgery may be performed after 3 months of DES placement if needed. The above mentioned time durations were decided to depend upon the requirement of minimum duration of uninterrupted dual antiplatelet therapy. If a patient is on dual antiplatelet therapy elective surgery is contraindicated.

The newer novel oral anticoagulants being used clinically are direct thrombin inhibitor (e.g. dabigatran) and direct factor Xa inhibitor (rivaroxaban, apixaban). These have a fast onset of action; short half-life and predictable pharmacodynamics. Their metabolism is affected by renal dysfunction. Tests for its activity is not available or these agents. Dabigatran should be stopped 5 days before surgery while other drugs need to be stopped before 2 days. For urgent reversal, PCC 50 IU/kg may be considered.

19.5.3 Autologous Blood Donation

Autologous donation before surgery is a good option and avoids allogenic transfusions rates. It may be used preoperatively when required. However, sufficient time is required before surgery and donation done at intervals to provide time for hematopoietic before surgery.

19.6 Prophylactic Strategies to Reduce Blood Loss

Various strategies are available and effectively being used in the perioperative period to reduce intraoperative allogeneic transfusion. Blood loss can be reduced by institutional protocols and triggers of blood transfusion, use of antifibrinolytics, and techniques of hemodilution like acute normovolemic hemodilution (ANH) for reducing actual blood loss.

19.6.1 Multimodal Protocols or Algorithms

The multimodal protocol is a standard operating procedure adopted by any institute that will ensure uniform management for blood transfusion-related concerns in the perioperative period. These strategies include various options and plans for reducing blood loss and thus avoid the needs of blood transfusion. The use of point-of-care testing also aids in the appropriate decision of need and type of blood transfusion.

The two types of blood management strategies restrictive and liberal strategies are described. But the definition of this strategy is not very clear. In a restrictive strategy, transfusion is administered with less than 8 g/dL of Hb and hematocrit value drops below 25%. Restrictive blood transfusion has been reported to reduce blood need as compared to liberal transfusion without affecting patient overall outcome and thus acceptable in cancer surgeries. A massive transfusion protocol may be needed in certain patients wherein perioperative life-threatening bleeding occurs. It is essential for oxygen delivery to tissues and thus optimizes outcomes to reduce the side effects of dilutional coagulopathy and hypovolemia. Cut off the level of hemoglobin that should trigger red cell transfusion may be any value between 6 and 10 g/dL. Not just the Hb value but also clinical signs of oxygen delivery should be considered while deciding transfusion. Point-of-care testing like TEG and ROETM are included in different protocols.

19.6.2 Use of Antifibrinolytics

Certain antifibrinolytics agents like tranexamic acid have been used to reduce blood loss as it prevents impairment of fibrinolysis by inhibiting plasminogen activation. The recommended dose for adult patients is 1 gm bolus slow intravenous administration. It may be repeated to be administered as a continuous infusion as well. ε-aminocaproic acid (EACA) is another antifibrinolytics effective in the perioperative period.

19.6.3 Acute Normovolemic Hemodilution (ANH)

ANH is one of the strategies to reduce the need for blood transfusion intraoperatively. Understanding of fluid transfusion should be done timely for its optimal effect along with cardiovascular status.

19.7 Strategies for Management of Blood Loss

Various strategies need to be planned on an individual basis for perioperative management of blood loss.

19.7.1 Transfusion of Allogeneic Blood

The red blood cells are transfused whenever hemoglobin level drops below the predetermined cutoff level. If as per assessment, it is found that only one unit of RBC needs to be transfused, that transfusion may be avoided. But in case of continued blood loss, as the tissue perfusion is affected, RBCs needs to be replaced. Leukocyte-reduced blood is associated with reduced complications in comparison to normal allogeneic blood transfusion. In case of life-threatening hemorrhage immediate, group O red cells for transfusions is required and should be available. Transfusion-related adverse effects may have dreaded outcome. Appropriate identification of patients for a blood transfusion should be thoroughly checked and documented.

19.7.2 Perioperative Patient Monitoring

19.7.2.1 Blood Loss Assessment

Blood loss must be assessed at each step of the surgery and continued postoperatively. Any acute blood loss like some bleed during a surgical intervention should be appropriately monitored and assessed for its systemic impact. During surgery blood loss should be assessed from drains, sponge used, and surgical field visual assessment. This may be supplemented with laboratory investigations and assessing for signs of lesser tissue oxygen delivery like capillary fill time. Measurement of Hb and hematocrit may be measured but may not be good indicators of acute blood loss.

19.7.2.2 Monitoring for Perfusion of Vital Organs

Vital organ perfusion is a good indicator of the adequacy of blood and cardiovascular status. In addition to monitoring like pulse rate (and volume), blood pressure, oxygen saturation, other monitoring of values like urine output, invasive monitoring (arterial blood gas analysis) provides a useful indicator of cell perfusion.

19.7.2.3 Monitoring for Coagulopathy

Coagulopathy is monitored with the investigation including platelet counts, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels depending upon the clinical status requiring coagulation assessment. However, these tests may not be reliable during acute hemorrhage. Point-of-care (POC) testing has emerged as a better tool for coagulation assessment and truly reflects various aspects of coagulation. So POC testing is becoming increasingly popular. Nowadays, for Hb concentration blood gas analysis and the HemoCue are commonly used POC testing. Presently, two commercially available method for POC coagulation

testing are thromboelastometry (ROTEM) and thromboelastography (TEG). This directs a more appropriate assessment of specific blood products to be transfused and has been found to decrease the requirement of blood in various clinical scenarios.

19.7.2.4 Monitoring Blood Transfusion-related Side Effects

Monitoring of the adverse events related to blood transfusion needs to be done and its appropriate management, if required. The ABO incompatibility is a dreaded issue and all precautions for its prevention and timely recognition is paramount. The manifestations include oozing from the surgical site, cardiovascular collapse, and hemoglobinuria. The citrate toxicity may be seen in massive blood transfusion and manifests as hypocalcemia. In cases, if any such signs and symptoms occur during a blood transfusion, further blood transfusion needs to be stopped followed by supportive treatment along with appropriate monitoring of clinical signs and investigations. The blood bank needs to be notified for further assessment of the actual cause of adverse events. Further management includes the administration of drugs like antihistamine or steroid. Also, adrenaline may be required in life-threatening adverse events.

19.7.3 Management of Massive Bleeding

Massive hemorrhage is "defined as loss of > one blood volume within 24 h (around 70 mL/kg); 50% of total blood volume lost in <3 h, or bleeding over 150 mL/min." Such a scenario may be manifested by hemodynamic changes starting with increasing heart rate and subsequently falling blood pressures. Also, signs of organ perfusion deficit will become obvious and urine output remains a good indicator. The blood transfusion protocol should be initiated with the appropriate administration of blood-based on some end goal and using objective testing.

19.7.3.1 Initial Resuscitation

Resuscitation should be as per institutional protocol. Cancer surgery should follow the principles of avoiding blood transfusions to the minimal. In cases of massive bleed and hemodynamic instability, the fluid should be immediately administered until blood products are being arranged. Patients should be transfused with RBCs, platelets, and FFP based on the need of the patient. This should be accompanied by POC testing to guide further specific blood product transfusion. Group O red cells may be transfused if the time for testing is an issue for a life-threatening to bleed. Females of age bearing a child should receive O Rh-negative red cells to prevent cross-sensitization.

19.7.3.2 Hemostatic Resuscitation

Hemostatic resuscitation refers to optimized tissue perfusion along with an appropriate clotting process. Based on objective testing, appropriate blood products like RBCs, FFP, platelets needs to be administered in addition to hemostatic agents.

19.8 Biological and Clinical Consequences of Perioperative Blood Transfusion

The blood transfusion is associated with profound negative effects on the immune system. At the cellular level, some of the features of TRIM are (a) a reduction in the function of natural killer (NK) cells, (b) a decrease in the proliferation of T and B lymphocytes, (c) induction of T regulatory cells, and (d) a decrease in maturation and antigen-presenting activity of dendritic cells. To further illustrate some of the effect of BT on cellular immunity, the administration of allogeneic blood to patients undergoing gastrointestinal surgery caused a significant decrease in the number of NK cells that was not observed in patients who received autologous blood. Transfusion-related immune suppression can be mechanistically divided into two different types: (1) donor-specific transfusion and (2) "general-

ized" transfusion-related immune suppression. The former primarily suppresses adaptive immunity (lymphocytes T and B) and has been related to microchimerism, veto cells, and cytokines; in contrast, the "generalized" form appears to be mediated by macrophage and neutrophils and has a significant suppressive impact on the innate immunity. It has been proposed that infections and cancer recurrence would be a consequence of the "generalized" transfusion-related immune suppression rather than the donor-specific form. The timing of transfusion may also have different effects on the inflammatory and immune response. Thus, when blood products are administered during or immediately after surgery ("second hit"-first hit being surgical trauma), the so-called systemic inflammatory response syndrome can be further exaggerated by transfusions delaying mechanisms of resolutions of inflammation, which can also participate in the pathogenesis of transfusion-related adverse outcomes.

The administration of blood products might promote tumor growth and spread not only by inducing immune suppression but also facilitating the proliferative and metastatic properties of cancer cells via the action of angiogenic and oncogenic factors accumulated during the period of storage. It has been indicated that during storage, 10–15% of the stored platelets become active and able to release growth factors. TGF-β is one of the stimulating factors that is found in high levels in platelet concentrates; in vitro studies indicate that when supernatants of stored blood products are added to cultured cancer cells, the growth of these cells is stimulated at a faster rate than those non-treated with supernatant. Similarly, the supernatant of stored blood products promoted the cell growth (vascular mimicry) of head and neck cancer cells, which was inhibited when the cancer cells were cultured with the anti-VEGF antibody.

Several authors have tried to demonstrate causality or association between the administration of blood products in the perioperative period and cancer recurrence or cancer-related mortality. In 2006, a meta-analysis demonstrated that transfusions of RBCs were an independent factor for colorectal cancer recurrence. More recently, a larger meta-analysis confirmed the above finding. That study showed that transfused patients had a higher risk for all-cause mortality, cancer-related mortality, and recurrence-metastasis-death compared to non-transfused controls. In colorectal and hepatocarcinoma patients it is reported that there is more risk of an adverse outcome in those patients with ampullary cancer of the pancreas who received intraoperative allogeneic BTs compared to non-transfused patients. The results of studies in gynecological cancers and cystectomies are mixed. Cancer recurrence has been associated with allogeneic blood transfusion. Currently, there is no compelling evidence to conclude that the transfusion of FFP or platelet concentrates on patients undergoing cancer surgery worsens oncological outcomes.

19.9 Summary

Blood and blood products are a precious commodity and need to be administered cautiously. The point care of testing appropriately guides the need for specific blood products. Surgical oncology interventions are time-sensitive surgeries and hence preoperative optimization with regard to blood may not be feasible. Also, blood transfusion has been associated with cancer recurrence in recent reports. So a balanced approach needs to be taken for blood loss and its replacement in the perioperative period of surgical oncology interventions.

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20 Management of Surgical Wounds, Wounds Healing and Burst Abdomen

M. D. Ray

20.1 Introduction

A wound can be defined as a disruption or break the integrity of the normal structure and function of the skin and its architecture.

Surgical wound infection is called surgical site infection or wound dehiscence. It is a major concern for surgeons. So, management of surgical wound may be considered the most important aspect of management of surgical patients.

20.2 Basic Principles of Wound Management

The basic principles of surgical wound management are the following.

1. Removal of devitalized tissue and tissue tension.
2. Prevention of infection or control of infection.
3. Maintain vascularity, prevent venous and lymph stasis.
4. Elimination of dead tissue and control of exudate.
5. Maintenance of body fluid electrolytes balance, nutrition and haemoglobin.
6. Control of underlying diseases like diabetes, hypertension, malignancy, etc.
7. Correction of General factors like age, chronic illness, malnutrition, metabolic diseases, Immunosuppressive disease, steroid intake, self-care.
8. Last but not the least—be cost efficient.

20.3 Stages of Wound Healing: 5 Stages

1. Inflammation: last for 4–6 days (Exudative phase),
2. Granulation and organization : 7 days–6 weeks(Proliferative phase). Owing to Collagen & fibroblast activity,
3. Epithelialisation,
4. Scar formation and resorption and
5. Maturation 7 weeks–2 years (Remodelling phase)

(80–90% Post op wound achieves 80–90% of its final strength in 30 days).

20.4 Pneumonic ME Foreign Body

Margin—junction between normal epithelium and ulcer.

Edge—Area between margin and floor of the ulcer.

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Floor—Expose surface of the ulcer.

Base—on which the ulcer rests and which cannot be seen only will be felt.

The basic difference between wound and ulcer is, wound is always after some kind of trauma but ulcer may be spontaneous otherwise feature wise both are the same.

20.5 Different Types of Edges to Diagnose the Types of Ulcer

1. *Undermined edge*—The subcutaneous tissue being destroyed faster than destroying skin.

Example—ulcer for TB, amoebic ulcer, ulcer for pressure necrosis.

2. *Punch out edge*—The edge is at the right angle to the skin surface.

Example—Trophic , Diabetic, Syphilitic, Leprotic.

3. *Sloping edge*—All healing ulcer has a slopping edge. Reddish /purple in colour.

Example—Surgical wound, Traumatic, Ischaemic—Venous & Arterial

4. *Everted / rolled out edge*—Growing portion of the edge heaps up and spills over the normal skin yields this kind of everted edge.

Example—Ulcer for Squamous cell carcinoma, Adenocarcinoma

5. *Raised with beaded edge*

Cause—Invasive cellular disease and necrosis at the centre.

Example—Basal cell carcinoma (Rodent ulcer)

20.6 Types of Surgical Wounds

1. *Clean wound*

Example—Surgical incision lymph node biopsy, excision of a lump, etc.

Chance of development of infection is up to 2%.

Single dose of injectable antibiotic is recommended.

2. *Clean contaminated wound*—Any kind of bowel surgery, hepatobiliary tract surgery, appendicectomy, etc.

Chance of infection is 10–15%.

Maximum three dose of Injectable antibiotic is recommended.

3. *Contaminated wound*—Burst appendicular abscess, perforated bowel, accidental wounds, etc.

Chance of infection development is 15–35%.

Three doses of antibiotics recommended. If any sign of infection, continue it for 5 days.

4. *Dirty wound*—drainage of abscess, pyocele, empyema, faecal peritonitis (Fig. 20.1)

Chance of infection is very high.

Complete course of antibiotic as per culture sensitivity is recommended.

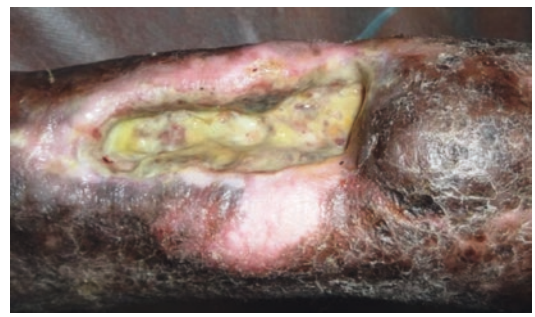

Fig. 20.1 Dirty wound

20.7 Features of Wound Healing

Namely three zones are there in a healing ulcer—(Fig. 20.2)

1. Red zone due to granulation tissue (Fig. 20.3).
2. Blue zone suggestive of progression of healing.
3. White zone suggestive of normalization of the skin.

20.8 Management of Surgical Wounds

Basic principles of wound management are as follows.

1. Wound Debridement.
2. Topical therapy.
3. Control of infection.
4. Wound coverage.
5. Dressing.
6. Adjunctive therapies.

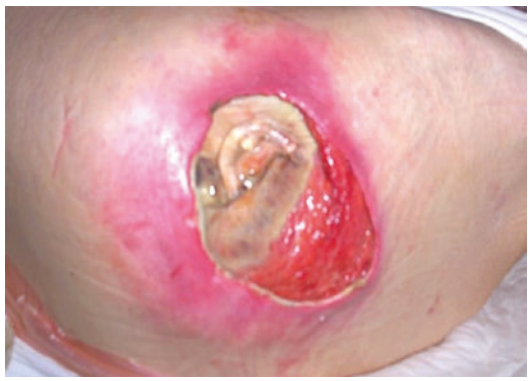

Fig. 20.2 Red, Blue and White Zone of wound healing

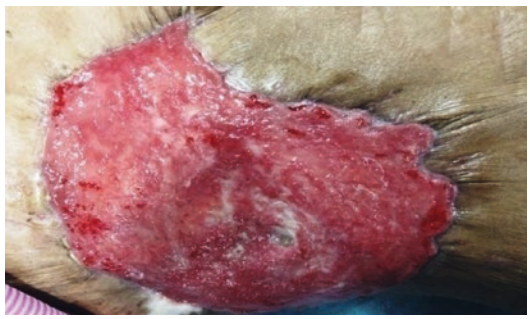

Fig. 20.3 Healthy granulation tissue

20.9 Wound Debridement

Introduction: Debridement of devitalized tissue, contaminated suture material is the basic step of wound management.

Serial debridements are required to promote healing of wound. Especially for chronic wounds in which there is accumulation of devitalized tissue, decreased angiogenesis, excessive exudate, biofilm (bacterial overgrowth on the wound surface) formation or hyperkeratotic tissue.

1. *Surgical Debridement*: Sharp excisional debridement to remove the devitalized tissue and biofilm, thereby stimulating wound epithelialization and growth of granulation tissue. Debride wound edge, deep tissue and always send it for culture and sensitivity to assess for infection and this will guide in administration of antibiotics.
2. *Irrigation*: Irrigation with normal saline decreases the bacterial load and loosens the devitalized tissues and slough. Even tap water could be used for wound irrigation. No role of diluted povidone iodine or other antiseptic solutions like Chlorhexidine because it has minimal action against bacteria with dilution and could potentially impede the growth of normal tissue thereby wound healing.
3. *Biological debridement*: Additional method of debridement using larvae, green bottle fly, sericata, medical maggots. These therapies are usually used where surgical debridement is not possible.
4. *Enzymatic debridement*: Exogeneous enzymatic agents like collagenase, may promote endothelial cell and keratinocyte migration thereby stimulating angiogenesis and epithelialisation.

20.9.1 Topical Therapy

I. Some studies suggest that topical therapy of different growth factors may enhance wound healing.

The recommended growth factors are:

1. Platelet derivative growth factors (PDGF) (Becaplermin):
   It is a kind of gel preparation that promotes cellular proliferation and angiogenesis.
2. Epidermal Growth factor (EGF).
3. Granulocyte-macrophage colony stimulating factor (GM-CSF).

II. *Antimicrobial agents*: Most of the topically applied antiseptic and antimicrobial are locally irritant and delaying healing rather promoting. Few agents like iodine based and silver based agents show potential benefits.

- *Iodine based*: Cadexomer iodine (Iodosorb)—study shows that it reduces bacterial load and promoting healing. It is bactericidal to all Gram positive and Gram negative bacteria.
- *Silver based*: Silver dressing may decrease heavy bacterial surface contamination thereby promotes healing. Many studies show controversial results for the use of topical Silver ointment for wound management.
- *Honey*: It has been described since ancient time for wound management. Owing to its high osmolarity, it has a broad spectrum antimicrobial activity. It contains high concentration of H_2O_2. Systemic reviews highlighted that variety of wounds heals with honey. It is available as Gel, paste, colloid dressings, etc.

Beta blockers: Beta blockers may stimulate Keratinocytes, influence its activity, maturation and migration as keratinocytes have beta-adrenergic receptors.

Timolol is commonly used topical beta blocker.

Control of Infection: Almost all wounds are colonized with microbes but not invariably infected. No clinical evidence supports antibiotic therapy as 'Prophylaxis' in non-infected long standing wounds. Definitely if any sign of infection like cellulitis, lymphangitis, purulent discharge or any systemic manifestation like fever chills, nausea, leukocytosis, low BP or hyperglycaemia, systemic antibiotics are required. Start broad spectrum antibiotics empirically after sending the discharge for culture sensitivity. Antibiotics may be changed as per culture sensitivity. Glycaemic control promotes wound healing as particularly in immunocompromised state classical systemic signs of infection may not be manifested on initial presentation.

Commonly used Antibiotics to cover:

1. Gram positive aerobes – Cephalosporins.
2. Gram negative aerobes – Aminoglycosides.
3. Gram negative anaerobes—Metronidazole / Vancomycin, etc.

20.9.2 Wound Coverage

Skin grafts: Commonly used for covering of the large wound which is long standing and in non-healing stage.

SSG, i.e. Split Skin Graft is commonly transplanted to cover the wound so-called Autograft.

Split Skin grafts include epidermis and partial dermal thickness whereas full thickness grafts consist of the entire dermis (Fig. 20.4).

Full thickness grafts are used commonly on well vascularized and small wounds. The sites of full thickness grafts harvesting are lateral thigh, groin, lower abdomen, lateral chest (Fig. 20.5).

Split skin grafts are preferred because these are more fragile, contract more during healing, prevent fluid and electrolytes loss and control infection (Figs. 20.6 and 20.7).

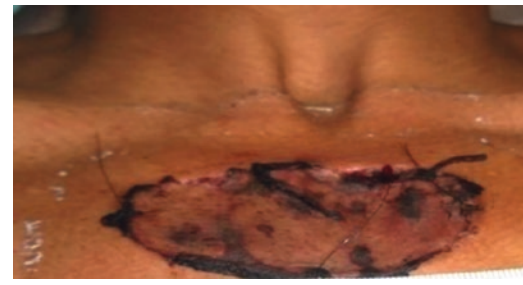

Fig. 20.4 Grafted skin

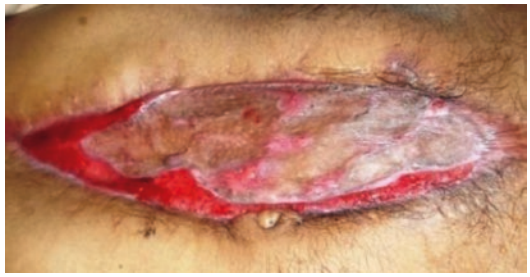

Fig. 20.5 Graft uptake

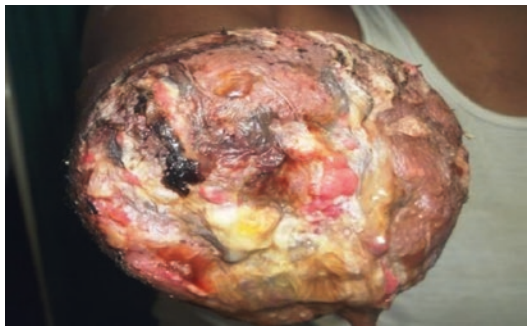

Fig. 20.6 Graft loss

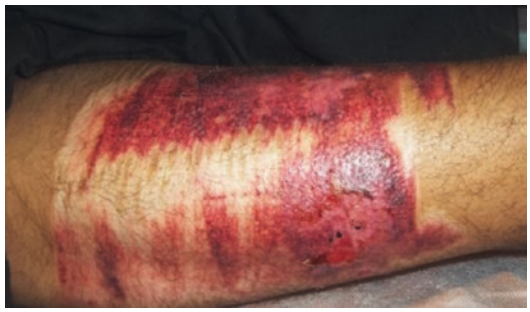

Fig. 20.7 Healed donor site

Cell based coverage: One layer of live allogenic cells can be used in chronic wound where additional cells and growth factors are deficient.

Alloderm—made of decellularized allogenic dermal component and Integra(a bovine collagen based dermal matrix). It has been used successfully for treating chronic wounds.

Wound dressing: Appropriate dressing can have a significant impact on the promotion of wound healing. Dressings manage the moisture level in and around the wound, control pain, odour, discharge, etc. We should evaluate our individual wounds and choose the best dressing for the wound.

20.9.3 Commonly Use Agents for Different Stages

Hydrogel—for debridement stage.

Foam/low adherence—for granulation stage.

Hydrocolloid/low adherence—for epithelialization stage.

Moisture is an important supporting factor of wound healing. Studies suggest that dressed wounds heal 20–40% more rapidly than opened wounds, because (1) in moist environment epidermal cells migrate effectively for rapid healing, (2) exposes to its own secretion, rich in platelet derived growth factors, fibroblast growth factor and metalloproteases, promotes wound healing.

But in chronic wound, the secretions are rich in cytokines which inhibits proliferation of fibroblasts, thereby occlusion of chronic wound is not beneficial for wound healing.

Various studies also suggest that occlusive dressings are associated with less prominent scar formation.

20.9.4 An Ideal Dressing

- Protect the wound from further damage.
- Maintain moist environment.
- Absorbs excessive secretion.
- Prevents bacterial invasion and spread.
- Reduces dead space.
- Debrides necrotic tissues and protect the surrounding viable tissue.
- Minimize pain and oedema.
- Maintains haemostasis.
- Cost effective.

20.9.5 Common Dressings

Saline soaked gauge is ideal for dressing not the dry gauge. Wet to moist gauge dressings are useful for large soft tissue defects till the closure.

Sometimes semi open dressing—consisting of mesh gauge impregnated with petroleum, paraffin wax/ointment, etc. These are relatively less expensive and easier to apply.

Different layers of dressing have different properties(occlusive properties, absorptive capacities, bacteriostatic activity, conformability/).

It includes (a) films, (b) foams, (c) hydrogels, (d) hydrocolloids, (e) alginates.

Films: Polymer films like tegaderm, bioclusive, blisterf, cutifilm, etc. are transparent sheets of synthetic self-adhesive dressing which are impermeable to larger molecules including protein, bacteria, etc. Studies indicate that these film dressings provide fastest healing rates, lowest infection, and cost effective, so these are widely used now a days.

Foams: it is a kind of film dressing with additional layer with increased absorbency. It consists of two layers—a hydrophilic silicon or ploy urethane based foam that lies over the wound surface and a hydrophobic gas permeable sheet that can prevent leakage and bacterial contamination.

In compare to films, better healing occurs in foams dressing (Fig. 20.8).

Hydrocolloids: This dressing material consisting of gel or a foam on a self-adhesive poly urethane film. Colloid components trap the exudate and create moist environment. Bacteria and debris also trapped and it can pack the wound like Duodenum dressing.

Hydrogels: These are matrix of various synthetic materials—the inner layer of two is placed over the wound and the outer layer is removed to make the dressing permeable to minimal secretions. It is usually used for dry wounds (Fig. 20.9).

Fig. 20.8 Foam

Fig. 20.9 Hydrogel

Hydroactives: A poly urethane matrix that combines the properties of a gel and a foam. It selectively absorbs excess secretions leaving behind protein and growth factors behind thereby promote the healing.

Alginates: Natural complex of poly saccharides from various types of algae, insoluble in water and commonly used in more exudative wounds.

20.10 EUSOL (Edinburg University Solution of Lime)

EUSOL is an antiseptic solution made from chlorinate lime and boric acid used in treating wounds. To make 1 l of solution 12.5 g of bleaching powder and 12.5 g of boric acid is mixed in distilled water. The solution has a pH range 7.5 to 8.5.

Mechanism of action: It acts by the release of nascent chlorine which in turn acts as a desloughing agent. It is also effective against Pseudomonas. It should be diluted before use. It may impair wound healing as in tissue cultures it is shown to kill neutrophils, fibroblasts and endothelial cells. It helps in removing slough and promoting granulation tissue. It is useful in diabetic, ischemic ulcers, burn wounds.

Oxum: Oxum is a stable, non-corrosive and non-flammable solution that has bactericidal, sporicidal, fungicidal and virucidal action and is a ready to use solution that requires no mixing or dilution. It is a super oxidized solution. Super

oxidized solutions are electrochemically processed aqueous solutions manufactured from pure solutions which is rich in reactive oxygen species with neutral pH and longer half-life (>12 months). It contains Hydrogen peroxide (H_2O_2), Ozone (O_3), Oxidized solution (H_2O), sodium hypochlorite (NaOCI), Hypochlorous Acid (HOCI), Chlorine dioxide (ClO_2), Sodium chloride (NaCl), Sodium hydroxide (NaOH) and Sodium Carbonate (Na_2CO_3).

20.11 Mechanism of Action

By electrolysis, molecules in the solution are broken and release free radicals and ions. The formed free radicals react rapidly with the bacterial cell wall proteins and denature them. They create an environment that causes direct difference in osmolarity between ions in solution and cell. This osmolarity difference destroys single celled organisms not the multicelled organisms, showing sparing effect on host tissues. They also exhibit anti-inflammatory properties.

Many studies have been conducted which have proved its efficacy and safety in diverse conditions such as diabetic foot ulcer, venous stasis ulcers, bed sores, burns, cuts, absasions, postoperative infective wounds, cellulitis and abscesses.

20.12 Role of Wound Closure

Primary closure is always better for wound healing either by suture or staple.

In delayed primary closure, skin edges are opposed following an interval ensuring that there is no infection at the wound.

Chronic wound should not be closed primarily.

Negative pressure wound therapy or Vacuum Assisted Closure (VAC) enhances wound healing by (1) reducing oedema, (2) enhancing circulation and (3) increasing the rate of granulation tissue formation. Wound manager acts under a controlled sub-atmospheric pressure with a foam dressing. It is usually apply for a large non-healing wound.

20.13 Adjunctive Therapy: Hyperbaric Oxygen Therapy (HBOT)

HBOT induces hyperoxia which improves endothelial progenitor cells mobilization. These progenitor cells play an important role in wound healing.

The HBOT is not targeted to the wound site. HBOT is implemented in a specialized chamber for proper monitoring of the patients. The chamber pressure to be maintained 2.5–3 atmospheric pressure. Daily 2 h for 20–30 day, may be more sittings, HBOT required for the healing.

It is used in the therapy of both acute and chronic wounds. To tell the truth, there is no clinical study to support the routine use of the therapy especially used for chronic diabetic ulcer.

Seizures, pneum0thorax may be serious consequences of this therapy.

Other therapies like low frequency ultrasound, electrical stimulation, phototherapy have been used in different varieties of chronic wounds like bed sore wounds, venous ulcer, etc.

20.14 Management of Very Specific Wounds

I. Malignant wounds—ulcerated/fungating: It is hard fact that there is no specific guideline for this kind of wounds. The question of wound closure is generally not possible!

In this kind of wound basic principle of management are -

1. Necrotic debris/ devitalised tissue to be removed regularly.
2. Non adherent dressing can be placed directly or absorptive foam dressing can be placed over non adherent dressing.
3. Analgesic ladder as per WHO starting from PCM to Morphine to control cancer related pain.

4. Control of infection and odour by mechanical debridement. It also reduces microbial bio burden.
5. Oozing from ulcer surface to be controlled with topical haemostatic agents, Silver Sucralfate ointment or elastic bandage to create gentle pressure.

   Local anaesthetic agents like epinephrine even hand held cautery may be useful.
6. Treatment of underlying causes are important aspects of management.

20.15 Pressure Sore/Ischemic Ulcer

1. Debridement of devitalized tissue.
2. Change of posture 2 hourly/ Air mattress.
3. Ensure haemoglobin is above 10 gm/dl.
4. Maintain nutrition.
5. Place inflated rubber tube to prevent further pressure over the wound.

20.16 Few Important Points to Remember

1. In a word for prompt wound healing (i) debridement of the wound, (ii) maintain good vascularisation to the wound, (iii) prompt control of infection and (iv) keep the wound under moist environment.
2. Sharp surgical debridement always far better than non-surgical methods for initial phase.
3. Dressing is an important aspect of wound healing that should be chosen appropriately to manage dead space, control exudate, prevent bacterial overgrowth, reduce pain during dressing and cost effectiveness.
4. Maintain nutrition, adequate glycaemic control, fluid electrolyte balance.
5. Primary and delayed primary closure of wounds—wound is closed primarily if no contamination is there within 6 h of trauma but in case of chronic wounds let the oedema and inflammation subside, then delayed primary suturing can be done usually after 3–10 days.

   Secondary suturing done 10–14 days after settling of infection. In case of burst abdomen secondary suturing done immediately if no sign of infection is there otherwise allow the wound to heal by secondary intension. Correct the incisional hernia if develops later.

   Before suturing, injury to deeper structures to be excluded.

   Suture to be removed on due time, for e.g. face 4 days, neck 5–6 days, chest 10–12 days, lower limb 14–16 days. Tension suture to be removed in 20–21 days.

20.17 Management of Burst Abdomen

Burst abdomen continues to be a major complication of abdominal surgery, associated with high morbidity and mortality up to 40% and 6%, respectively.

It occurs usually between 7 and 14 days in postoperative period. Serous discharge (so-called salmon pink) usually preceded by up to 85% cases (Fig. 20.10).

Factors associated with burst abdomen- Male to female ratio 2:1, obesity, emergency operation, haemodynamic instability, malnutrition, low albumin level, immunocompromised state. Midline incision has more chance than transverse incision as midline incision is non-anatomic.

- Contraction of abdominal wall laterally directed tension on the closure. Suture material cut through by separation of the transversely oriented fibres.
- Continuous closure technique with non-absorbable monofilament is safe, effective in compared to others.
- Follow the rule of 1, 1 cm apart, 1 cm from the edge and 1 cm depth into tissue is still considered as a golden rule to prevent burst abdomen!
- Suture length to wound length should be 4:1 or greater. A ratio <4:1 increases the risk of wound dehiscence and incisional hernia later.
- Abdominal binder helps to prevent wound dehiscence to minimize the laterally directed

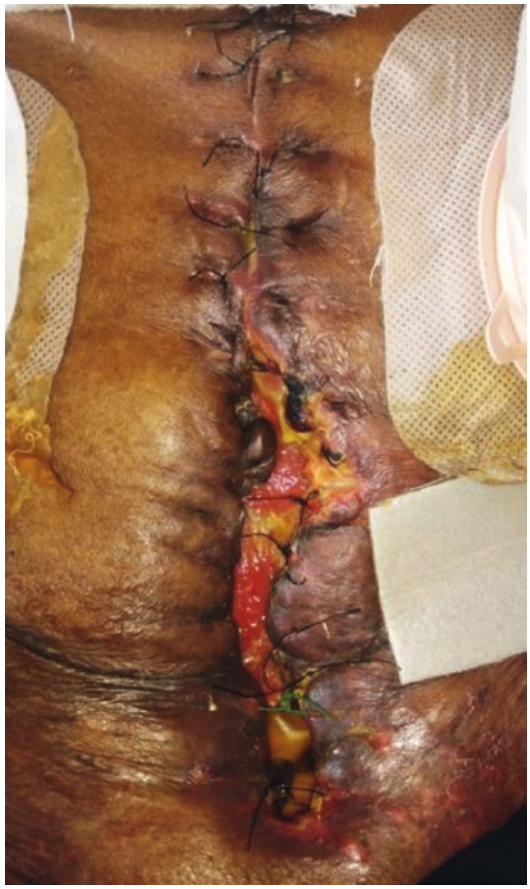

Fig. 20.10 Serous discharge—preceded burst abdomen

tension caused by post op muscle contraction of the abdomen.

- If burst abdomen develops in the absence of gross infection, immediate resuturing (usually with a mass closure) with the placement of deep retention sutures without any tension is preferred.

Take all layers except skin with no. I, Prolene/monofilament, 3 cm apart. Each suture should pass through a 4–5 cm plastic/rubber tube to prevent suture erosion into the skin and to be left in place for 3 weeks.

In case of difficult abdomen (wide gap due to excessive contraction of abdominal muscle, sepsis, retroperitoneal haematoma, loss of abdominal wall tissue due to necrosis), forced closure may lead to abdominal compartment syndrome.

Management of such wounds include (1) Infection control, (2) regular cleaning/irrigating the wound, (3) normal saline soaked gauge dressing, (4) improve general condition.

If possible close the skin edge only after ensuring infection control and allow it for secondary healing. Tackle hernia later, if develops at all with different layers of mesh repair.

In cases of no healing by secondary intention, delayed operative closure to be done after improving general condition of the patient.

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Medical Negligence, Consumer Protection Act (CPA) and Surgeons

21

Rashpal Singh and M. D. Ray

21.1 Introduction

No doctors know everything, that is why it is called practicing medicine

Doctor owes certain duties towards the care of patient and any breach on the part of doctor in this aspect is considered as a 'negligence'.

Worldwide including India, each country has framed or framing new rules, acts and legislations towards the welfare of common man grievances, towards deficiency in delivering services and negligence by health care agencies.

Medical Negligence is defined as, when doctor is unable to deliver skills which are required at the time of treating patient or any deviation in the standard protocol or guidelines defined by different societies and organisations. Liability both civil as well as criminal arises due to medical negligence.

Consumer forum has to compensate every person's complaint filed in the forum against any act or behaviour reflecting medical negligence. After 1986 onwards, complaints in consumer forum have been increased significantly as a sequel of Consumer Protection Act (CPA) brought into action.

Being a health care professional, it is considered as one of the best and noble profession since ages. The patient and the doctor share a bond of trust and patient is having firm belief that the concerned doctor will treat and cure the patient and make him/her disease free.

Consumer protection Act (CPA) enactment is a good initiative taken by government in the welfare of public. Its best role is for layman and public who are totally unaware of the real facts and keep on paying over and unnecessary charges and payments during their treatment.

Consumer protection Act (CPA) is a legislation and acts as a guider too to safeguard each and every patients from irrelevant and unnecessary financial expenses. Consumer can use this Act as a sword to make sure fair and honest services.

As the awareness of common man has increased significantly especially in last two decades, maximum patients practices and availing the implementation of this act whenever they feel or experience any medical negligence. Every health care professional is supposed to render his or her professional services in the welfare of mankind.

The main motto of this Act is to mainly take care of fundamental rights of patients whenever medical negligence is there. All doctors are supposed to have at least a basic knowledge and awareness of how medical negligence makes a formal judgement in the various judicial courts of India.

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21.2 Definition of a "Consumer"

The definition of 'Consumer' carries different meanings for both services as well as goods.

Definition of 'Consumer' Under section 2 (d) of Consumer Protection Act, 1986, says consumer is one who -

1. Purchases any items for which payment has been done on the spot or instantly by cash or making of payment to be done later either by making full or partial commitments or had paid the amount of articles purchased partly or to make the remaining payment later or seeking or opting some other way outs to make the payment later on. All this should be done only after the permission or agreement of above person. Means a person who has purchased some items from a dealer or buisnessman but he is nearly or partially fulfilling the payment related terms and conditions and then trying to sale the same item to other third party for his personal monetary related benefits.This person is not able to fulfull the criteria of an ideal 'consumer' or fits into the definition of a 'consume'.
2. Engages or charters any service which provides payment on the spot or instantly or by cash or making of payment to be done later either by making full or partial commitments or had paid the amount of articles purchased partly or to make the remaining payment later and after permission of the above person, this also includes any assignee or recipient who takes the responsibility to make the payment instantly or make promise to pay later on by opting some other ways of delayed payment [1].

   Any patient who visits/consults a medical practitioner after paying the all dues and fees related to treatment of the treating doctor, he/she comes within the purview of Consumer Protection Act, 1986,section 2(1) (0).

   A 'patient' also comes under the definition of a consumer. All the hospitals and medical professional people who provides or willing to provide their services or any kind of professional assistance to the people are covered in the boundary of Consumer Protection Act, 1986,section 2(1) (0). The patient here mentioned above who avails all this service fulfils the definition of a 'consumer' [2].

A consumer is not only the person who hires or avails any services for consideration but also the person who is beneficiary of such services [3].

Aims and Objectives of Consumer Protection Act

, 1986 are well defined and basically deals with the betterment and welfare of consumers.

Revision of CPA was done in 1993 with the following aims:

1. Provision of fruitful and proficient methods to the consumers to tackle any type of victimisation and unequal dealings.
2. It acts as a protective measure for consumer to protect their rights and get the good and standard treatment for their medical illness.
3. Establishment of council centres for the settlement of complaints, grievances and other issues related to negligence.

Two types of councils:

1. Consumer protection council (state, district).
2. Central protection council.

21.3 Objectives of Consumer Protection Act (CPA)

1. Safeguarding all the rights against each and every proponents who provides any type of articles or items and any deals which endangers their life and poses any sort of threat to assets or belongings.
2. To protect the consumer against malpractices related to their business or any commercial deal, this revision of the act provides them the right to be familiar with the, originality, standard, number, strength of products or services provided by the dealer.
3. Right to approach to variety of different items, getting services at reasonable rate whenever feasible and verify the goods purchased or going to purchase.

4. At all suitable levels, there should be guarantee that consumer's betterment will be given preference and the right to have all relevant information.
5. Right to off putting all business deals, seek justice in support of any unfair business deal or fraudulent misuse of consumers.
6. Right to tutoring of buyers.

21.4 Medical Negligence

Negligence is nothing but just simply failure of health care professional to give the required care. Negligence is formed by five components as mentioned below:

1. Commitment of concern to the petitioner by the defendant.
2. Turning away or incomplete fulfilment of the responsibilities and duties assigned to the defendant.
3. Cause in fact.
4. Proximate.
5. Damages.

When the doctor is the defendant, it defines medical negligence case.

As per Bolitho test, it is based on principle:

Medical Negligence means 'failure to act in accordance with the medical standards in vogue and failure to exercise due care and diligence'.

It is a wrongful action or omissions of professional in the field of medicine, failure to practice or achieve reasonable skill required in order to reproduce as per the general standards guidelines laid by the governing body or organisation. To prove negligence the aggrieved consumer must prove following.

1. Duty of care owned by physician.
2. Applicable standard of care violated by physician.
3. Compensable injury to patient.
4. Injury to the patient caused as a result of suboptimal knowledge, treatment standards and malpractice.

Any patients who consult doctor for illness or any ailments like feeling sick or not feeling well, there are defined duties of the treating doctor and any deficiency in his duty will be considered as a negligence. Breach of duty means failure to satisfy moral, legal or ethical obligation, especially where someone has a corresponding right to satisfaction.

In India, all the health care centres and professionals providing medical service are covered under the Consumer Protection Act, 1986.

21.5 Deficiency in Medical Service

The Consumer Protection act, 1986 defined Deficiency under section 2(1) (g) which means any law, person or service provider organisation having the contract under which they are supposed to cross check or corrects the limitations, defect and any error, or insufficiency in the superiority, nature and method of presentation are not found to be up to the mark defines deficiency [4].

In case of emergency situations, epidemic, pandemics and life-saving scenarios, all medical professionals wheresoever's they are working, they can extend their service in the interest of country, state or public.

Professional incompetence having poor or inadequate skills of delivering quality services to consumer can be considered as deficiency in services whereas negligence is simply defined as 'any act performed without due diligence'. sometimes the treating health care professional whether doctor, nurse, healthcare workers etc. being competent and skilled enough but due to logistics issues, lack of infrastructure and proper armamentarium in the hospital or centre which is a very common scenario in a developing nation like India, the concerned person is not able to provide their skill to desired patients which ultimately leads to a catastrophic event related to patient outcome e.g. lack of emergency drugs when a patient presents to a doctor , surgical instruments during emergency surgeries, equipments required for diagnosis of disease. These all cannot be categorised under negligence on healthcare personnel part as it is due to circum-

stances which leads to fatal consequences not the lack of skill of person.

Types of negligence:

1. Gross negligence.
2. Criminal negligence.
3. Active/passive negligence.

In landmark case in **England Bolam vs Frien Hospital Management Committee** [5] the court held that, a doctor cannot be considered guilty of negligence if he acted or performed his duty or skill which are lying in the domain and fulfilling the criteria or guidelines laid down by different medical societies or organisations who are skilled enough and routinely performing such procedure or providing treatment guidelines. A doctor can choose any one of the treatment options as per his decision what he or she thinks is suitable for patient at that time and he cannot be considered liable for taking one choice out of two for favouring one line of treatment rather that another.

21.6 Liability of Medical Services and Doctor

The Jurisdiction of the Consumer Protection Act, 1986 covers Medical services. If there is any dearth or scarcity in providing medical services, consumers can secure their part by lodging a complaint under this Act. However, medical services are not specifically mentioned in this act.

But as per section 2 (0) of the Consumer Protection Act Services means; availability of any service or facilities for the expected users related to insurance, finance, journey, water or power supply, entertainment, real estate/housing, all these services are payable and consumer should not take them as a feast or treat free of cost from government or issuing authority.

The liability of doctor is only when the duties, responsibilities and any technical skill is not provided by the attending doctor to the patient. If there is no breach in the duties and treatment protocol, then doctor will be not considered liable.

A doctor is not always considered liable in every case or patient he is attending. There can be error of judgement or simply a negligence leading to error of judgement.

If any consumers files complaint or grievances against ill services or wrong services by the healthcare agency, consumer body provides the compensation to the exploited party.

21.7 Judicial Approaches

The Judicial system of India justifies its care and concern towards the consumer by safeguarding and maintaining their privileges as well as increasing the wakefulness of society regarding the consumer's civil rights. These examples mentioned below, reflects the knowledge, responsibilities, role and precautions to be taken by the doctor while treating patients. These examples conveys a message to all health care professional and these messages act as an eye opener which helps them to avoid all such incidences in future.

In **Indian Medical Association Vs Santha**, the Supreme Court has decided that the intelligence, skill and proficiency of all medical professional cannot be compared with each other and is vary from person to person. Or alternatively, doctor will be proven guilty only when the treatment protocol, management and other procedures proved to be wrong or inappropriate, eventually all these acts reflect the incompetency or lack of knowledge of the doctor towards patients care. 'Merely because the operation did not succeed, the doctor cannot be said to be negligent' [6].

Laxman B. Joshi vs T. B. Godbole [7], in this case the responsibilities as well duties of a doctor towards his patients are clear. A person who holds a desired medical qualification recognised by the central/state medical council is considered skilled enough to give medical advice and treatment. Any patient who consults above mentioned person is supposed to have certain duties towards the patient which includes what type of care is suitable to that particular patient, what type of best treatment can be provided and what other ancillary measures can be performed in order to make the treatment best. Patient keeps the total right to take action against any type of negligence or any infringement of above mentioned duties by the doctor. Any task a practitioner is performing, it should be a justified mixture of dexterity and intelligence and it must implemented in a sensi-

ble level of concern which should lie at a moderate level neither too high nor it carries too low level of concern and proficiency. These all traits like skills, moral responsibilities about work and duties, these all are estimated and interpreted and compared with the standard parameters and guidelines as per the International Journal of Law 109 law requires.

Marrin F. D'Souza v. Mohd. Ishfaq [8] in this case court held that, act or recital of the role should not be unjustifiable by the doctor and nursing homes. If despite relentless efforts of treating doctor towards his patient well being turned out to be futile and doctor loses the patient's life, still the doctor is not considered to be liable as all his actions fits under the standard treatment guidelines.

Following suggestions may be made to medical practitioners to avoid litigations arising out of deficiency in medical services.

1. Increasing awareness among all the doctor and other health care professionals about relevant update in medical field and advances in legal and law related to medical negligence by organising continued medical educations, meetings, conferences, etc.
2. Any failure on the part of patient in the form of non-compliance to follow up, medicines prescription or keeping the records of readings should be mentioned in patient record.
3. During every visit, doctor should maintain the accurate record of all clinical findings and treatment given to every patients.
4. Informing the patient and their attendants regarding treatment plan, line of action, surgical procedures and associated complications in details and making them understand the prognosis of disease from time to time helps in creating strong faith and trust between doctors and patient.
5. Taking a detail informed consent explaining all relevant information in front of the patients and their relatives should be the part before embarking upon any type of intervention.
6. Before administering any injections, medicines or treatment, every doctor should take adequate precautions.
7. To opt for a good insurance policies in order to have security or protection against loss or other financial burden in case medical negligence proven.
8. Seek consultation of a good legal advisor in case of involvement in medical negligence.
9. Establishment or creation of a forum or association or council in the medical associations who can take care of all the grievances from patients part as well as from medical staff part.

21.8 Conclusion

The **Consumer Protection Act**, came into action in 1986 and revised in 1993, is a sort of weapon which protects and take cares the common man grievances and facilitate in availing healthcare related compensation. It also gives an outlook and overview of the duties and responsibilities of medical professional in the interest of the consumers. This act basically deals with the consumer's grievances and sorted them as soon as possible. Using this act, consumers can prevent their exploitation by money heist healthcare agencies and prevent unnecessary financial burden on them.

This Act provides a platform to the person who suffered negligence or unfold the all deficiency and malpractices in medical services. The judicial council considers both the victim and accused part permitting them to provide their explanations against the medical negligence case filed and achieving the final result without any bias.

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22 Classification of Surgical Complications: Clavien–Dindo and Review

M. D. Ray

22.1 Introduction

With the over growing demand for health care, variations in clinical practices in various settings, rising costs of health care and its variations and quality of health care, need to be standardized without any doubt.

What is really a successful surgery in terms of define complications and there severity remains limited by the lack of consensus [1, 2, 3].

The effectiveness of various classifications is based on the tenets of classifying the complications in different grades. It includes surgical interventions and treatment of complications. This approach allows identification of most of the complications and prevents the high rate of complications. Hospital stay for a relatively longer time cannot be counted as a grade of complications.

Classifications of surgical complications are proposed by Clavien et al. in 1992 [1], which is commonly utilized classification worldwide!

22.2 So why and What Is the Need of Such Classification

1. As there is no such defined concensus for the grading of adverse postoperative events.
2. Complications, any kind hampers the evaluation of surgical procedures and assessment and interpretation of surgical outcome.
3. Variations of major, minor, mild, moderate or severe complications from surgeon to surgeon and center to center, i.e. there is no uniform policy to understand the real classification of Surgical complications.
4. Post op complications increase the length of hospital stay, increased mortality, cost, and the headache for both the sides—Surgeons, patient, and party.

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22.3 Daniel Dindo and Pierre A Clavien

Daniel Dindo Vascular Proctologist at Zurich, Switzerland.

Pierre A Clavien Transplant surgeon Zurich, Switzerland.

Significance of Clavien–Dindo Classification and its Modifications

- Measures **MORBIDITY.**
- **Deviation** from **NORMAL** postoperative course (Grade I–IV).
- Classification via **THERAPEUTIC** consequences.
- **GRADE** allocation to each complication identified.

1992….

Clavien and Dindo proposed general principles

Classify complications of surgery based on a therapy-oriented, 4-level severity grading.

Severity grading was refined, applied to compare the results of laparoscopic versus open cholecystectomy and liver transplantation.

1992: Definition of Negative Outcome

Three definitions of negative outcomes.

Differentiated: complications, failure to cure, and sequelae.

Complications: any deviation from the normal postoperative course.

This definition also takes into account asymptomatic complications such as arrhythmia and atelectases.

Sequelae is an "after-effect" of surgery: inherent to the procedure (e.g., inability to walk after an amputation of the leg).

Finally, surgery may be well executed without any complications but still fail. If the original purpose of surgery has not been achieved, this is not a complication but a "failure to cure" (e.g., residual tumor after surgery).

It should not include sequelae and failure to cure in the new classification of complication: 2004.

2004….

Merits…..

Allows identification of most complications and prevents down-rating of major negative outcomes.

Important in retrospective analyses.

(We also felt that) that the duration of the hospital stay can no longer be used as a criterion to grade complications.

2004…..

Grade 1: minor ailments not needing treatment (Exclusions: antipyretic, analgesics, antidiarrheal, and antiemetic pharmacotherapy or other agents required for UTI).

Grade 2: Major life-threatening events needing therapy or a hospital stay more than two times of the median hospitalization for the similar interventions.

Grade 2: two subclassifications according to the invasiveness of the therapy needed to deal the complication.

Grade 2a complications required only pharmacotherapy.

Grade 2b complications required invasive interventions.

Grade 3: complications contributing to prolonged deblitation or organ damage.

Grade 4: Morbidity because of a complication.

2004: Demerits

Therapy used to correct a specific complication remains the cornerstone to rank a complication.

Significant modifications compared with the previous classification increased the number of grades from 5 to 7, including 2 subgroups for grades 3 and 4.

(The justification to break up some grades into 2 subheadings is that such types of complication are prone to be merged due to modest numbers)

Grades I and II complications in revised version correspond to Grades I and IIa complications in the initial classification.

Why Modified?

Grade IIb events (need for invasive procedures) in the former classification are now listed as a separate entity (grade III complications), further subdivided into grades IIIa and IIIb depending on the need for general anesthesia.

The length of hospital stay as a criterion to rank grade 2 complications was eliminated.

Life-threatening complications: ARDS with the need for mechanical ventilation, listed as grade IIb complications in the initial classification, are now recognized as a higher grade (grade IV complications).

Disability: any impairment of a body function.

Neurologic deficits of an extremity due to positioning of the patient during surgery.

Hoarseness after thyroid surgery is no longer a grade on its own (grade III in the previous version), but is now highlighted by the suffix "d" (for "disability").

Thus, any grade of complication may be supplemented with this information.

22.4 Modified Clavien–Dindo Classification (Table 22.1)

22.4.1 Sub-grouping of Clavien–Dindo Classification

Major—Grades- I and II.

Minor—Grades- III, IV, and V.

22.4.2 Limitations

Proposed for elective surgeries only.

Organ dysfunction to be assessed properly prior to surgery.

Majority of oncological procedures done in elderly; already comorbid or compromised organ function.

22.5 The Clavien-Dindo Classification of Surgical Complications [4]

22.5.1 Aim

To critically evaluate the classification from the perspective the literature.

To establish correlation of classification grades with patients', nurses', and doctors' perception.

Table 22.1 Clavien-Dindo Classification (2004)

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. this grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade IIIa	Surgical, endoscopic, or radiological intervention that is not under general anesthesia
Grade IIIb	Surgical, endoscopic, or radiological intervention that is under general anesthesia
Grade IVa	Life-threatening complication requiring intermediate care or intensive care unit management, single organ dysfunction (including dialysis, brain hemorrhage, ischemic stroke, and subrrachnoidal bleeding)
Grade IVb	Life-threatening complication requiring intermediate care or intensive care unit management, multi-organ dysfunction (including dialysis)
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a folloe-up to fully evaluate the complication

*Brain hemorrhage, ischemic stroke, Subarachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit

22.5.2 Material and Methods

1. Systematic analysis of reports from the published literature was done in which this classification systems was used and 11 scenarios illustrating difficult cases were developed out of it.
2. Seven centers from various countries, having often adopted classification, separately evaluated the 11 scenarios.
3. A **protocol evaluation** was done to test the **efficiency and reliability** of the classification.
4. Perception of the **severity** was tested in patients, nurses, and physicians by presenting 30 scenarios, each depicting a distinct grade of complication.

22.5.3 Results

They noted a dramatic increase in the use of the classification in many fields of surgery.

About half of the studies used the contracted form, whereas the rest used the full range of grading.

Two-thirds of the publications avoided subjective terms such as minor or major complications.

The study of 11 difficult cases among various centers revealed a high degree of agreement in identifying and ranking complications (89% agreement).

Enabled a better definition of unclear situations.

Each grade of complications significantly correlated with the perception by patients, nurses, and physicians ($P < 0.05$, Kruskal–Wallis test).

22.5.4 Conclusion

This 5-year evaluation provides strong evidence: classification is **valid and applicable** worldwide in many fields of surgery.

No modification in the general principle of classification is warranted in view of the use in ongoing publications and trials.

Subjective, inaccurate, or confusing terms such as **"minor or major"** should be **removed** from the surgical literature.

22.6 Applicability of the Clavien-Dindo Classification to Emergency Surgical Procedures [5]

22.6.1 Aim

To approve the Clavien–Dindo classification in general emergency surgical patients.

To furnish guidelines and recommendation for the utility of this classification in emergency surgical patients.

To form a valid tool for prospective monitoring of morbidity and mortality with the incorporation of suitable preoperative data for risk compensation of postoperative complications.

22.6.2 Material and Methods

Retrospective analysis, single center database.

All emergency general surgical procedures between 21stApril 2012 and 23rd June 2012.

Emergency general surgical procedures included; reoperations for complications after elective surgery.

Data retrieval added preoperative variables: comorbidities for the computation of the Charlson comorbidity index, performance status, organ failure, perioperative and postoperative ailments.

Preoperative Organ Failure Assessment

SOFA(sequential organ failure assessment)-score -(2 or more) pertain to specific organ.

OR

Whether patient needed preoperative intermediate level intensive care unit (ICU) care or intermediate level (IC) care for organ failure.

22.6.3 Results

Preoperatively 37 (8.3%) patients had organ dysfunctions.

Emergency surgical patients required a new definition for Grade IV complications (organ dysfunctions).

Only new onset organ dysfunctions or complications significantly contributed to worsening of preoperative organ dysfunctions: classified as grade IV complications.

Postoperative complications developed in 115 (25.9%) patients.

Grade IV complication: 14 (3.2%) patients.

Charlson comorbidity index, preoperative organ dysfunction, and the type of surgery predicted postoperative complications.

22.6.4 Conclusion

Utility of Clavien–Dindo classification of surgical complications in emergency surgical patients is possible while establishing postoperative grade IV complications preoperative organ dysfunctions should be taken into account.Patient's comorbidities, preoperative organ dysfunctions and the type of surgery should be used for risk stratification.

22.7 Charlson Comorbidity Index (Table 22.1)

Developed and validated as a measure of 1-year mortality risk and burden of disease.

CCI reduces comorbidities into a single numeric score that assists health professionals in stratifying patients into subgroups based on disease severity, developing targeted models of care, and resource allocation.

CCI consists of 17 comorbidities; two subcategories for diabetes and liver disease.

Comorbidities weighted from 1 to 6 for mortality risk and disease severity: total CCI score.

Age: independent predictor of mortality.

Combined Age-CCI (CA-CCI) score generated by adding 1 point to the CCI score for each decade of age over 40 years.

Due to low cost, ease of administration and interpretation in efficient timeframes.

CCI is feasible in various healthcare settings, including those with limited access to medical records (e.g., primary care, outreach).

The CCI can be incorporated into electronic medical record and data collection systems (Table 22.2).

Table 22.2 Charlson comorbidity index

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabets without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or several renal disease
	Diabets with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumour without metastases (exclude if>5 years from diagnosis)
	Leukaemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour
	AISD (not just HIV-positive)

Abbreviations: AIDS = acquired immunodeficiency syndrome; CVA = cerebrovascular accident; ECG = electrocardiogram; HIV = human immunodeficiency virus; TIA = transient ischaemic attack

** For each decade >40 years of age, score of I is added to the above score

22.8 Clinical Examples

Example 1: 52 years old male underwent D2 Radical Gastrectomy for Carcinoma Stomach. Six days postoperatively developed left sided facial and limb weakness. His CT head showed no acute changes. Several hours later weakness resolved spontaneously and diagnosis of TIA was made and Aspirin 75 mg PO started. **Clavien–Dindo Grade?**

Example 2: 65-year-old man underwent left hepatectomy for HCC. Following surgery he had significant nausea and vomiting. Symptoms settled with adequate antiemetic therapy. Later, he developed wound infection requiring antibiotics according to hospital policy. **Clavien–Dindo Grade**?

Example 3: 52-year-old male underwent left hemicolectomy for carcinoma descending colon. On POD 2 he developed pneumonia and started on empirical antibiotic therapy. His breathing continued to deteriorate, leading to critical care escalation and ventilatory support. He recovered following a prolonged stay in critical care. **Clavien–Dindo Grade?**

Example 4: 40-year-old lady underwent anterior resection for recto-sigmoid tumor. On postoperative day 1 she spiked a temperature and was given paracetamol and next day she was found to develop hypokalemia and received potassium supplementation for the same. **Clavien–Dindo Classification?**

22.8.1 Summary

The classification of surgical complications can be recommended in its current form for use in retrospective and prospective studies.

To prevent the abuse of poorly defined terms, omitting terms, such as minor, moderate, or major is recommended as those terms will never be used consistently among authors.

Applicable in emergency surgical procedures.

Surgical complications are potentially a significant independent predictor of patients' impairs postoperative psychosocial well-being.

22.8.2 Conclusion

Clavien–Dindo classification for surgical complications has been well accepted by the most part of the world (Table 22.3).

This classification seems to be applicable for all Surgeons including upcoming and less experience surgeons. The application of this classification may expedite the assessment and comparison of surgical results among various centers, surgeons, and surgical modalities.

Table 22.3 The Clavien–Dindo classification of surgical complications

Full scale		Short form	
Grades	Definition	Grades	Definition
Grade I:	Any divergence from the routine postoperative course with no pharmacotherapy or interventions requiring surgical, radiological, and endoscopic interference	Grade I:	Similar to full scale
	Excepted pharmacological interventions: Agents as antipyretics, analgetics, diuretics, antiemetic, and physiotherapy also electrolyte supplementation. Wound infections needing bed side management included in this grade.		
Grade II:	Needed pharmacotherapy with agents other than such required in grade I complications. (TPN) total parenteral nutrition and blood product transfusions are also included.	Grade II:	Similar to full scale
Grade III:	Needing surgical, radiological or endoscopic intervention	Grade III:	Grades IIIa and IIIb
Grade IIIa:	Intervention does not require GA(general anesthesia)		
Grade IIIb:	Intervention require GA(general anesthesia)		

(continued)

Table 22.3 (continued)

Full scale		Short form	
Grades	Definition	Grades	Definition
Grade IV:	Potential major life-threatening complication (which includes CNS complications)[a] needing ICU/IC-care	Grade IV:	Grades IVa and IVb
Grade IVa:	Organ dysfunction(single organ) (dialysis included)		
Grade IVb:	Organ dysfunction (multi-organ)		
Grade V:	Death of a patient	Grade V:	Similar to full scale
Suffix 'd':	The suffix "d" (for "disability") is added for those patients suffered from a complication at discharge, in respective grade of complication. This label requires full follow-up for complication evaluation		

[a]ischemic stroke, brain hemorrhage, Subarachnoidal bleeding, but excluding TIA(transient ischemic attacks); ICU: Intensive care unit, IC: Intermediate care

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23 Immediate Postoperative Complications: An Overview for Better Management

M. D. Ray

Contents

23.1 Introduction

Successful outcome of a major surgery depends on three stages: preoperative rehabilitation, intraoperative technique and management, postoperative care. The assessment of complications and their appropriate management is essential for the successful outcome of surgical patients in the postoperative period. The presence of complications like respiratory, surgical wounds, cardiovascular, haematological, gastrointestinal delays the surgical outcome. After surgery, there are various common complications which are evaluated below along with the risk factors presentation and practical guidelines for the treatment. Fluid and electrolytes management is the most important aspect of healing and expected progression.

23.2 Wound Complications

Proper surgical wound healing depends on sufficient delivery of oxygen, absence of bacterial contamination and adequate nutrition. Wound healing is impaired by various factors which include surgical site infection (bacteria $>10^6$ CFUs/cm^2), poor blood supply, low blood pressure, hypothermia, immunosuppressive patients like in cancer, ascites, multiple comorbidities and intraoperative contaminations. Apart from abovementioned, other factors are diabetes, smoking, malnutrition and emergency surgery. One important thing to note is that excessive tension while closure causes impaired blood flow and compromises wound healing and further leads to dehiscence and incisional hernia.

Surgical site infection occurs from deep organ spaces to superficial skin because of bacterial contamination, e.g. the spill of the intestinal contents while surgery may cause surgical site infection. If the anastomosis does not heal properly, it may form an abscess and further, leak of GI contents may occur in a delayed fashion because it is temporarily sealed with ischemic tissue which may lead to delayed leak after several days. Thereby, postoperative day 5–7 is a critical time

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Table 23.1 Diagnostic test

Diagnostic test	
Wound	Laboratory/imaging tests
Wound complication	CBC, wound culture, CT scan

during which patients may present with intraabdominal abscesses due to anastomotic leak.

Most surgical wounds are contaminated by bacteria which are found endogenously in the skin and the GI tract. Common skin flora includes Staphylococcus and Streptococcus and intestinal flora includes a combination of gram-positive, gram-negative and anaerobic organisms but infection does not occur if the host defence is intact despite heavy bacteria contamination (Table 23.1). We know the surgical wounds are divided into four categories in terms of the development of surgical site infection.

1. *Clean wound*: non-traumatic and no violation of the mucosal barrier, surgical incision may have a risk of 2% infection.
2. *Clean contaminated*: GI tract, genitourinary tract or respiratory tract without spillage may have a risk of 3–5% infection.
3. *Contaminated*: gross spillage from GI tract, genitourinary or biliary tract surgery, fresh traumatic wound, a major violation of sterility may have a risk of 5–10% infection.
4. *Dirty:* faecal contamination, abscess, devitalise tissue, debridement of necrotic tissue, an old traumatic wound may have a risk of 25–30% infection risk.

Management: Usually every hospital has its protocol regarding the appropriate antibiotics for each type of surgery. Adequate skin preparation before surgery, maintaining hygiene at home, clipping the hair and not shaving, using prophylactic antibiotic in selected surgeries, sugar control, smoking cessation at least 30 days before surgery will help to prevent the surgical site infection. Appropriate surgical barrier, antiseptic scrub, preoperative antibiotics for clean-contaminated cases and above are helpful. It is better to administer the antibiotics 30–60 min before skin incision.

The grossly contaminated wound should be kept open with wet to dry dressing. The preoperative albumin is an important marker for malnutrition and value less than 3 gm/dL points towards it. Prehabilitation before surgery is a very important aspect to prevent wound-related complications.

Dehiscence: Disruption of a previously closed wound can lead to loss of barrier protection provided by skin and fascia. Dehiscence occurs because of impaired wound healing due to the various factors mentioned above. The poor surgical technique has got an important contribution to dehiscence. Too tight or too loose closure, poor handling of tissues may develop dehiscence.

Because of incomplete healing of fascia which allows abnormal protrusion of contents through the defect may lead to *incisional hernia*. It usually takes 6–8 weeks for the surgical wound to completely heal after the surgery. At this point of time, the tensile strength across the wound is maximum, i.e. approximately 80% of the normal tissue. Thereby hernia can develop during this period because of impaired wound healing, increase tension on the abdominal wall. Persistent cough, ascites may contribute to developing an incisional hernia. Surgical site infection has a higher risk of developing an incisional hernia. Incarceration risk is higher in smaller fascial defects like at abdominal drain sites and laparoscopic port sites. The patients with incarceration present with symptoms of obstruction like nausea and vomiting, abdominal distension and inability to pass flatus and faeces and can eventually, if left untreated, progress to strangulation of the bowel, though, in ventral incisional hernia with large defects, these symptoms are rare.

23.3 Postoperative Fever

Postoperative fever has always remained a diagnostic enigma to surgeons (Table 23.2). It could be due to various causes starting from an inflammatory response to the procedure, infectious causes to the unidentified factors. By definition,

Table 23.2 Diagnostic test for fever

Diagnostic test	Laboratory/imaging tests
Fever	CBC, BMP, UA, urine culture, blood culture, sputum culture and wound culture if applicable, CXR

post-op fever is a temperature above 100.4^0 F (38 °C). We are going to discuss here the most common causes of postoperative fever and to emphasise diagnostic workup. In general, postoperative fever is associated with release of cytokine IL-1 by activated macrophages as well as neutrophils. TNFα also may cause fever by disrupting the temperature set point in the hypothalamus. Importantly, the surgical trauma itself can cause fever due to an inflammatory response but usually, it is limited and does not occur after 24–36 h. The criteria for systemic inflammatory response syndrome (SIRS) are as follows:

Hyperthermia or hypothermia: temp >38 °C or < 36 °C, tachycardia: heart rate > 90/min, tachypnea: respiratory rate > 20/min or $PaCO_2$ < 32 mmHg, leucocytosis/leukopenia or left shift WBC >12,000/dl or WBC < 4000/dl or > 10% immature bands. The patient must show two out of these criteria to meet SIRS. SIRS is physiological but along with infection it may lead to sepsis, septic shock, cardiogenic shock, multiorgan failure or even death.

Causes of fever from *postoperative day 1–3* may be due to the following:

First or second post-op day fever may be due to *atelectasis*—collapse of alveoli during surgery or it could be secondary to pain which can activate neutrophils, thereby releasing IL-1. Secondary to the prolonged collapse of alveoli or aspiration may develop *pneumonia* on postoperative day 3. Hospital-acquired pneumonia is caused by Pseudomonas and MRSA and is the most common nosocomial infection in the intensive care unit. There are multiple risk factors which may develop atelectasis and pneumonia including pain, shallow breathing, depressed cough from narcotics, immobility, pulmonary oedema, aspiration and history of smoking. The patient complains of respiratory difficulty, cough and purulent sputum.

Causes of fever from *postoperative day 3–5*: Urinary tract infection (UTI) due to foley catheter is a very common cause of fever on post-op day 3–5. Most common organisms include *E. Coli*, Proteus and Klebsiella, they colonise the foley catheter and cause urinary tract infections. Overall, UTI is the commonest nosocomial infection. The patient complains of burning urination, cloudy urine, blood mixed urine along with fever.

Causes of fever from *postoperative day 5–7:* Deep vein thrombosis (DVT) or pulmonary embolism (PE) can cause fever because of inflammatory reaction. Patient complains of calf swelling and pain along with fever. PE presents with a sudden attack of respiratory distress, cough, chest pain, tachycardia, tachypnea and hypoxemia. Surgical site infection, anastomotic leak, high dose antibiotics like sulbactam, cefoperazone may lead to fever from 5 to 7 post-op days. Surgical site infection shows incisional erythema, purulent discharge and pain.

Causes of fever from *postoperative day from 7 onwards*: Colonisation of the central line and seeding of the blood may cause central line infection which may further cause fever. Redness at the catheter incision site may raise suspicion for the infection. Central line infection directly seeds the vascular space and may cause bacteremia/septicemia. Apart from this, drugs like Sulfa drugs, continuation of antibiotics, transfusion reactions may cause continuous fever.

Prevention and management: Prevention of the causes of infection involving the foley catheter, central lines and drains to be taken care of properly. In other words, for the successful treatment of most of the infections, source control is usually necessary. Any catheter which is causing infection should be removed and abscess must be drained. It is a better practice to obtain culture, sensitivity report and start appropriate antibiotics and this should not delay the treatment.

23.4 Respiratory Complications

Respiratory complication is the most common cause of death of surgical patients which accounts for up to 77%. The different postoperative respi-

ratory complications are atelectasis, aspiration, pneumonia, pulmonary oedema, pulmonary embolism, acute respiratory distress syndrome (ARDS) and fat embolism. *Atelectasis* and pneumonia are the most common respiratory complications in the postoperative period. The patient complains of respiratory difficulty, cough, purulent sputum. *Aspiration* in the postoperative period may cause chemical pneumonitis and progress to bacterial infection. In aspiration, the gastric contents enter into the respiratory tract. It can occur during anaesthesia or in postoperative period due to vomiting. Usually, the right middle and lower lobes are affected by aspiration due to the calibre and straight course of right bronchus but in the prone position, it may affect right upper lobe. In *pneumonia, the patient will have reduced breath sounds and abnormal breath sounds* like wheezes, crepitations along with fever and productive cough and one-sided opacity on chest X-ray. *Pulmonary oedema* causes hypoxemia and shortness of breath. The mechanism involves abnormal transport of fluids across the alveolar–capillary membrane which leads to building up of fluid in the interstitial and alveolar spaces and thereby decreasing the diffusion capacity. Fluid overload can cause pulmonary oedema even in a patient with normal ejection fraction. *Acute respiratory distress syndrome (ARDS)*: the common causes of ARDS are sepsis, pneumonia, aspiration, severe trauma and massive transfusion. The Berlin criteria used to clinically define ARDS includes acute onset of lung injury within a week, bilateral opacities on chest imaging, decrease PaO_2/FiO_2 ratio (categorised as mild, moderate and severe; <300, <200 and < 100, respectively), without heart failure or fluid overload (Table 23.3). The underlying pathophysiological phenomenon is complex and is characterised by widespread inflammation in the lungs. It is mediated by overwhelming response by inflammatory cytokines such as IL-1, IL-6 and TNF, which causes raised permeability of alveolar–capillary membrane and accumulation of protein and cellular rich fluid in the alveolar spaces leading to an impaired diffusing capacity of oxygen and hypoxemia. *Pulmonary embolism (PE)* presents with a sudden attack of respiratory distress, cough, chest pain, tachycardia, tachypnea and hypoxemia. It is caused by migratory thrombus in the pulmonary arterial system. The impedance of flow in pulmonary arteries/arterioles increases the afterload in the heart causing a ventilation-perfusion mismatch and precipitating haemodynamic instability and hypoxemia. The significant amount of the cases of PE develops from the migration of thrombus from deep vein thrombosis (DVT) in the iliofemoral system. Risk factors of venous thromboembolism (VTE) using Virchow's Triad are stasis of blood flow, endothelial injury and hypercoagulability. Hypercoagulability is the main cause of VTE in a cancer patient. Prevention and management of VTE and PE include a prophylactic dose of subcutaneous unfractionated heparin or low molecular weight heparin (LMWH) 12 h before surgery and 6 h after surgery when complete haemostasis is achieved along with intermittent pneumatic compression. Treatment involves subcutaneous LMWH at a therapeutic dose and if permissible and needed, clot removal may be required from the pulmonary artery. Endovascular procedures by an interventional radiologist are the important tools in the armamentarium and also, open pulmonary artery embolectomy by sternotomy is reserved for a few selected cases.

Table 23.3 Diagnostic test for respiratory distress

Diagnostic test	Laboratory/imaging tests
Respiratory distress	CXR, ABG, EKG, echocardiogram, CT-angiography of the chest

23.5 Paralytic Ileus

Due to various reasons, paralytic ileus is one of the most common complications in admitted patients especially post-surgical procedures (Table 23.4). Persistent and unresolved ileus may necessitate to rule out mechanical obstruction

Table 23.4 Diagnostic test for ileus

Diagnostic test	Laboratory/imaging tests
Ileus	BMP, abdominal x-ray

which if untreated has high chances of perforation. There are various risk factors involved such as major abdominal surgery after HIPEC, significant electrolytes imbalances, sepsis, immobilisation, narcotic pain medications and metabolic acidosis. There may be a physiological ileus due to bowel handling, prolonged surgery and peritoneal irritation. The physiological ileus lasts for a maximum of 72 h. The small bowel is the first to regain the function followed by stomach which regains motility in the first 24 h and colon takes time up to 48–72 h. The patient complains of nausea and vomiting, inability to pass flatus and faeces, abdominal distension, pain and intolerability to diet. The symptoms of ileus are same as mechanical bowel obstruction and these two should be differentiated by laboratory investigation and imaging.

Management of ileus: Before managing paralytic ileus, mechanical obstruction, leak and intraabdominal abscesses should be ruled out. The management includes the bowel rest, intravenous fluids and managing electrolyte balance, nasogastric tube decompression and ambulation. Sometimes, total parenteral nutrition may be required where ileus persists more than 7 days.

23.6 Hypotension

A blood pressure below 90/60 mm Hg or main arterial pressure (MAP) below 65 mm Hg is taken as hypotension (Table 23.5). The general signs of hypoperfusion and shock due to hypotension include cool skin, pale-looking, tachycardia, confusion, decrease urine output and lactic acidemia. Postoperative hypotension is an alarming cause of bleeding, sepsis, adrenal insufficiency or may be due to cardiac causes. The most common cause of hypotension in the postoperative period is hypovolemia. The hypovolemia may be due to insensible losses, reaction to certain drugs like narcotics, sedatives, epidural anaesthesia, post-op bleeding, incomplete haemostasis during surgery, coagulopathy may lead to hypovolemia. Distributive shock can be caused by sepsis due to a massive inflammatory response to infection. Apart from bacteria, fungi, viruses, parasites also can cause sepsis. Inflammatory cascade may cause vasodilatation and increased capillary permeability causing decreased circulatory volume and thereby hypotension. Cardiogenic shock may occur due to pump failure in cardiac hypotension because of intra-op and post-op fluid overload. Abnormal heart sounds, cardiomegaly and left ventricle dysfunction in echocardiography are the manifestations. Adrenal insufficiency may cause refractory hypotension even after fluid resuscitation in a patient with primary adrenal insufficiency or with a history of chronic steroid use.

Table 23.5 Diagnostic test for hypotension

Diagnostic test	Laboratory/imaging tests
Hypotension	CBC, BMP, lactate, ABG, ACTH stimulation testing and cortisol level; coagulation studies

23.7 Renal Function Derangement

In adults, if the postoperative urine is less than 0.5 ml/kg/h or < 300 cc/8 h it is considered low urine output or oliguria. Patients with blocked foley catheter may mimic oliguria. Prolonged low urine output (oliguria) may lead to fluid overload, thereby causing peripheral and pulmonary oedema. Monitoring of the intake and output with persistently increasing weight also suggests hypervolemia. Various significant electrolytes and acid–base imbalances, metabolic acidosis and uremia may result from decreased urine clearance. Especially, severe hyperkalemia in AKI can lead to life-threatening arrhythmias. Acute kidney injury (AKI) is considered when the serum creatinine level is greater than 1.5 times the baseline. As per Acute Kidney Injury Network, the absolute rise of creatine 0.3 mg/dL or more in 48 h period is considered AKI. The indications for acute haemodialysis are refractory electrolyte imbalances, refractory metabolic acidosis, severe volume overload and uremia. *Management*: AKI is treated by correcting renal hyperfusion. Intravenous hydration along with the removal of nephrotoxic drugs

is the most important step. Intravenous bicarbonate, sodium thiosulphate, N-acetylcysteine before long surgery may reduce AKI.

23.8 Stress Ulcer

Major surgery especially in cancer patients may give rise to stress ulcer or stress gastritis. Post-surgical sepsis, psychological stage, organ dysfunction may lead to stress ulcers. During severe surgical trauma and psychological stress, the protective mucus layer in the stomach is a less effective barrier for the gastric acidic content to protect the gastric mucosa due to decreased bicarbonate concentration. It is also noted that stress causes decrease blood to the gut, thereby mucosal lining may get affected by ischemia and lead to an ulcer. It is to remember that hypersecretion of acid does not play a significant role in the formation of stress gastritis or gastric ulcer as acid secretion is also reduced during this phase (Table 23.6).

Prevention: Stress ulcer or gastritis can be prevented or treated with H2 blockers like ranitidine or proton pump inhibitors like omeprazole, pantoprazole to suppress the acid secretion. Prophylactic acid suppression should be given to all major surgical patients including cancer patients. Endoscopic application of haemostatic agents, cautery or clipping may be necessary for severe intractable bleeding.

Table 23.6 Diagnostic test for stress ulcer

Diagnostic test	Laboratory/imaging tests
Stress ulcer	CBC, upper endoscopy

23.9 Neurological Complications

Most common postoperative neurologic complication is delirium. The incidence of stroke is low with general oncosurgical procedures. Post-op delirium occurs mostly in older surgical patients (10–50%) and mostly seen in the patients of ICU. Delirium is a self-limited state and is related with the stress of major surgery in some susceptible patients. It is mostly due to the loss of physiological sleep patterns. The risk factors that can increase to develop delirium are advanced age, previous history of dementia, history of delirium, coli pharmacy and sensory impairment. The precipitating factors that can lead to delirium are psychological instability, any post-op infection and sepsis, electrolyte imbalances, acid–base imbalances, hypo or hyperglycaemia, renal and liver dysfunction, hypoxia and hypercapnia. Few medications may cause delirium like opioids, sedatives and antihistamines and withdrawal of benzodiazepines. The patient has altered mental status, disoriented and odd behaviour like agitation, hallucinations. Delirium is an acute onset and which is the most important feature to differentiate from underlying dementia. It is noted that if a patient of bowel anastomosis presents with delirium after 3–5 post-op day, one should consider abscess or anastomotic leak.

24 Intestinal Obstruction in Cancer Patients: An Overview

M. D. Ray

24.1 Introduction

We know hernia and adhesion are most common cause of intestinal obstruction. Malignancy in the gut wall may lead to dynamic intestinal obstruction after tubercular stricture. Common causes of a dynamic intestinal obstruction are postoperative period, electrolyte imbalance, diabetes, retroperitoneal surgery hematomas, renal surgery, pseudo obstruction, etc. Patients with intestinal obstruction may present as acute (frequently seen in small bowel malignancy), chronic or acute on chronic (frequent with large bowel malignancies), and close loop obstruction.

In proximal bowel, i.e. in duodenum and jejunum congenital and malignant obstruction are common but TB and malignancy are the predominant causes in distal small bowel malignancies. On the contrary malignancy is predominant than TB in large bowel. Following obstruction mortality can reach up to 13% without strangulation and up to 25% with strangulation. In around 80% patients presenting with mechanical bowel obstruction, the small bowel gets involved [1, 2] while the small bowel was actually affected in 76% [1].

The most important risk factors include:

- Prior abdominal or pelvic surgery.
- Abdominal wall or groin hernia.
- Intestinal inflammation.
- History of or increased risk for neoplasm.
- Prior irradiation.
- History of foreign body ingestion.

Studies suggest that the postoperative bowel obstruction occurs in 9.4% cases with adhesive disease in 2.4% [3]. Common causes of small bowel adhesive obstruction are a past history of intra-abdominal surgery or pelvic surgery and those with surgery of the large bowel. Other less common causes include surgery of female reproductive tract, appendectomy, adhesiolysis [3–6].

Specific Etiologies—The possible cause can be suggested by the age of the patient and antecedent medical history. For instance, in the West (USA and Western Europe), intraperitoneal adhesions, tumors, and hernias account for most common cases of mechanical SBO [1, 7]. Other causes include Crohn's disease (5%), gallstones (2%), volvulus (11%), and intussusception (6%) [8–13].

Those patients presenting without any history of abdominal surgery but presenting with clinical features suggestive of SBO, should be considered to have small intestinal tumor unless another cause could be proven.

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Specific clinical and diagnostic features of SBO are shortly reviewed below:

- *Adhesive bowel obstruction*—This is the most common cause for SBO, with up to 70% patients contributing to bowel obstruction in developed countries [14]. Around 80% of patients with adhesive SBO presents with a past history of abdominal surgery. Remainder of the patients have prior peritonitis or occasionally without a precipitating cause [14].
- Adhesive peritoneal bands occurring after an abdominal or pelvic surgery are the most commonly encountered causes of bowel obstruction. Even when a majority of these postoperative patients (90%) develops some form of intra-abdominal adhesions, only a few patients will need surgery for a bowel obstruction. Larger studies suggest that around 10–15% of patients will need admission for SBO related to adhesions [6, 15–17]. Out of these only 2–5% will need adhesiolysis.
- *Tumor*—The second common cause of SBO is obstruction due to tumor metastases (20% cases) [18].
- *Primary tumor*—Small intestinal tumors or primary tumors of the colon may be responsible for symptoms and signs of SBO. Carcinoid tumors, small bowel carcinoma, and lymphoma are common neoplasms of the small bowel that can cause SBO. Most frequent primary small bowel tumors reported to cause SBO were gastrointestinal stromal tumors (35%), lymphomas (25%), and adenocarcinomas (20%). Most common site is the ileum [19]. Patients with clinicoradiological features consistent with SBO but without a history of prior abdominal surgery or other usual risk factors for intestinal obstruction, further studies are necessary to diagnose small bowel etiology.
- *Distant spread of disease*—The most commonly encountered neoplastic cause of SBO is tumor metastases. SBO caused by metastases are usually preceded by a period of partial SBO. Sometimes, a part of bowel may get twisted around a metastatic tumor deposit leading to small bowel volvulus.
- Tumors with a tendency to cause widespread peritoneal metastases includes: colonic, ovarian, pancreatic, and stomach malignancies [14]. SBO has been described in nearly 30% patients with colorectal carcinoma and in more than 40% patients with ovarian carcinoma [20]. SBO can also occur due to tethering of bowel loops by serosal deposits.

Clinical features includes Severe vomiting, dehydration, and colicky pain in proximal SBO. Mild abdominal distension, pain, vomiting, dehydration in distal SBO. Constipation, obstipation in large bowel obstruction.

Many patients with chronic, partial obstruction may present with symptoms one superimposed over the other [8–10, 21–32]. Pain occurs more commonly in the periumbilical area along with cramping and paroxysms of pain every 5 min [29]. Progression from this cramping pain to more focal and constant pain indicates peritoneal irritation due to complications like ischemia, bowel necrosis. Sudden onset of this severe pain may indicate intestinal perforation. With proximal SBO, nausea and vomiting may become relatively severe. Patients with proximal SBO typically cease to take orally food or liquids and thereby reduced urine output. In multiple studies, abdominal distension was noticed as the most common finding on clinical examination occurring in 56–65% of patients [7, 24, 27].

Clinical features of acute mechanical bowel obstruction include pain, high-pitched "tinkling" sounds, abdominal wall or groin hernias or abnormal masses. In SBO, all these may indicate an abscess, volvulus, or tumor. A rectal examination may suggest fecal impaction or rectal mass. Passage of blood (either occult or gross) may be related to tumors, inflammatory disease, or intussusception.

Blood examination—This includes a complete blood count with serum electrolytes, urea and creatinine. A leftward shift with leukocytosis suggests complications. Metabolic alkalosis can result from severe vomiting, but lactic acidosis can also occur due to ischemia [33]. An increased blood lactate levels is sensitive for ischemia (sensitivity = 95%, specificity = 70%) [30, 31].

Chronic obstruction—Chronic SBO occurs in a fixed segment of bowel. The obstruction is partial. Common etiologies of chronic, partial SBO include chronic stricture from Crohn's disease and adhesions.

Recurrent SBO—These patients should be distinguished from the patient with a chronic, partial SBO. Adhesive recurrent obstruction due to adhesions can occur in a fixed or multiple segments of bowel. Focal band-like adhesion is more likely to respond to surgery compared with those due to diffuse adhesions, for which surgery is more harmful than help. The likelihood of recurrent obstruction increases with increasing number of episodes in the past [34]. Those after three prior episodes, the likelihood of recurrent obstruction is very high (80%) [35].

Abdominal X-ray and contrast-enhanced computed tomography scan of the abdomen are the most frequently performed imaging modalities to diagnose the cause of obstruction.

Pathophysiology Proximal to the obstruction

1. Increased peristalsis

↓

Persistently increasing

↓

Obstruction not relieved

↓

Cessation of peristalsis

↓

Flaccid, Paralyzsed, and dilated bowel

2. Accumulation of fluids:

Derived from saliva, stomach, pancreas, and by own secretion of bowel

↓

Absorption decreases (because ofoedema and inflammation)

↓

Sequestration of fluid from circulation into the lumen

↓

Bacteria (like E coli, Klebsiella, anaerobes, and others) multiplies

↓

Release of toxin

↓

Toxaemia

↓

Severe dehydrationand & electrolytes imbalance

3. Air accumulation:

Proximal to the collected fluid from swallowed air — 70%

Diffusion from blood into lumen — 20%

From digestion and bacterial action — 10%

Nitrogen and hydrogensulphidesulfide — 90%and10%, respectively

↓

Due to increase peristalsis air enters into the distal fluids, causing multiple air fluid level.

4. Defective absorption:

Loss of fluid by vomiting sequestration into bowel lumen and due to less intake

↓

Severe dehydration

↓

Fluid electrolyte imbalance

5. Changes in bowel wall:

Intestinal wall hypoxia and as a result of inflammatory response of bowel wall accumulated neutrophils, macrophages release reactive enzymes and cytokines which may lead to bowel wall dilation.

↓

Increase intraluminal pressure causing ischemic bowel wall injury when it excess venous pressure.

↓

More increase luminal pressure block arterial perfusion

↓

Bowel wall necrosis / gangrene

↓

Perforation

↓

Toxaemia

↓

Faecal peritonitis

↓

Septic shock

Systemic disorder because of

Dilation of bowel proximal to the obstruction

↓

Decreased absorption

↓

Increased secretion and collection in lumen

↓

Intramural inflammation less tissue oxygenation

↓

Increased intramural pressure

↓

Venous congestion and venous pressure

↓

Disruption of mucosal barrier

↓

Bacterial translocation

↓

Septicaemia and consequences

Close loop obstruction (Figs. 24.1 and 24.2):

Malignant obstruction in large bowel

↓

with competent ileocecal vulva

↓

Pressure in the caecum

↓

Stercoral ulcer in the caecum

↓

Gangrene

↓

Perforation

↓

Faecal peritonitis

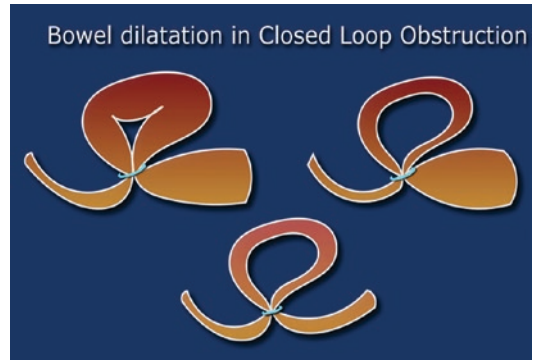

Fig. 24.1 Bowel dilatation in closed-loop obstruction

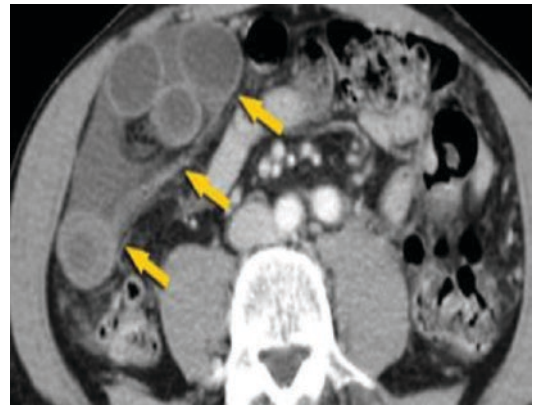

Fig. 24.2 CT scan shows close loop obstruction

Perforation may be at the site of obstruction due to malignant infiltration of the bowel.

Distal to the obstruction, the bowel becomes collapsed and inactive.

Clinical features:

1. Abdominal pain:

Main feature initially colicky and intermittent

↓

Later constant and severe

- SBO—pain starts around umbilicus, crampy, and repeated episode almost every 30 seconds.
- Large bowel obstruction: pain usually diffuse, mild to moderate repeated episode of 1–2 min.
- Paralytic ileus persistent diffuse pain.

2. Vomiting:

In pyloric and jejunal obstruction—it is early and persistent.

In ileal obstruction—Recurrent bilious Feculent later on.

In large bowel—Nausea is predominant feature. Vomiting is a late feature.

3. Distension: it is common in large bowel obstruction.

Ileal obstruction:

– It is visible.

– Borborygmi sounds.

– Step ladder pattern of persistalsis.

In pyloric or jejunal obstruction—it is usually absent or sub clinical.

4. Constipation: Either it is only absence of passing feces or absolute where neither flatus nor feces is passed.

Instead of constipation there may be diarrhea in the following conditions:

(a) Partial obstruction of lumen by tumor or hard feces.
(b) Richter's hernia.
(c) Gallstone obstruction.
(d) Mesenteric ischemia.
(e) Pelvic abscess.

On Examination Vitals-Tachycardia, tachypnea, Raised temperature, cold periphery, sunken eyes

Abdominal tenderness—localized and diffused.

In strangulation—guarding and rebound.

Tenderness may present.

Bowel sounds:

High pitched metallic

↓

Tinkling metallic sound in a dilated bowel.

Only continuous metallic sound in paralytic ileus.

↓

Silent abdomen on perforation peritonitis

DRE:

- Empty dilated rectum
- May be tender
- Boggy swelling in pelvic abscess

Investigations:

- X-Ray supine to see air-fluid levels >3 in number. (Normal in three sites—Fundus of stomach, Duodenum, Caecum.) Proximal obstruction—less air-fluid levels. Distal the obstruction—more air-fluid levels.
- X-Ray erects to see gas under diaphragm if perforation is suspected.

X-Ray features of

(a) Jejunum—concertina effect due to valvulae conniventes. (It appears herring bone pattern.)
(b) Ileum—Smooth and characterless
(c) Large bowel shows—haustration and dilated caecum indicates large bowel obstruction.

Definition of dilation:

- Small bowel > 3 cm.
- Ascending colon > 6 cm.
- Transverse colon > 5.5 cm.
- Sigmoid colon > 5 cm.

Abdominal X-ray with features of SBO includes:

- Multiple dilated intestinal loops with air-fluid levels
  - Supine position: Here the air-fluid interface is found to lie parallel to the x-ray plate. The distension caused by air and fluid-filled loops allow an approximate estimation of the amount of distention.
  - In either upright or lateral position: In these patients the air-fluid interface is perpendicular to the X-ray film. Multiple air-fluid levels with distended small bowel loops can be noticed.
- Proximal bowel dilation with collapse bowel distally—Diagnosis of SBO can be done if the proximal small bowel is dilated >2.5 cm and distally the small bowel is not dilated [7, 14]. Stomach can also be dilated. The diagnosis of mechanical SBO can be done if the air-fluid levels differ by >5 mm from each other within the same loop of small bowel on upright films [36].
- Gasless abdomen—Complete filling of loops of bowel with sequestered fluid can lead to a gasless picture on X-ray. Severity of the bowel obstruction may be unknown in such situation. In predominantly fluid-filled small intestinal loops, upright or lateral films may show a string of pearls sign. This is due to small amounts of intraluminal gas collected along the superior intestinal wall separated by the valvulae conniventes [14].

On plain abdominal X-ray, the sensitivity and specificity of SBO can range, respectively, from 79 to 83%, 67 to 83% [36–38].

Plain abdominal films are less useful for differentiating between small and large intestinal obstruction [37, 39].

Role of CT scan in Intestinal obstruction:

- 93–95% sensitivity.
- 95–96% accuracy.
- 99–100% specificity.

Abdominal CT scan—An abdominal CT scan helps in identifying the site and severity of obstruction [40]; It is helpful in identifying hernias, masses or inflammatory changes; and possible complications (ischemia, necrosis, perforation) [14, 41–43]. In patients with high-grade SBO, the sensitivity, specificity of CT scan are, respectively, 90–94% and 96% [44–49]. Among those with a low-grade obstruction, the accuracy of CT is decreased [50].

- 50 mm: sensitivity 79%, specificity 87%.
- 5–10 mm: 87% sensitivity, 81% specificity.
- 0.75 mm: sensitivity 96%, specificity 100% (one study).

An abdominal CT scan features suggestive of bowel obstruction includes [51–54]:

- Transition point.
- Bowel hernias and mass lesions.
- Bowel wall thickening >3 m.
- Submucosal edema/hemorrhage.
- Mesenteric edema.
- Ascites.
- "Target sign"—alternating hypo/hyperdense layers, indicative of intussusception.
- "Whirl sign"—rotation of small bowel mesentery, suggesting a twist or a volvulus.
- "Venous Cut-off Sign"—venous flow to a loop of small bowel that is "cut-off" suggests thrombosis.

CT correlates intraoperative site of bowel obstruction in about 60–70% of patients [55, 56]. The presence of a transition point on abdominal CT should not be used to influence a decision to operate [55, 57]. Abdominal exploration will be required to make a definitive diagnosis in many patients [58]. A closed-loop obstruction often appears on CT as a distended, fluid-filled, C-shaped intestinal segment with prominent mesenteric vessels converging on a point of torsion [51]. A triangular loop (the beak sign), and the presence of two collapsed bowel loops adjacent to an obstruction site are other features that may be seen on CT scan [52]. Presence of intraluminal air should suggest a diagnosis of perforation.

- Pneumoperitoneum: It is a sign of perforation of the intra-abdominal gastrointestinal tract (small bowel, transverse colon, sigmoid colon) and may be detected either as one of

the following: (1) Air under the diaphragm on upright abdominal X-ray, (2) Air over the spleen or liver on lateral abdominal film or abdominal CT, and (3) Air as a "football sign" on supine abdominal film or abdominal CT.
- Free air in the retroperitoneum may indicate perforation of the duodenum or retroperitoneal portions of the colon: This can be detected as (1) Psoas sign on supine abdominal film and (2) Air adjacent to the second portion of the duodenum on plain abdominal film or abdominal CT.

Having said that, none of these signs are highly sensitive or specific [59, 60]. A combination of these findings on clinicoradiological evaluation increases the reliability of diagnosing ischemia [61, 62].

- Poor or absent segmental bowel wall enhancement.
- Delayed hyperenhancement.
- Bowel wall thickening.
- Small bowel feces sign.
- Air in the bowel wall (pneumatosis intestinalis).
- Edematous, thickened mesentery.
- Engorgement of mesenteric vessels.
- Hemorrhage in the mesentery.
- Portal or mesenteric venous gas.
- Ascites.

Paralytic ileus—This condition occurs to some extent after almost all open abdominal surgeries. Other causes include peritonitis, trauma, intestinal ischemia, and medications like opiates, anticholinergics, etc. Electrolyte disorders, especially hypokalemia increases paralytic ileus. The patient may experience symptoms similar to mechanical obstruction when intestinal loops get distended. Sometimes on imaging air may be observed in the colon and rectum but on abdominal computed tomography (CT) no demonstrable mechanical obstruction can be found [63, 64].

To differentiate early postoperative ileus from postoperative adhesive disease, it should be noted that nearly all patients with early postoperative bowel obstruction resumes the return of bowel function and oral intake. This is followed by nausea, vomiting, abdominal pain, and distention. In adynamic ileus there is no return of bowel function [65].

Pseudoobstruction—This is a chronic condition characterized by features of recurrent abdominal distention. This may be associated with nausea, vomiting, and diarrhea. The large bowel is more frequently involved than the small bowel. Usually no mechanical cause can be demonstrated in such occasions. The patient frequently has a history of several previous operations for bowel obstruction but no etiology could be found for obstruction.

In patients with colonic volvulus, one study reported that the most frequent symptoms of colonic obstruction in their study were abdominal pain in 58% and obstipation 55% cases [28].

Complications Peritonitis, Hypovolemic shock, septic shock, acute renal failure ARDS, Intra-abdominal abscess.

Management Diagnosis and Treatment.

Diagnosis apart from confirmatory X-Ray, CT Scan, Routine investigations are required

CBC, LFT, KFT, Electrolytes

Usually high count acidosis, hypokalemia and thrombocytopenia are the features.

Treatment

1. Ryles tube—aspiration to relieve symptomatically and to prevent aspiration Pneumonia.

   I V lines—replacement of fluid electrolytes.

   Foly's Catheter—monitor urine output.
2. I V Antibiotic—Ciprofloxacin/Cephalosporin, Amikacin/Gentamycin, Metronidazole.
3. Blood and FFP transfusion.
4. ICU Care: CVP, ARDS, DIC.
5. Surgery:
   - If conservative management fails.
   - Relieve of obstruction like bypass of the tumor occlusion (Figs. 24.3 and 24.4).
   - Perforation—Toileting, Resection, and anastomosis of feasible.

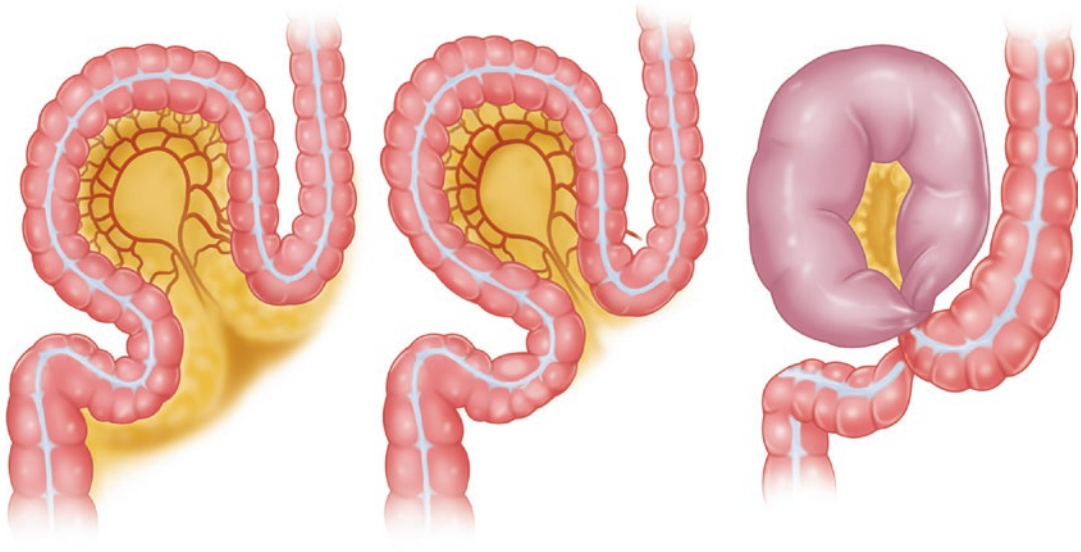

Fig. 24.3 Closed loop large bowel obstruction

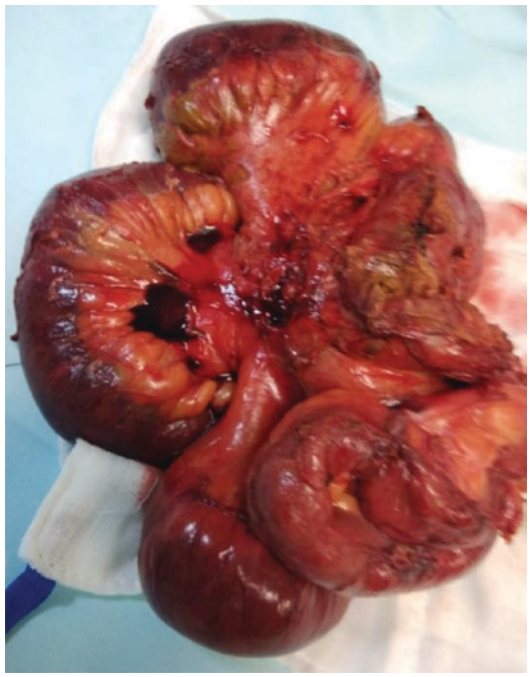

Fig. 24.4 Resection after close loop colonic obstruction by tumor

24.2 Summary

- Intestinal obstruction occurs when the normal flow of bowel contents is interrupted. This leads to bowel dilation and sequestration of fluid within the lumen of the intestine proximal to the blockage.
- Blood flow to the intestinal tissue can be compromised due to excessive bowel dilation or strangulation. This can lead to complications (ischemia, necrosis, perforation), which significantly increase mortality associated with bowel obstruction.
- Commonest cause of mechanical SBO is postoperative adhesions from prior abdominal or pelvic surgery. These adhesions cause extrinsic compression of the bowel. Patients who had undergone appendectomy, gynecologic surgery, prior adhesiolysis, exploration for abdominal trauma, and prior resection for malignancy are particularly prone to adhesive SBO. Adhesions can also occur in the absence of prior surgery due to intestinal inflammation (Crohn's disease, diverticular disease). Other conditions that can cause extrinsic compression of the intestine are hernia and volvulus.
- Intestinal obstruction can also be due to disease limited to the wall of the intestine (e.g., tumor, stricture, intramural hematoma). This can also occur from other situations causing intraluminal obstruction (e.g., intussusception, gallstones, foreign body). Those patients who present with symptoms highly suggestive

of SBO but no past history of abdominal surgery, should be considered to have small bowel tumor until proven otherwise.

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25 An Overview of Post-operative Enterocutaneous Fistula and Vasicovaginal Fistula in Cancer Patients

M. D. Ray

25.1 Introduction

Enterocutaneous fistula and vesicovaginal fistula could be challenging, frustrating or may be rewarding at a point of time. Post-operative enterocutaneous fistula account for about 75–80% cases [1]. Rest of the fistulas may occur spontaneously in malignancy and post-radiation patients and it is defined as a communication between two epithelialized surfaces. Fistulas related to malignancy, irradiation or along with active inflammation are less likely to close spontaneously. Post-operative fistula formation is most common following the various treatments for cancer patients. Treatment requires understanding of metabolic and anatomic derangements. Malnutrition with concomitant sepsis remains principle causes of death in patient with fistulas.

25.2 Definition and Classification

By definition, a fistula is a communicating tract between two epithelial lined surfaces. It could be classified best on the basis of anatomy, physiology or etiology (Table 25.1). The anatomy of fistula suggests its etiology and can estimate likely hood of spontaneous closure. Knowledge of the anatomy of fistula is important to plan the operative strategy for the closure. Physiological classification is best on output in ml/day. High output fistula >500 ml/day, most likely to originate from the small bowel. Low output fistula is <200 ml/day, most likely to be of colonic origin. Moderate output fistula drains between 200 and 500 ml/day. Post-operative fistula accounts for 75–80% of all cutaneous fistulas. Post-operative fistula is most common following cancer operations, inflammatory bowel disease operation, and lysis of adhesions.

In a case of enterocutaneous fistula the diagnosis is very obvious. The typical post-operative fistula is manifested on day 5 or 6 post-operative period with fever and persistent ileus [2].

25.3 Prevention

In the post-operative period, it is necessary to ensure that the patient continues to receive full nutritional support. Adequate protein and calories must be provided to maximize healing and minimize complications. Although enteral nutrition may be attempted early in the post-operative course, it is nearly impossible to meet the patient's entire nutritional demand by this route. Thus, post-operative care will most likely include parenteral and enteral supplementation in an overlapping manner.

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Table 25.1 Types of fistula

Category	Type of fistula	Uses of information
Anatomy	Internal vs. external	Can help identify cause of fistula
	Anatomic course	For planning operative closure
		Can predict spontaneous closure
Physiology	Output (ml/day)	Predictor of mortality
	Low (<200)	Predictor of metabolic derangements
	Moderate (200–500)	
	High (>500)	
Etiology	Based on the underlying disease process	Predictor of fistula closure rate
		Predictor of mortality

After fistula closure, whether by spontaneous or surgical means, the patient will need to resume oral intake. This may be especially difficult in an individual who had little or no oral intake for 4–6 weeks or more, and enlisting the assistance of a dietician and the patient's family is often helpful. Weaning enteral and parenteral nutritional supplementation and switching to nocturnal tube feeds may help to increase appetite (Table 25.1).

25.4 Etiology and Risk Factors

Post-operative fistulas are results of bowel injury during surgery, a leak from a bowel anastomosis, erosion of foreign material into adjusting bowel like after mesh repair for hernia. Many pre-operative factors like malnutrition, immunosuppression, infection, even emergency procedure may develop this kind of fistula [3].

Cancer—In a patient with cancer may develop enterocutaneous fistula, vesico vaginal fistula (VVF) on the process of disease progression.

Radiation—Radiation especially pelvic radiation may cause recto vaginal fistulas, VVF or enteric fistula.

25.5 Clinical Features

Initial presentation is often abdominal drainage depending upon the location and origin of the fistula. Development of diarrhea or gastrointestinal bleeding may be another mode of presentation. In post operative cases, fistula formation is likely among patients who fails to recover normally from abdominal surgery. Patients can present with abdominal discomfort, distension, tenderness, fever or features of abdominal sepsis. Usually wound infection is diagnosed 7–10 post op day following the drainage from the incision side and enteric contents come out. Symptoms may include also abdominal pain, nausea, vomiting, obstipation or constipation.

25.6 Diagnosis

In the post-operative patients with incisional drainage continuously after 5–7 post op days is the clinical diagnosis for enterocutaneous fistula. CT scan abdomen is the investigation of choice to demonstrate the anatomy of fistula and fluid collection, site of distal intestinal obstruction, abscess [4].

Fistulogram can also document intestinal continuity and evaluate the distal obstruction. The fistulogram is performed by injection of a water soluble contrast agent into the fistula tract. Different dyes can be used like indigo carmine, methylene blue which can be injected IV, ingested or added to enteric feeding instilled as solution into the bladder or rectum through a catheter or during endoscopy. Endoscopic evaluation both vaginal and rectum can also help to evaluate the tract of fistula.

Before diagnosis of fistula, one has to exclude surgical site infection, serous discharge through the abdominal wound, localized gastro intestinal perforation.

25.7 Initial Management

Initial management of enteric fistula include the correction of fluid electrolyte balance, control of infection, drainage of abscess, nutritional support, skin care, etc.

Fluid therapy—Proper correction of hypovolemia and electrolyte imbalance is essential [5]. Hypokalemia is the most common electrolyte imbalance. Ongoing fluid loss to be supplemented by normal saline and potassium. High output fistula may require electrolyte analysis from the effluent to make an appropriate choice of fluid. Replacing fluid losses (cc per cc) is essential to prevent dehydration and hypovolemia.

Control of infection—Associated infection, abdominal sepsis related to GI perforation causing the fistula, needs to be recognized and promptly treated with antibiotics. Peritonitis is a surgical emergency requiring laparotomy to control the source of infection. In case of uncontrolled sepsis, exteriorization of the fistula or ostomy to divert the fecal stream is essential.

Percutaneous drainage of abscess or infected collection are important to control sepsis. The drainage catheter usually left in place until drainage is <10 ml in 24 h, which may take as long as 30 days. Catheter fistulogram during this period permit the assessment of resolution of the cavity. Surgical intervention is required if improvement does not occur with the drainage.

Covered enteric stents are used to treat early post-operative leaks of the esophagus or colon thereby allowing the patients to stabilize.

Nutritional support—In an initial phase of treatment till the time source of fistula is controlled, patient to be on NPO. Nutritional support to be initiated slowly after correction of fluid, electrolyte, and vitamin deficits. Base line requirement of carbohydrate, fat, and protein are increased for patients with ongoing peritonitis. Usual requirements are 20–30 kg cal/day of carbohydrate and fats along with 1–2.5 g/kg of protein/day. In addition, omega 3 fatty acid improves immune function. If fistula is low to moderate patient may be allowed to eat to preserve the intestinal mucosal barrier and has positive effects on immunologic and hormonal gut function. Some patients require parenteral nutrition support. Approximately 1/3rd of enterocutaneous fistula heal spontaneously with these majors. Patients who do not respond to conservative measures will require surgical management.

25.8 Management of External Fistula Output

Owing to the enteric contents, the surrounding skin may be eroded. Skin protection cream and effluent collection bags must be applied to care the stoma and skin. For enterocutaneous fistula sump or pouch should be placed around the fistula, the adjacent skin to be protected by barrier dressing or with other skin protectants.

Controlling intestinal contents draining out from the fistula is essential to minimize damage to the healing granulation tissue bed.

Pharmacological therapy—Anticathartics and somatostatin analogs have been used to reduce the output from intestinal fistula. Anticathertics such as Loperamide, atropine, diphenoxylate may be used to control diarrhea and high output fistula. Maximum dose of 16 mg low paramide and 20 mg diphenoxylate could be used 20 min prior to the consumption of food. Somatostatin analogs like octreotide may have some role to reduce output and facilitate absorption of water and electrolytes. With the distal obstruction octreotide will be futile and will delay the surgical procedure.

Negative pressure treatment of wound—Use of negative pressure wound therapy in fistula management becoming white spread. It may accelerate fistula closure by promoting wound healing [6]. Continuous suction of fistula output is necessary to minimize contact time between intestinal content and peritoneum thereby controlling intestinal spillage. Using this technique, majority of intestinal effluent can be collected in the tube (Fig. 25.1).

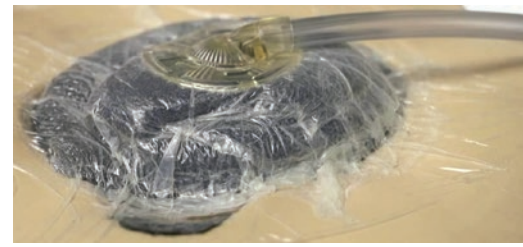

Fig. 25.1 Negative pressure wound therapy

25.9 Entero-atmospheric Fistula

Superficial—Direct local closure should be attempted whenever possible. However, in most of the cases, a superficial entero atmospheric fistula will required placement of skin grafts to the surrounding granulation tissue to allow placement of stoma bag. After the grafts heal stoma management can be adapted to the specific requirement of fistula [7].

Deep—For deep entero-atmospheric fistula, immediate surgery is indicated to manage peritonitis. Most of the patients with deep fistula will not have any option for early closure. Exteriorization or proximal diversion is often difficult because of excessive edema of both bowel and abdominal wall as well as mesenteric thickening and shortening. In this case tube drainage is not practical or useful as it may enlarge the opening around the tube. So creation of a "floating stoma" can gradually convert a deep entero-atmospheric fistula into a superficial fistula over a period of several weeks. To create a floating stoma, the whole edge of the fistula in the bowel is sutured to a similar size hole tailored in a plastic seat. This serves as a temporary abdominal closure device. By this way it separates the intestinal drainage from the open peritoneum.

The goal of definite surgery is to resect fistula re-establish gastrointestinal continuity and provide a tension free closure. Before consideration for definite repair, correction should be done for nutritional deficit and any wound infection be treated. Also assessment should be done for availability of adequate soft tissue adjacent to the fistula.

25.10 Vesico Vaginal Fistula

Vesico vaginal fistula is one of the common and distressing consequences after surgery in many developing countries. It represents a significant morbidity in female [8]. Most probably the cause of high incident and prevalence of VVF is socioeconomic.

Classification Simple fistula are usually small in size <0.5 cm. The complex fistula includes large size >2.5 cm and intermediate sized fistula between 0.5 and 2.5 cm.

Etiology Postsurgical, especially after the surgery for gynecological malignancy, wrong suture technique during closure of vaginal vault after hysterectomy, radiotherapy, advanced pelvic malignancy itself can cause VVF.

Clinical presentation The classical presentation is continuous in passage of urine from the vagina after a recent pelvic surgery. If fistula is smaller than the watery discharge from the vagina may be accompanied by normal voiding for a sort time. However, radiation induced fistula may present even after a long time.

Diagnosis The evaluation of fistula size number, exact location are important and better pre op diagnosis may have better surgical plan. Postoperative VVF is easily diagnose with urine leakage through the vagina. This usually occurs between 7th and 12th day following a pelvic surgery. Diagnosis can be made by filling the bladder with a dilute solution of methylene blue dye solution. Cystoscopy also helps and can clarify the exact anatomic origin. Physical examination also plays an important role. CT urography recently has developed to diagnose the fistula accurately. Trans vaginal sonography also can evaluate the site, size, and course of fistula. An intravenous pyeloureterogram should also be done to rule out concomitant ureteral fistula before deciding for definite surgical repair. Postradiation involvement of rectum may change the surgical approach.

Treatment In around 10% of cases the fistula closes spontaneously within 2 months after catheterization and anticholinergic medication especially in case of small fistula. If diagnosis is delayed and fistula has epithelized, electrocoagulation of mucosal layer should be done along with 2–4 weeks of catheterization. Estrogen (Estradiol) vaginal cream 4–6 g weekly or 2 g thrice weekly on alternate days should be used for 4–6 weeks. Classically a delayed repair is

done usually after 3–6 months. A minimum of 8–12 weeks is allowed for healing of any inflammation and edema even after radiation damage delay of minimum 1 year is reasonable. The first step before repair is to control infection. Simple VVF could be repaired through vagina. For complex VVF repair should be done either vaginally using myocutaneous flap or through an abdominal approach [9]. The O' Coonnner operation utilizes suprapubic access for extra peritoneal dissection of the retro pubic space to mobilize bladder followed by long sagittal cystotomy till the fistula is reached. The fistula tract is excised followed by two layer closure. Abdominal approach for repair has good results with durable success (80–100%). VVF after radiation therapy should be repaired using flaps. Omental flap is most versatile. Laparoscopic/Robotic repair of VVF has also been described successfully in selected patients [10]. It is performed without opening of bladder and using intracorporeal suturing and omentum inter positioning.

Post op care Continuous bladder drainage is essential for a minimum of 3–4 weeks. During this period a high fluid input and output should be maintained till the urine becomes clear. Anticholinergic drugs should be administered. Patients should avoid coitus for 3 months. Antibiotics to be given for a long time, usually till the catheter is removed. In patients with recurrent disease and large fistulas the interposition flap is considered to be a protective factor.

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Management of Chylous Ascites: A Short Review

26

M. D. Ray

26.1 Introduction

Chylous ascites is a rare type of ascites characterized by milky triglyceride rich peritoneal fluid due to iatrogenic injury of lymphatic channels or malignant obstruction. Though rarely reported in world literature, it is relatively common after retroperitoneal lymph node dissection which is common to a variety of cancer treatment. Literature reports an incidence of 0.17–3% of chylous ascites after RPLND. Treatment options include conservative measures, interventions, and surgical options. Conservative options include paracentesis, medium chain triglyceride (MCT) based low fat and high protein diet, somatostatin, alpha-1 agonists, diuretics, and total parenteral nutrition (TPN). Interventions include embolization and image-guided sclerotherapy. Surgical options include peritoneovenous shunts and lymphatic duct ligation. Due to rarity of the condition and scarce literature on management options, no guidelines or systematic treatment guide is available but in most of the cases it is managed conservatively or with minimal intervention.

26.2 Anatomy of Lymphatic System

Unidirectional flow of lymph occurs through the lymphatic system comprising a complex of lymphatics, lymph nodes, and lymphoid organs. Along with immune function, they play a role as a return route for excess interstitial fluid to blood and absorption of nutrients from gut. Initial intestinal lymphatics present in villi absorb fat and fat soluble vitamins and drain into the sub mucosal lymphatic system. These lymphatic drains into retroperitoneal structure, cisterna chyli, which also receives lymphatic drainage from the lumbar lymphatic trunks [1]. Cisterna chyli marks the termination of retroperitoneal lymphatic system and start of thoracic duct. It marks a transition point of chylomicron rich lymphatic fluid and fluid with less chylomicron. Injury above the level of cisterna chyli leads to accumulation of odorless, alkaline, and sterile fluid rich in triglycerides (>200 mg/dl) and chylomicrons in peritoneum. Any injury below its level leads to leakage of clear serous fluid low in triglyceride containing creatinine and BUN corresponding to concentration in serum [2] (Fig. 26.1).

26.3 Composition of Chyle

Chyle is a sterile milky fluid formed in the lacteal system of the intestine containing primarily protein, fat, fat soluble vitamins, and T-lymphocytes.

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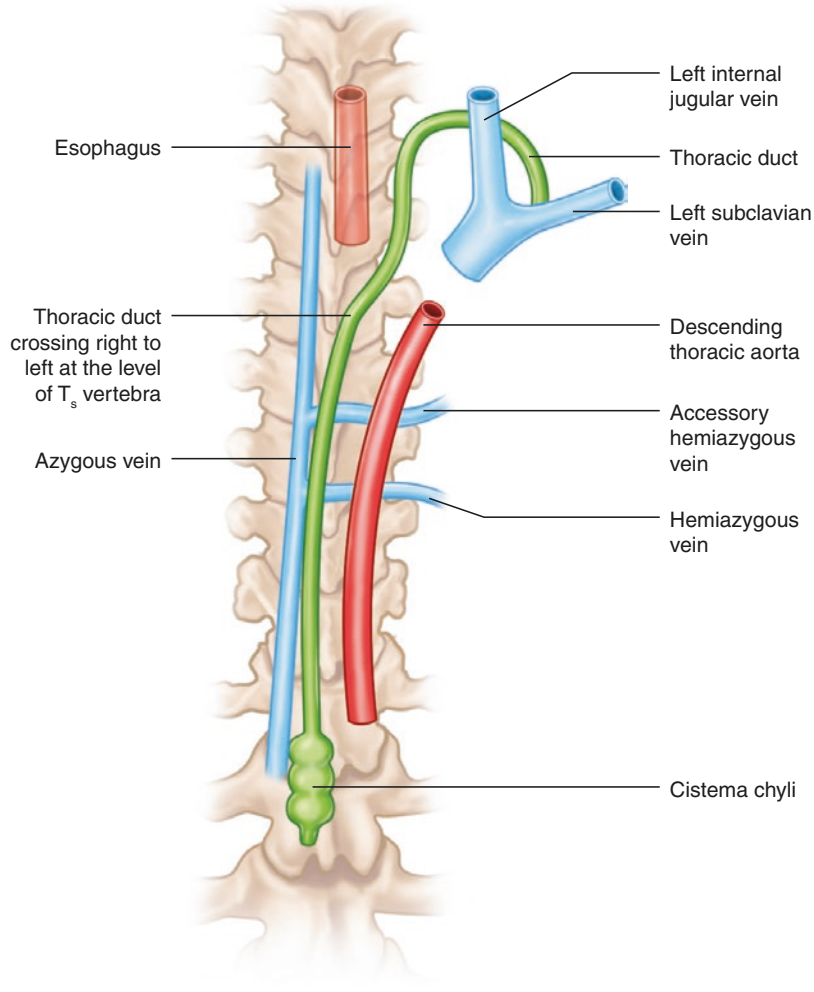
Fig. 26.1 Course of thoracic duct



Course of thoracic duct

Long chain fatty acids released from long chain triglycerides (LCT) are transported in combination as chylomicrons through the lymphatic system thereby imparting milky and cloudy appearance of the chylous lymph. In contrast, fatty acids released from medium chain triglycerides (MCT) are transported via portal vein. The easier and rapid absorption of the MCT is the principle behind use of MCT based diet in initial conservative management for chylous ascites with enteral feeding. In a study by Blalock et al., based on animal studies, they observed that chylous ascites is usually not seen in cases of thoracic duct obstruction alone due to opening of anastomotic channels for lymph flow. However, in patients with limited patent anastomotic channels due to prior surgery or malignancy there is higher risk of developing chylous ascites in cases of obstruction or injury of lymphatic channels.

26.4 Pathophysiology of Malignant Chylous Ascites

1. Direct leak of chyle from intestinal subserosal lymphatic system into peritoneal cavity due to malignant obstruction of draining lymphatics and lymph nodes.

2. Malignancy may cause fibrosis of the primary lymph nodes and may lead to leakage.
3. As a result of surgery, like retroperitoneal lymph nodes dissection, resulting in direct leakage of lymph to the peritoneal cavity. Cytoreductive surgery, surgery in IVC or around it, nephrectomy may cause chylous ascites. Liver cirrhosis is one of the important causes of chylous ascites which is to be kept in mind.
4. Radiotherapy for gynecological malignancies may lead to 3–5% incidence of Chylous ascites.

Etiology Most common cause of chylous ascites in adult is malignancies (25%), cirrhosis (16%), and tuberculosis (15%). Post-traumatic chylous ascites, including post surgial interventions, is one of the important causes for chylous ascites [3, 4]. Among the group of malignancies, lymphoma is responsible for 30–35% cases [3]. Germ cell tumor of testis, cancer stomach, pancreas, gynecological malignancies are most important malignant causes for chylous ascites. Direct infiltration or extrinsic compression may also obstruct the normal lymphatic flow and as a result of disruption chylous ascites can form [5]. In developing countries like India, abdominal tuberculosis is one of the most important causes to develop chylous ascites [4].

Clinical presentation The presentation of patients depends on the cause and amount of fluid accumulated. Small chylous ascites due to lymphatic obstruction in malignancy can be asymptomatic and incidental finding [2, 6]. Large ascites present with abdominal distension and discomfort. Most common symptom is abdominal distension seen in 80–85% cases, other important causes are pain abdomen and features of peritonitis in 10–15% cases. Pain may be due to distension of retroperitoneum and mesenteric serosa or may be direct contact of lymph with peritoneum. Weight gain, shortness of breath, anorexia, malaise, nausea, early satiety may be the other presentation. Post-surgery it may present as large drainage volume in drains (either chyle or lymphatic fluid), leakage of fluid per vagina, abdominal distension, bloating, fever, etc.

Complications In post-operative patients chylous ascites may lead to increased morbidity and even mortality. Long standing and large chylous ascites leads to malnutrition, dehydration, immunosuppression, increased susceptibility to infections and failure to thrive. Repeated paracentesis provides relief from symptoms but nutritional deficiency will persist [7].

Clinical Diagnosis In post-operative period, particularly, after RPLND or nephrectomy if drain fluid appears cloudy and turbid, this could be chylous ascites. One thing to remember is that in case of cancer or infection there is cellular degeneration from infection and drain fluid may appear turbid and cloudy—which is called pseudochylous ascites but it is without high levels of triglyceride. This cloudy fluid should be sent for triglyceride estimation which if more than 110 mg/dl should be considered suspicious and >200 mg/dl is mostly confirmatory for chylous ascites. Aspirated ascitic fluid is sent routinely for total and differential cell count; culture and sensitivity; fluid biochemistry for total protein and albumin, LDH, amylase; cytology for any malignant cells; and adenosine deaminase activity (ADA) for tuberculosis. Gold standard investigation for diagnosing chylous ascites is lipoprotein electrophoresis for identification of chylomicrons.

Ascitic Fluid

Characteristics	Value
Color	Turbid and cloudy
Cell count	>500 lymphocytes predominance
Total protein	2.5–7 g/dl
LDH	120–200 IU/l
Glucose	<100 mg/dl
Cytology for malignant cells	Positive in malignancy
ADA	≥40 IU/l in TB

Management of Chylous Ascites multiple options are available for management of chylous ascites, including nutritional regimens, pharmacological, and surgical therapies. But still there is no clear consensus on the optimal management of chylous ascites. Treatment of causes, infec-

tion, inflammation, and hemodynamic instability are the basic aspects of management in resolution of symptoms and complications of chylous ascites. Treatment aims at reducing the chyle production and flow, maintenance of nutrition, and prevention of infection.

Dietary management The appropriate management of chylous ascites includes dietary modifications for decreasing chyle production, correcting fluid and electrolyte imbalance, and supplementing proteins and carbohydrate for malnutrition. High protein, low fat diet is recommended.

- As long chain fatty acids are main constituent of chyle, restriction of Long chain triglycerides (LGT) in diet leads to decreased chyle production. Low fat diet with Medium chain triglycerides (MCT) which are directly absorbed and transported via portal circulation to liver as glycerol and free fatty acid. Remember, in liver cirrhosis MCT may lead to coma if it is used as narcotic agent. In such case low sodium diet with diuretics are advisable. The MCT diet includes coconut oils, coconut water, milk, and milk products.
- Bowel rest and Total Parenteral Nutrition (TPN) reduces the lymphatic flow to <1 ml/min and also prevent from nutritional deficiency. This is an effective therapy for the management of chylous ascites. Somatostatin/octreotide can be used as an adjunct to TPN for symptomatic relief and closure of lymphatic fistula. Surgeons usually prefer a trial of dietary modifications before opting for TPN because of its complications such as catheter related complications, dyselectrolytemia, nutritional deficiencies, etc. although no head to head trial between MCT based enteral feeding and TPN has been done [8, 9].
- Promising results have been there by the use of somatostatin/octreotide [10]. Receptors of somatostatin are present in pancreas, vascular tissue, gastrointestinal tract, and smooth muscle cells of thoracic duct. As a result of action on their receptors there is reduction of splanchnic blood flow, reduced portal pressure, reduced gastrointestinal motility, and reduction of chyle production due to decreased absorption of fat. Typically drain output is decreased after 24–72 h of administration. Hundred percent resolution of chylous ascites was reported when octreotide was added to MCT diet or TPN. Other drugs like orlistat (reversible lipase inhibitor) and etilefrine (sympathomimetic) have been used to treat chylous ascites but enough evidence is warranted [11–13].

Abdominal paracentesis Repeated paracentesis or permanent catheter placement can provide palliation from symptoms in initial duration if not already in situ. But there is a risk of nutritional depletion and deterioration of immune status. The replacement of albumin especially in patients with liver cirrhosis after paracentesis for prevention of circulatory dysfunction is usually not recommended [14–16].

26.5 Interventional Procedures

1. *Transjugular Intrahepatic Portosystemic shunt (TIPS):* For chylous ascitis not responding to conservative therapy, TIPS may be one of the viable options. In cirrhotic patients, placement of TIPS may have a significant problem such as sepsis, DIC, catheter blockage or migration, air embolism, etc., so patient selection is an important issue [17].
2. *Angiography:* Lymphangiography with or without embolization is another promising technique when conservative therapy fails [18].
3. *Surgical Management:* Surgical intervention may be beneficial especially in post-operative and malignant cases. Pre-operative lymphangiography or/and lymphoscintigraphy are beneficial in localization of chyle leak or fistula. Surgical intervention may be required if all the above conservative managements fails. Closure of retroperitoneal fistula is most effective operation [19]. But surgical intervention is associated with high inci-

dence of morbidity and mortality and occasionally fails to identify the leak [20]. Conservative measures are undertaken for 6–12 weeks before surgical options are explored. Although there is no consensus guideline for indication of surgical exploration, few authors generally consider exploration for a chylous leak >1000 ml/day for >5 days or a persistence of chylous leak for >2 weeks with optimal conservative management. At our institution, we prefer to keep surgical options as a backup plan if leak continues >15 days in order to prevent nutritional and metabolic complications. Some authors advocate early surgical intervention to reduce postoperative stay.

26.6 Our Institutional Protocol

Eleven patients out of 255 had significant postoperative lymphatic leak following surgery for gynecological malignancies (lymphorhea-7, Chylous ascitis-4).

Management Our management initially includes conservative management as described below:

- Control Hypertension especially in obese patients.
- Diet modification (high protein diet with low fat and MCT's) in all patients.
- TPN—in patients who are not allowed orally 4/5 days after surgery.
- Tab Lasilactone (Frusemide + Spironolactone) once daily.
- Alpha 1 blocker like Prazosin 2.5 mg in two divided doses aiming to prevent post-operative vasoconstriction and thereby reducing the formation of ascitic fluid along with lymph.

We prefer to keep surgical options as a backup plan if leak continues >15 days in order to prevent nutritional and metabolic complications. None of our patients required surgical exploration and all were managed conservatively.

26.7 Conclusion

To conclude, chylous ascites is a rare form of ascites commonly associated with iatrogenic injury to lymphatic system especially during surgery or secondary to obstruction due to malignancy or tuberculosis. Clinically, patients present with abdominal distension, signs of malnutrition and recurrent infection due to immunosuppression. Chylous ascites is diagnosed by elevated triglycerides level on paracentesis. Patients are managed initially conservatively with low fat MCT based high protein enteral feeding, TPN with bowel rest, somatostatin/octreotide, and surgical exploration if conservative management fails.

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Management of Anastomotic Leak

27

M. D. Ray

27.1 Introduction

As a surgeon we know how much we are concerned with gastrointestinal anastomotic leaks. It is the most dreaded complications after gastrointestinal surgery. In this chapter we should sought to define the true incidence of anastomotic leaks along with presentations, complications, and management.

Anastomotic leaks have been the major cause of post-operative morbidity and mortality irrespective of the present day technology and improvements in surgical techniques [1–3].

27.2 Rate of Leaks

As per the literature varying rates of leaks in different anastomotic sites.

Esophagus	2–16% [4] at neck 10–15%, at chest 7–10%
Stomach	1–9% [5–7]
Pancreas	9–16% [8, 9]
Bile ducts	10–16% [10, 11]
Colon	3–29% [12, 13]
Small Intestine	1–3% [10, 14]
Rectum	8–41% [15]
At upper and middle Rectum	5–15%
At lower Rectum	10–20%

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Patients with anastomotic leaks show poorer long-term functional results, reduced survival and increased local recurrence rates [16, 17] along with post-operative morbidity and mortality.

It could cause significant pressure and burden on us as well as the patients and party, apart from the possible negative clinical outcomes [18].

27.3 Causes

Anastomotic leaks may be (1) Ischemic or (2) Mechanical.

Generally the ischemic cause for anastomotic leak occurs 5–6 days after surgery usually called "intermediate."

Mechanical—Direct tissular injury or stapler misfiring may cause mechanical anastomotic leak [19]. Such leak usually appears 2 days following surgery called "early."

Proximal leaks are common in presence of distal stenosis [6, 20].

"Late" leaks occur even after discharge of the patient.

Patients having Anastomotic leak, classically develop (1) sudden agonizing abdominal pain, (2) Tachycardia, (3) high fever, (4) hypotension.

Patients may have rigid abdomen, hemodynamic on instability, prolonged ileus, failure to thrive [21], leukocytosis.

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Unexplained tachycardia and fever are the most important factors of suspicion index. A strong indication of leak and systemic compromise indicated by >120/min [22].

In early leak, patient usually present with fever, tachycardia along with sudden abdominal pain.

On the other hand late leaks, patients present with fever associated with insidious abdominal pain [23].

27.4 Investigation

- Blood—leukocytosis
  - ↑CRP
- CECT abdomen and pelvis is considered to be the most important investigation to diagnose the leaks [24].
- Gastric leak—detection 86–90% [25].
- High BMI, obesity produce artifacts, thereby quality of image may be compromised. In that case endoscopic evaluation may be advisable.
- Gastrografin swallow test, performed 48–72 h postoperatively. It is still debatable, as it fails to identify the leak 60% of the time!

27.5 Treatment

Early diagnosis and treatment is the key factor to save the patients of anastomotic leaks [25].

Mortality is in the range of 10–15% [26]. Highest in gastric leak—up to 40%.

Conservative: Small leak with localized extravasation and early diagnosed case may be considered for conservative management.

There should be no septic symptoms and malignancy [27, 28].

The conservative management includes

(a) Fluid and electrolytes balance.
(b) Broad spectrum antibiotics.
(c) Nasogastric aspirate.
(d) Nothing per oral.
(e) Proton pump inhibitor.
(f) Nutrition.

Pain management should not be done on routine basis. It should be on demand basis.

Intense, clinical, and radiological assessment to be done.

27.6 Suturing Devices

Endoscopic suturing with absorbable or nonabsorbable suture can be done.

Suture may be continuous or interrupted. Simple suture or figure of eight.

It can close acute GI perforations, Anastomotic leaks and endoscopic resection sites [29, 30] suturing at a subserosal depth in colon or full thickness [31].

Stents The placement of a stent, at the leak site, diverts the enteric contents away and thereby producing less septic symptom.

Varieties of stent

- Plastic—covered, expandable.
- Metallic—covered fully or partially

Even the leak is large (>2 cm) the stent still permits continuous enteral nutrition [32, 33]. Frequent radiological monitoring is required as, the stents are prone to migrate (20–30% cases) [33, 34]. To prevent migration some surgeons/Gastroenterologist place clips to anchor the stents.

Omentoplasty Anastomotic leaks can be reenforced by omentoplasty. This is suitable for mechanical leak, i.e. early leak. It provides additional support to the defective site. Neovascularization is greatly increased by omentoplasty, thereby reducing further leak [19].

Adhesive glue Adhesive like Fibrin sealant may be useful to prevent/reduce Anastomotic leak fibrin sealant can cover and protect anastomosis.

Glues connect two different lumens by attaching them together without interfering the process of healing [35].

Vicryl Mesh Vicryl mesh may be used as a net and helps in healing of larger defect owing to rapid cell growth [36].

VAC therapy Endoscopy vacuum assisted closure (VAC) may seal the Anastomotic leaks with the help of endosponge which acts by creating negative pressure!

It is well tolerated but it has to be changed every 48–72 h.

Deep cavities and larger defects can be efficiently closed by this technique [37].

Other methods are Leaks can also be repaired through the scope clips— Which are deployed from within the GI tract lumen by passing through the endoscopic working channel.

Over the scope clips (OTSC)—These clips have got the capacity to close full thickness leaks measuring 2 cm [38].

27.7 Few Words on Anastomotic Complication of Colorectal Surgery

Major risk factor—Age >70, co-morbidities like cardiorespiratory, neurologic, hypoalbuminemia, ASA grade III & IV, and nutritional status.

Anastomotic complications—Minor and major bleeding, leaks and dehiscence, stricture and fistula. We will talk about only dehiscence and leaks.

Dehiscence and leaks—Overall incidence 2–7% in the hands of experienced surgeon. The Lowest leak rates are found with ileocolic anastomoses (1–3%) and highest occur with coloanal anastomosis (10–20%).

The clinical presentation is (1) pain, (2) fever, (3) Tachycardia. Others are feculent drainage, purulent drainage and peritonitis, prolonged ileus.

Most anstomotic leaks are usually apparent between 5 and 7 days post operatively.

Radiographic Sign—gas containing fluid collection.

Extra peritoneal anastomotic leaks—Highest (8%) with ultralow anterior anastomoses, anastomotic ischemia, male gender obesity.

Intra peritoneal anastomotic leak—ASA grade III, grade IV, emergency surgery, prolonged operative time, hand sewn ileocolic anastomosis (6.7% vs. 1.3%).

Protective stoma—It is controversial whether protective stoma can prevent a leak but it is definite that it can reduce the septic symptoms. A metaanalysis shows patients with protective stoma had significantly fever anastomotic leaks compared with patients who had no protective stoma (9.6% vs. 22.8%).

Mechanical bowel preparation (MBP)—The role of mechanical bowel preparation is controversial. A metaanalysis found that there is no significant difference in overall leak rates for patients with and MBP compared to those not having (4.2% vs. 3.4%).

Rather nutritional factors including hypoalbuminemia, smoking, alcohol intake, weight loss have shown variable results.

27.8 Outcomes

Anastomosis dehiscence and leaks are associated with increased risk of mortality, especially in cancer patients as well as prolonged hospital stay in compare to noncancer patients (32% vs. 4%).

27.9 Conclusion

Anastomotic leaks following gastrointestinal surgery may be the major cause of morbidity and mortality. It is a constant headache for a surgeon too. It prolongs the hospital stays, cost, and agony.

So prevention is always better than cure. Basic principles of anastomosis should be followed always, i.e.

1. Good bleeding and contractility at the end of both the lumen.
2. Anastomosis without tension plan for diversion/defunctioning/covering ostomy is required when

(a) Surgeon is not happy with anastomosis,
(b) Lack of vascularity,
(c) Anastomosee with tension,
(d) Low albumin and hemoglobin level,
(e) Previous history of radiotherapy,
(f) History of smoking, etc.

A greater understanding of the advantages and limitations of available techniques and devices in use in the prevention and treating anastomotic leak to attend the expected overall outcomes.

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Palliative Care for Incurable Cancer Patient

28

M. D. Ray

28.1 Introduction

Palliative care is an approach which is intended to improve the quality of life of the cancer patients, along with their families, facing life-threatening illness.

Early identification, impeccable assessment, treatment of devastating symptoms like pain and others physical, psychosocial agony.

Palliative care positively influences the course of illness, may prolong the life with fulfillment of earthly desires. Palliative care not only requires symptomatic supports by medicine, it may need surgery, radiotherapy, chemotherapy too.

Empathetic communication, psychological counseling are an integral part of palliative care.

In short, palliative care provides relief from pain and all other distressing symptoms. It affirms life and regards dying as a natural process. It neither hastens nor postpones death. It helps the patients of cancers to live as active as possible, not only physically, mentally and socially too.

Palliative cares support the families of the patients to cope up with the situation and their own bereavement.

A team approach is mandatory to fulfill the need of the patients and their families empathetically.

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What is the need of palliative care in cancer patients?

Cancer is a devastating disease until it is detected early. In advanced cancers, patients suffer not only for cancer progression but also from different co-morbidities, adverse effects of cancer treatment which may be physical, social, and emotional.

The goal of palliative care is a "total care." So it requires a team approach. This team consisting of specialist doctors, nurses, dieticians, counselors, social workers to offer best quality of life of cancer patients.

When to start palliative care? In ideal scenario, palliative care start at diagnosis of malignancy.

By definition palliative care starts when definitive/curative options end for the disease. A multidisciplinary team has to decide at early as possible that further curative approach is not appropriate for that particular cancer patient.

When the management team makes a conclusion that curative treatment is not possible for the patient, then the role of palliative care starts aiming to provide best quality of life for the unfortunate human for rest of the life.

The focus has to be on the patient now, not on the disease. Palliative care team helps the patient to remain functional throughout the last day of life and helps to live with maximum comfort.

Thereby the point to be noted that palliative care can be given in a palliative care unit of a hospital, a hospice, nursing facility, at home too.

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The next of Kin and close relatives need reassurance and support as a whole.

28.2 Different Dimensions of Palliative Care

Physical The common physical health of a cancer patient are—pain, weakness, smelling, swelling, ulcers, sleeplessness, loss of appetite, nausea, vomiting, anxiety, depressing suicidal tendency, etc.

These kind of physical problems may be due to co-existing disease, because of advanced cancer, as a results of side effects of cancer treatment.

Specific and supportive medications are basic requirements. Apart from this mental support, rehabilitative support, nutritional care is essentials.

In my practice, what I do is I talk to the patient and patient relative empathetically always. I strongly believe that this main open secret of successful handling of cancer patients.

Regular Yoga, meditation, breathing exercise, and walk are very important part of palliative care. Let them enjoy their lives the way they want.

If patients ask to have other therapy like Ayurvedic, urinary, homeopathic, all encourage them to have the same for their mental as well as physical support.

Palliative pain care For pain progression opioids like morphine are the drug of choice. According to WHO pain ladder, pain killers are given in combination.

Psychological care Fear of impending death leads to anxiety, depression in various severity. Self-help techniques like meditation, relaxation breathing, counseling and psychological support are helpful alongwith anxiolytics and antidepressant medications.

To tell the truth, most of these things are theoretically. Practical points are really difficult to tackle. But what I believe, well behavior and empathetic talk are most important two components of the palliative care!

Spiritual care It is a neglected but an important approach called life as death approaches. Let them express their feelings, needs, meet their desire, finish pending tasks, and sort out misunderstandings. It is the time to forgive, thank people, and to say a final goodbye. It's life! it's really!!! So hard! So Cruel!!!

Family care Family care or care to the care giver is an integral part of palliative care. It prepares the patient as well as the family members for all stages of the cancer progression. The family members can share their anxiety, pain to the palliative care team. As a whole palliative care is a complete task to sustain quality of life for the patients and their family members.

Home or hospital for palliative care To tell the truth, most of the cancer patients want to spend their last counted days at their homes only, in a well-known setting with loved ones around.

Hospital is a frightening and busy place where all aspects of palliative care could not be delivered in an ideal manner. Definitely in sudden situation, hospital is a better place particularly in acute condition.

At home a team of doctor, nurses, counselor, social worker, volunteer may take care to patients and their families.

28.3 The Different Way of Management

1. *Patient assessment*: There are various ways to assess cancer patients.
   (a) *Assessing symptoms*—Commonly used symptom management tool is emotion symptom assessment scale (ESAS). ESAS includes ten common symptoms on a scale of 1–10 (0 = No symptom and 10 = worst possible symptom). The symptom may be pain (common), weakness, tiredness, nausea, depression, anxiety, drowsiness, loss of appetite and

well-being, shortness of breath, etc. This symptoms can be assessed and tracked over the time and monitored on base of changes in symptoms and treat the patient accordingly.

(b) *Assessing performance*—Patient functional status is an important component for any treatment initiation. There are several tools are used to assess the performance. The commonly performed tools are (1) Eastern Cooperative Oncology Group (ECOG) performance status and (2) Karnofsky performance status (KPS) (Table 28.1).

- *Cancer pain management*: Management of pain, I believe, the most important aspect of palliative care. WHO recommends three steps ladder for pain management.
  - First step is for mild pain. Non-opioid adjuvant like simple Paracetamol is the drug used commonly.
  - Second step is for moderate pain. Weak opioids like tramadol or its combination with PCM are used.
  - Third step is for severe pain: Strong opioids like oral morphine are used along with other analgesics. The combination takes care about 80–90% pain.
  - Nerve block may be used in some cases.

  A trained doctor must treat the patient who knows how to treat breakthrough pain and also how to switch opioids from oral form to a patch on the skin.

  Morphine causes respiratory depression is basically a myth. So many studies amply established this truth. Rather morphine itself improves quality of life even in the last stage!!

  Availability of morphin in India: It is fast that only 1–2% of cancer patients really require morphine. As per Narcotic Drugs and Psychotropic Substances (NDPS) Act without license, no hospital, or medical setup can procure oral morphine!

  But with the amendment of NDPS in 2014, a cancer patient will have easy access to oral morphine for their pain.

Table 28.1 ECOG performance status and Karnofsky performance status

ECOG performance status	Karnofsky performance status
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any self-care; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

Even authorized NGO can have a license and procure morphine for cancer patients. Can support is such a NGO runs the largest home based palliative care programme in the country.

In 1994, Indian Association of Palliative Care (IAPC) established and leading the palliative care in India, today.

Commonly used pain medication are Hydrocodone—Acetaminophen/Oxycodone

up to 335 mg, Acetaminophen four times daily for moderate to severe pain.

Morphine 15 mg four times daily. Oral morphine usually started with 5mg every four hourly and titrated according to pain relief.

Fentanyl may be used transdermally. It is useful even in significant kidney dysfunction where Morphine cannot be used.

Antidepression Tricyclic antidepression is most commonly used because of fever side effects, once daily at bed time.

Constipation Constipation is one of the common symptoms among cancer patients. The common causes are side effects of Opioids other medications, decreased oral intake, immobility, metabolic imbalance, or secondary to abdominal malignancy.

Management High fiber diet, plenty of water, regular physical activity are the main stay of treatment. Medication can help in the symptomatic management. Visacodyl also comes in suppository form. Hyper osmolar agents like lactulose 30 ml with water at bed time is very useful. Emollient laxative and enema are other options.

Nausea, vomiting The causes are treatment related like after chemotherapy or other medications. The surgical cause may be due to bowel obstruction, pain, infection or constipation. Treatment—Ondansetron 8 mg four times daily or granisetron 1 mg 12 hourly.

Haloperidol 0.5–1 mg, olanzapine orally or IV or subcutaneous 6 hourly, metoclopramide 10–20 mg 6 hourly.

Centrally acting antiemetic like lorazepam 0.5–1 mg 6 hourly, dexamethasone 2–4 mg.

2. *Palliative Surgical management*: Palliative surgery, like feeding Gastrectomy, jejunostomy, gastrojejunostomy like bypass surgery, esophageal, duodenal, stenting all are useful in palliative care. Giving some other example in metastatic breast cancer sometime mastectomy is to be done because of ulceration, pain, or bleeding. The same way in ovarian cancer, renal cell carcinoma role of palliative surgery, called debulking surgery are helpful.
3. *Discussion with patient and family*: I believe personally and very strongly, a good communication with the patient and patient's relative solve all the problems. The following goals of care and discussion should be at the beginning of treatment. Patient's level of understanding of the disease, hope for the treatment, the scientific way of treatment and its side effects and patient & relative should understand the consequences of the disease and overall patient's satisfaction, joy and quality of life to be given are more important. The conversation should be on the mnemonics is S-P-I-K-E-S. *S-setting*, it is better to have a private room for discussion along with the appropriate people. Make an eye to eye contact and talk heartfully. *P-Perception,* understand the perception of patient and family. Let the patient ask whatever he or she wants to ask along with family. Reply to all the questions politely without showing any irritation. *I-invitation,* from your side show the heartfullness to the patient and allow them to ask more questions, even it is silly. *K-knowledge,* share the information about current status as per the global standard and explain all the things in layman language so that they can understand better. *E-empathy,* listen more and talk less to allow to express their emotion. You feel what exactly going on their minds. If you feel this all problems solve immediately even some mishappening is there on the course of treatment you would always be safe. So as per my opinion the tone of voice is the secret of your success as a surgeon. *S-strategy and summary,* it is your duty to summarize your strategy and probable outcomes of the treatment and the probable expenditure and we more value on quality of life and focus on what patient wants. The negotiation and the understanding are the key.

Palliative Care of Patients with Ovarian Cancer

29

M. D. Ray

A short history of a patient with ovarian cancer.

Mrs Ma 60-year-old lady, a known case of breast cancer presented with a history of heaviness in pelvis and unexpected vaginal bleeding. She also gave history of nausea, weight loss, and breathlessness. She was treated for triple negative breast cancer earlier but was not tested for BRCA gene due to financial issues. She was diagnosed as carcinoma ovary on basis of presentation, elevated Ca-125, and CT scan. The disease was advanced and had disseminated in peritoneal cavity with omental caking. She was very distressed, had abdominal pain, intermittently was frustrated, and could not help asking "why me". She was offered neoadjuvant chemotherapy and planned for interval cytoreduction and was also referred to the palliative care OPD for management of her distress and pain, along with the primary treatment.

29.1 Introduction

Ovarian cancer is the most lethal malignancy among all the gynecological cancers. The incidence is growing gradually day by day and in India it is touching almost the incidence of Ca Cervix. The lifetime risk of developing ovarian cancer is 1 in 70 women [1]. Despite multimodality treatment, the survival is very dismal and 5 years survival is 15–30% over the past three decades. With the advancement of HIPEC (Hyperthermic Intraperitoneal Chemotherapy), 5 years survival may increase 30–50% [2]. Etiology of ovarian cancer is mostly unknown; apart from this reproductive history like nulliparity with incessant ovulation, endometriosis are found to be independent risk factors. Environmental and lifestyle factors such as asbestos, talc powder exposures, and cigarette smoking increases the risk of ovarian cancer. Certain germ line mutations in DNA repair genes like BRCA1, BRCA2, MSH1, MSH2, MSH6, and PMS2 account for 10–15% of ovarian cancer. A prophylactic risk reduction surgery with bilateral salpingo oophorectomy can decrease the risk of developing cancer by 96% [3]. The diagnosis of early ovarian cancer is difficult to detect because of vague symptoms. More than 75% of patients present in advanced stage requiring mutimodal management [4], when the treatment options are multimodal. Ovarian cancer patients may succumb to death due to multiple bowel obstruction and malnourishment. Early detection, impeccable assessment, and treatment of devastating symptoms like distress, pain and others physical and psychosocial symptoms requires palliative care intervention.

So, the symptom management and palliative care becomes important to improve the quality of life (QoL) of the patient. Along with the definitive treatment, palliative care is essential to relieve of

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sufferings in all aspects, i.e. physical, mental, psychosocial throughout the course of the illness. It cares the patients with advanced disease burden and its symptoms burden, its assessment and control. It also deals with opened and empathetic communication with the patient and family.

Palliative care positively influences the course of illness, may prolong the life with fulfillment of earthly desires to some extent [5]. Palliative care not only requires symptomatic supports by medicine, but it may also require palliative surgery like relieving of obstruction, radiotherapy, chemotherapy too.

29.2 Pathophysiology

Ovarian cancers are heterogeneous histologically and molecularly. Epithelial ovarian cancer (EOC) accounts for 90% of all ovarian cancer. High-grade serous carcinoma accounts for 75% of advanced ovarian cancers [6, 7].

The development of EOC is a complex and multifactorial process. The exact etiology and cellular origin are still is a matter of debate [8]. The incessant ovulation hypothesis suggests that disruption and repair of ovarian surface epithelium during ovulation causing the genetic alterations, leading to ovarian cancer [9].

Circulating hormones like gonadotropin, estrogens, and androgens stimulate the ovarian epithelium and promoting tumor formation. Cancer developing stem cells may play a crucial role to develop EOC also.

Recent evidence suggests that high-grade serous carcinoma rises from fallopian tube [10]. The risk of cancer of the fallopian tube/ovary increases in woman with BRCA1 and 2 mutations. A prophylactic salpingo oophorectomy reduces the risk of development of ovarian cancer by around 96% [3]. Ovarian cancer usually spreads through peritoneum (peritoneal carcinomatosis), lymph nodes along the pedicles in pelvis and retro peritoneum. Only in 2–5% cases, it spreads beyond the abdominal cavity, i.e. chest, groin, etc. [11].

29.3 Clinical Signs and Symptoms (General Symptoms)

Early ovarian cancer is typically asymptomatic and often difficult to diagnose. More than 2/3rd of (>75%) patients present in advanced stages and with vague symptoms of abdominal discomfort such as routine constipation, distension, and loss of appetite. The symptoms could be irregular menses, vaginal bleeding, or urinary frequency. Patients may have dyspepsia, abdomino pelvic discomfort, etc.

Physical finding includes ascites, most common or pelvic mass. The dictum is any pelvic mass in a post-menopausal (more than a year) woman is suspicious for ovarian cancer.

Staging Staging 2018 is the latest staging of Ca Ovary [12]

FIGO Stage 1 The cancer is only in the ovary (or ovaries) or fallopian tube(s).

IA The cancer is in one ovary, and the tumor is confined to the inside of the ovary; or the cancer is in one fallopian tube, and is only inside the fallopian tube.

IB The cancer is in both ovaries and fallopian tubes but not on their outer surfaces.

IC1—Surgical spill, *IC2*—The tumor has ruptured before surgery, *IC3*—Cancer cells are found in the fluid (ascites) or washings from the abdomen and pelvis.

FIGO Stage II The cancer is in one or both ovaries or fallopian tubes and has spread to other organs (such as uterus, bladder, sigmoid colon, or rectum) within the pelvis or there is primary peritoneal cancer.

II A The cancer has spread to or has grown into the uterus or the fallopian tubes, or the ovaries.

II B The cancer is on the outer surface of or has grown into other nearby pelvic organs such as the bladder, the sigmoid colon, or the rectum.

FIGO Stage III A The cancer is in one or both ovaries or fallopian tubes, *or* there is primary peritoneal cancer and it may have spread into nearby organs in the pelvis retroperitoneal (pelvic and/or para-aortic) lymph nodes only.

IIIB There is cancer in one or both ovaries or fallopian tubes, *or* there is primary peritoneal cancer and it has spread or grown into organs outside the pelvis. The deposits of cancer are no bigger than 2 cm.

IIIC The cancer is in one or both ovaries or fallopian tube, *or* there is primary peritoneal cancer and it has spread or grown into organs outside the pelvis. The deposits of cancer are larger than 2 cm and may be on the surface (the capsule) of the liver or spleen.

Stage IVA Cancer cells are found in the fluid around the lungs (called a malignant pleural effusion) with no other areas of cancer spread such as the liver, spleen, parenchyma, intramural infiltration of the bowel, or lymph nodes outside the abdominal pelvic cavity.

IVB The cancer has spread to the inside of the spleen or liver (parenchyma), to lymph nodes other than the retroperitoneal lymph nodes (groins), and/or to other organs or tissues outside the peritoneal cavity such as the lungs and bones.

Symptom burden Intractable ascites, high upper abdominal disease burden, involvement of the subdiaphragmatic peritoneum, diaphragmatic muscles, involvement of porta hepatis, hepatorenal pouch, small bowel mesentery, multiple segments of bowel, involvement of the bladder and peritoneum both visceral and parietal. Patients usually succumb to death because of intestinal obstruction and cachexia.

Management options Upfront surgery followed by adjuvant chemotherapy (Texel based) is the gold standard for ovarian cancer management [13]. But as per the CT Peritoneal cancer index, if the disease burden is more and not feasible for complete Cytoreductive surgery (CRS), then neoadjuvant chemotherapy followed by surgery is the way to tackle the disease burden [14]. In ca ovary role of radiotherapy is still evolving.

29.4 Role of Palliative Care in Ovarian Cancer Patients

Ovarian cancer is a devastating disease until it is detected early. In advanced cancers, patients suffer not only for cancer progression but also from different co-morbidities, adverse effects of cancer treatment which may be physical, social, and emotional. The goal of palliative care is a "total care," by a team consisting of specialist doctors, nurses, dieticians, counselors, social workers to offer the best quality of life of cancer patients.

29.4.1 When to Start Palliative Care?

Commonly palliative care starts when definitive or curative options end for the disease but the early palliative care for ovarian cancer has been introduced [15].

A multidisciplinary team must decide early regarding the possibility of improving QoL if further curative approach is not appropriate for that particular cancer patient. The focus must be on the patient now, not on the disease. Palliative care team helps the patient to remain functional throughout the last day of life and helps to live with maximum comfort. Thereby the point to be noted that palliative care can be given in a palliative care unit of a hospital, a hospice, nursing facility at home too. The next of Kin and close relatives need reassurance and support.

29.4.2 Early Integration of Palliative Care

Temel et al., 2010 found that patients who received early palliative care had better QoL than who received conventional care. They had lower rates of depression and were more likely to have their resuscitation preferences. They concluded that those who received early integral palliative care had longer median survival compared to standard care group [15].

Though Bakitas et al., 2009 concluded from their study that multicomponent nursing led intervention increased the median survival but not statistically significant [16].

29.4.3 Different Dimensions of Palliative Care

Physical The common physical health of a ovarian cancer patient are pain, weakness, smelling, swelling, insomnia, loss of appetite, nausea,

vomiting, anxiety, depressing suicidal tendency, etc. These kinds of physical problems may be due to co-existing disease, because of advanced cancer, as results of side effects of cancer treatment. Apart from this mental support, rehabilitative support, nutritional care is essentials. In my practice, what I do is I talk to the patient and patient relative empathetically always. I strongly believe that this is the main open secret of successful handling of cancer patients. Regular Yoga, meditation, breathing exercise, and walk are specially important. Apart from this high protein diet, hematinics, hygiene, spirometry, water intake are important to relieve symptomatically [17].

Psychological care Fear of impending death leads to anxiety and depression. Self-help technique, counseling, mental support along with anxiolytic, antidepressants are essential. In my practice a good behavior and empathetic talk are the most important two components of taking care of psychosocial issues.

Spiritual care is a neglected but an important approach called life as death approaches. Let them express their feelings, needs, meet their desire, finish pending tasks, and sort out misunderstandings. It is the time to forgive, thank people, and to say a final goodbye.

Family care Family care or care to the care giver is an integral part of palliative care. It prepares the patient as well as the family members for all stages of the cancer progression. The family members can share their anxiety, pain to the palliative care team. Palliative care is a complete task to sustain quality of life for the patients and their family members.

Home or hospital for palliative care Most of the cancer patients want to spend their last counted days at their homes only, in a well-known setting with loved ones around. Hospital is a frightening and busy place where all aspects of palliative care cannot be delivered in an ideal manner. At home a team of doctor, nurses, counselor, and social worker, volunteer may take care of patients and their families.

29.5 The Different Way of Palliative Management

Patient assessment: There are various ways to assess cancer patients.

Assessing symptoms—Commonly used symptom management tool is Emotion Symptom Assessment Scale (ESAS). ESAS includes ten common symptoms on a scale of 1–10 (0 = No symptom and 10 = worst possible symptom). The symptom may be pain (common), weakness, tiredness, nausea, depression, anxiety, drowsiness, loss of appetite and well-being, shortness of breath, etc. These symptoms can be assessed and tracked over the time and monitored on base of changes in symptoms and treat the patient accordingly.

Assessing performance—The functional status of the patient is an important component for any treatment initiation. There are several tools that are used to assess the performance. The commonly used tools are Eastern Cooperative Oncology Group (ECOG) performance status and Karnofsky performance status (KPS). We all routinely use them in our practice. This is routinely followed in any cancer surgery.

29.6 Ovarian Cancer Pain Management

Palliative pain care Intensity of pain in ovarian cancer patients varies widely and is usually vague in early phase. Patient may have stretching pain due to abdominal distension as ovarian cancer often produces ascites.

The pain may be cramps and intermittent because of subclinical subacute intestinal obstruction as a part of natural history of the disease.

In advanced cases, when the tumors including retroperitoneal lymph nodes infiltrate the hypo gastric nerve plexus, may cause circuiting intractable pain.

Management of pain is the most important aspect of palliative care. WHO recommends

three steps ladder for pain management (Discussed earlier in chapter in details). A combination of drugs including most common drug we use a PCM combination like PCM + Diclofenac Sodium or PCM + Tramadol, non-opioids adjuvant like Paracetamol (*step 1*) and weak opioids like Tramadol along with drugs to manage neuropathic pain like gabapentin, amitriptyline (tricyclic antidepressants), etc., (*step 2*) are often started. In patients who do not get relief with these strong opioids like morphine is started and titrated to achieve acceptable pain relief. Nerve block may be used in some cases. As we know common cause of pain in ovarian cancer is subclinical subacute intestinal obstruction.

In advances disease it may involve retroperitoneal nerve plexus due to nodal involvement. Carcinoma ovary is a PSM and involve abdominal wall especially in stage III & IV leading to persistent abdominal pain. It may spread all over the serosa including the bowel serosa and sometimes invade the bowel leading to decrease gut motility and obstruction.

As a palliative care specialist we must know about treatment of breakthrough pain and switching opioids from one route to other (IV to oral to a skin patch). Many of us are afraid to use morphine as it causes respiratory depression, but it is a myth. A number of studies have proven its role in improving QoL of the patients. Fentanyl may be used transdermally. It is useful even in significant kidney dysfunction where Morphine cannot be used.

Alternative medicines in palliative chronic pain care and for controlling depression are essential components of palliative pain care.

Hypo gastric nerve block Hypo gastric nerve plexus block is required sometimes. 20–22 G needle is positioned at paravertebral space at the level of L5/S1 intervertebral space under fluoroscopy.

6–8 ml of (25–50%) bupivacaine can be used for therapeutic purpose. 6–8 ml of 10% phenol in telebrix solution injected at each side of the vertebra.

Constipation Constipation is one of the common symptoms among cancer patients. The common causes are side effects of opioids and other medications, decreased oral intake, immobility, metabolic imbalance, adhesions due to previous surgery or secondary to abdominal malignancy. In ovarian cancer, subclinical subacute intestinal obstruction is commonly seen.

The management of constipation includes high fiber diet, plenty of water, and regular physical activity. Medication like bisacodyl, lactulose, emollients, and enemas may help in the symptomatic patients. Bisacodyl used as suppository. Lactulose when liver function is compromised and emollients make stool soft by absorbing water used in general constipation in patients who take narcotics specially.

Nausea, vomiting are *common* symptoms *in patients with ovarian cancer. The seven causes include side effects of* chemotherapy, bowel obstruction, pain, infection, or constipation. It can be managed by Ondansetron 8 mg three times daily or granisetron 1 mg 12 hourly. Other drugs include Haloperidol (0.5–1 mg oral/IV), olanzapine orally or IV or subcutaneous 6 hourly, and metoclopramide 10–20 mg 6 hourly. Centrally acting antiemetic like lorazepam 0.5–1 mg 6 hourly and dexamethasone 4–8 mg may also be required in certain cases. In advance disease both physical and mental component centrally acting agents are useful; because of its central action, act as placebo too.

Palliative Surgical management for ovarian Cancer Palliative surgery like debulking Surgery, anterior, posterior, or total exenteration for symptomatic relief. Ileostomy in case of large bowel obstruction. Ascitic fluids tapping from both abdominal and pleural cavity time to time. Palliative chemotherapy, radiotherapy, and metronomic therapy have got some role in ovarian cancer palliation.

Palliative chemo	Radio	Metronomic
In the form PIPAC (Pressurized Intraperitoneal Aerosol Chemotherapy) Cyclophosphamide Doxorubicin Capecitabine Yuliya Malayev et al. (2012) [18]	When bonny pain is there	Etoposide 50 mg OD Cyclophosphamide 50 mg OD Pazopanib 400 mg OD Aparna Sharma et al. (2019) [19]

Discussion with patient and family Good communication with the patient and patient's relative is utmost important and solve all the problems. The goals of care should be defined in the beginning of treatment. The patient's level of understanding of the disease, treatment and its side effects, and quality of life are important. The conversation should be on the mnemonics is S-P-I-K-E-S. (Ref) *S-setting*, it is better to have a private room for discussion along with the appropriate people. Make an eye to eye contact and talk heart fully. *P-perception,* understand the perception of patient and family. Let the patient ask whatever he or she wants to ask along with family. Reply to all the questions politely without showing any irritation. *I-invitation,* from your side show the heartfulness to the patient and allow them to ask more questions, even it is silly. *K-knowledge,* share the information about current status as per the global standard and explain all the things in layman language so that they can understand better. *E-empathy,* listen more and talk less to allow expressing their emotion. You feel what exactly going on their minds. If you feel this, all problems solve immediately even some mishappening is there on the course of treatment you would always be safe. So as per my opinion the tone of voice is the secret of your success as a surgeon. *S-strategy and summary,* it is your duty to summarize your strategy and probable outcomes of the treatment and the probable expenditure and we more value on quality of life and focus on what patient wants. The negotiation and the understanding are the key.

Hospice care for advanced ovarian cancer Hospice care begins for end of life management after standard cancer treatments are not sustainable. Supporting care focuses on providing comfort, relieving pain and other symptoms and improving quality of life. Hospice care is very personalized and is offered towards the end of life, i.e. when the patient is expected to survive less than 6 months. Hospice team will focus on making the patient as comfortable as possible like taking care of bedsore, skin care and the team should fulfill the demand of patient. A hospice team member is generally on call 24 h a day to provide support.

Barriers to palliative care: To tell the truth, the term palliative care itself is not still well defined. Being an Onco surgeon, I knew palliative care starts when option of curative treatment ends, truly speaking palliative care is often underutilized and a late referral in the disease trajectory! Physicians often equate palliative care with end of life care and have feelings that referral to palliative care will destroy hope (Hui et al. 2012) [20].

Both surgeons/physicians and patients should understand that presently palliative care can optimize the patients of the grave illness and improve quality of life and for better outcomes.

Key Points More than 2/3rd cases of ovarian cancer patients present with advanced stage >70% patients having recurrence despite multimodality treatment.

Last three decades 5 years survival is 30–50% with multimodality treatment including HIPEC.

Palliative care is always playing an important role for maintaining QoL till the last breathe. Earlier palliative care is better for better survival too.

Palliative care is a team approach. The team includes palliative and pain care experts, surgeons, anesthetists, counselor, trained nurses, supporting staff, and family members of the patients.

Palliative care should not be restricted in those who are at the end of life, rather it is meant for

allowing patients to overcome the agony, anxiety, and distressing symptoms related to the disease from the beginning of the treatment.

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30 Comprehensive Surgical Training & Mentorship: Foundation of the Excellent Onco-surgical Services

Ashutosh Mishra and M. D. Ray

Surgical training and education have evolved mostly in the last couple of centuries. It started with the qualification of Barber-surgeon or Mister which required no formal training, qualification, or the degree as in the currently adapted apprenticeship model.

An apprenticeship model can be defined as "a system of training a new generation of practitioners of a trade or profession with on-the-job training and often some accompanying study (classroom work and reading)." Apprenticeships also help trainees or residents to obtain an authority to practice in a particular profession. The said surgical model is still the gold standard method of surgical training, but in near future, some evolutionary modifications will be needed to maintain its efficiency and effectiveness.

30.1 Landmarks of Surgical Training Evolution

- In the thirteenth century, The College de Saint Come in Paris was the pioneer who addressed the issue of surgical training and they segregated the surgeons as per their skills mainly university-trained surgeons and academicians as long robe surgeons and barber-surgeons as the short robe surgeons. This school was established with its clear aim to systematically instruct barbers in surgery [1].
- Around the sixteenth century, surgical education and training was centered around the apprenticeship model. Since then this long-established model has been *practiced till date with some modifications and evolutions*. In this model, the transfer of surgical education and surgical skills is usually percolated by senior trainee who has observed and learned the skills from a trained mentor or senior surgeon. But it was unstructured and without any time frame. In the mid of the sixteenth century, surgical training used to start around the age of 14 years and continued for a variable period of 5–7 years [2–4].
- Over the period of time apprenticeship model has significantly improved surgical training program. In this current era a trained and well-qualified mentor interacts with their trainees to share and transfer their knowledge and skills to the best. Mentors used to observe their trainees and taught them surgical procedures in ORs. Although this entire program was not well structured or defined in terms of depth of knowledge, skills, time frame and surgical outcomes [5, 6].
- The major paradigm shift towards well-structured apprenticeship training program was noticed in the beginning of the twentieth century which was an era of Dr. William Halsted. The current methods of surgical training, which are being practiced in large

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part of the United States, are influenced by him. Dr. William Halsted established a surgical institution to ensure the surgical safety pertaining to meticulous surgical dissections, better tissue handling, and perfect hemostasis. He is on the top list of surgeons who conceptualized an effective and efficient resident training program in the USA [7, 8].

30.2 First Structural Model by Halsted

The Halstedian training model was the fundamental platform to produce several leading surgeons for training systems in various distinguished institutions.

30.2.1 Halsted's Surgical Training Principles

- The resident must have intense and repetitive opportunities to take care of surgical patients under the supervision of a skilled surgical teacher.
- The resident must acquire an understanding of the scientific basis of surgical disease.
- The resident must acquire skills in patient management and technical operations of increasing complexity with graded enhanced responsibility and independence.

30.3 The Mall Model

Franklin P. Mall was the head of Anatomy at The Johns Hopkins Medical School and his training program was somewhat similar to his contemporary William Halsted. Their approach and philosophy to surgical training and medical education was almost similar which was "*to teach by not teaching.*" This model used to have a group of trainees of different residency years who are provided with needed educational material including operative surgery books, textbooks, and other SOPs. They were also advised to instruct themselves essentially and, sometimes, other colleagues. Faculty members were supposed to be out of scene from training, or might have a minimal association with trainees, but this involvement was not as big as in earlier model.

This model might have been in practice at some places but because of evolution in medical education, the increasing legality, it will completely disappear in the coming future [8–12].

30.4 The "Osler" Model

Dr. William Osler's model is the most modern version of the apprenticeship model. The Osler model consists of one or more residents of differing postgraduate training levels (apprentices) closely working with one or more faculty members (masters or mentors).

For better exposure of residents to different skills and technique, Osler emphasized on Rotatory training program but at the same time he ensured that the essence of this model of training should be maintained means the faculty should be devoted, dedicated, and involved in the education of their trainees. Faculty should be more focused on Evidence and protocol-based education. In this model, Residents are in direct contact with faculty and that provide them an opportunity to learn faster and comprehensive. Surgical techniques and procedures have been studied systematically in a pre-defined staged manner to assess almost all best possible aspects, from preoperative skin preparation and antibiotics to methods of performing the best possible incisions and techniques for dissection to morbidity and mortality [10–12].

30.5 Is Simulation in Surgery Changing the Training Future?

The apprenticeship traditional model utilizes the passage of time (i.e., years in training) and volume of experience (i.e., hours worked per week) as surrogate markers of competence. There is no formal and structured tool for the assessment of trainee's technical proficiency at the completion

of his training. In fact this traditional model of training is continuously being challenged by several issues, e.g. short training period, limited working hours, technological evolutions, subspecialization, and most importantly, changing public interest and attitudes [13].

These days it has become quite objectionable that the surgical trainees practice their operative skills on patients. Therefore, there is an obvious need to design a better and evolved model of surgical training which could encourage and ensure our budding surgeons to achieve expertise in reduced stipulated time with sufficient exposure to the latest technology in surgery.

These days simulations in surgery have been deployed for laparoscopic surgery and endoscopic or endovascular procedures. This simulator based skill development makes the learning curve more flat and develop confidence in trainees while they are performing on patients. Still, most surgical procedures are being performed using an open incision. Therefore, there is a real need for surgical fraternity to develop a virtual reality *simulator* for *such open surgical* procedures.

30.6 Surgical Oncology Training: Global and Indian Perspective

Training in any subspeciality has multiple described paths—either an integrated course with broad specialty (general surgery) or a longer path of further system/organ-based advanced training after training in a broad speciality. A survey conducted amongst the leading surgeons of America concluded that most of the senior surgeons still believe that broad speciality surgical training is superior. The most common stages in a career at which a surgeon becomes interested in a particular subspeciality or area of expertise were at junior residency or assistant professor level. Therefore, broad speciality learning followed by subspeciality training is considered the best method of training in the modern world [14].

With the increasing cancer burden worldwide and heterogeneity in surgical oncology training programs, it was considered essential to frame a uniform global curriculum of surgical oncology. A global curriculum committee convened by the Society of Surgical Oncology (SSO) and the European Society of Surgical Oncology (ESSO) developed a global curriculum in Surgical Oncology. According to this global curriculum, the core domains of general oncology include knowledge and understanding of the principles of the epidemiology of cancer, screening for cancer, radiation therapy, chemotherapy, targeted therapy and immunotherapy, pain and palliative care, functional imaging, multidisciplinary care, diagnostic pathology, surveillance, cancer biology, research, delivering care across all resource settings and hereditary cancer syndromes. A Surgical Oncologist is supposed to attain competency in holistic patient care, surgical knowledge, professionalism, inter-disciplinary communication skills, research methods, organ-based practice, surgical skills, and understanding of precision and predictive medicine [15].

Currently, In India, multiple long-term and short-term training programs are available including 3-years MCh and DN B Surgical Oncology, and other short-term subspeciality fellowships. Apart from this non-academic senior residency and observerships are available in many institutions. In the current scenario, because of the different academic programs under different umbrellas, there is an obvious heterogeneity in surgical oncology training and education.

The training policy may vary from institute to institute but the basic design of the curriculum should be the same. Surgical training should not be limited up to simulator or operation theater as it has a vast spectrum including basic knowledge of allied branches, disciplined professional life, dedicated work culture, deep commitment for patients, mental toughness, good communication skills, physical stamina, etc.

The Surgical Oncology training curriculum should go through these phases:

1. Observation
2. Assistance
3. Performance in a controlled environment
4. Independent performance
5. Supervision

Every institution should promote the maintenance of logbooks by the trainees. This logbook should contain all the information related to the academic and teaching achievements along with the surgical training and experience obtained during the whole residency period. The awards received, papers presented, and conferences attended during the residency tenure must be duly mentioned in the academic activities part of the logbook. All the publications done by the trainee in national/international journals should also be highlighted. The number of surgeries performed/assisted organ-wise should be logged into the surgical training part of the logbook. This included both major and minor surgeries assisted/performed/supervised by the trainee.

Now Simulation-based training should also be the part of surgical training and definitely, that may shorten the learning curve and will improve confidence. As most of the malignancies are being managed by a multidisciplinary approach, the surgical oncology trainee must be acquainted with the multidisciplinary environment, data management, clinical trials, biostatistics, and palliative care.

Coronavirus disease-2019 (COVID-19) pandemic has adversely impacted surgical training all over the world. This is attributed to the diversion of health resources towards COVID management resulting in a decrease in the elective surgical workload. There have been cancellations and postponements of surgical conferences and CME programs globally. Surgery residents have experienced emotional problems, burnouts, and psychological distress owing to the unexpected course of the pandemic and also felt uncertainty about the acquisition of adequate surgical skills and future career prospects. These factors call for reshaping of the residency program which includes, but are not limited to, newer ways of scientific learnings (in the form of webinars, e-conferences, etc.), cutting short or even omission of rotation postings in other specialties, psychological support, and counselling of the residents and even extension of residency program by few months.

In India, there are multiple hurdles in the way of comprehensive surgical *training* including limited infrastructure, resources, dedicated surgical tutors, lack of surgical training regulatory bodies, etc. The surgical training program should be upgraded from the apprenticeship model and should focus more on the quality and the confirmation of surgical technical knowledge at the time of exit from residency or any other dedicated training. At the time of exit, it must be ensured by mentors or surgical tutors that their fellow is capable of performing a needed surgical procedure optimally and independently.

Teaching and training are integral parts of the surgical curriculum. Hence, surgical faculty and seniors must train their surgical heirs well. The stronger relationships between individual faculty and resident would encourage the development of programs that may deliver more thoroughly trained and more competent surgeons. In *The Doctor as Teacher the* General Medical Council states that "all doctors have a professional obligation to contribute to the education and training of others…," and that "every doctor should be prepared to oversee the work of less experienced colleagues" [14].

Dedication, passion, and perfection are the three important gems for a surgeon. Translating these values and modules into practice should be the aim of our surgical training. What we need to do now is to begin to incorporate these factors in surgical training so that trainees get effective training and long-lasting surgical skills.

We would like to share a story on perfection here:

> A king asked his sculptor to make an idol to install on pillars of 25 feet height at the front gate. At the end of his stipulated time he noticed, there is a scratch on the nose and requested king to give him more time to make another one.
>
> King saw the idol and started laughing stating that, you are going to place it at 25 feet height. Who is going to see the scratch? The sculptor replies, it's me, Maharaj, I will keep seeing it always even after closing my eyes.

Being a surgeon, we should be perfect like the sculptor to excel at a task, not necessary for

someone else to notice but for our inner satisfaction. Sometimes it's difficult to achieve the exact level of perfection but if we try to catch perfection, we can catch the excellence at least.

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Role of MIS in Onco Surgery

31

Areendam Barua and M. D. Ray

"A surgeon should give as little pain as possible while he is treating the patient"

The above statement explains why minimally invasive techniques are so important. It's time the surgical oncologists embrace MIS techniques and use it as an armamentarium against cancer. Evidence is accumulating that MIS is as good as open surgery at least in the early stages in certain cancers. MIS is already the preferred route in non-malignant diseases. The advantage related to a small scar and consequent better postoperative inflammatory response gives MIS the upper hand. MIS in surgical oncology is an attempt to combine the advantages of MIS while retaining the radicality of surgical procedures in oncology.

Laparoscopy, robotic surgery, NOTES (natural orifice transluminal endoscopic surgery) and thoracoscopy are the commonly used MIS procedures. A multitude of surgeries are now done in a variety of malignancies via MIS. RCTs are now being undertaken that have confirmed the safety and efficacy of MIS procedures and confirm non-inferiority over the open ones. Some trials have not found an equivalence, mostly involving advanced stages of cancers. Currently, we eagerly await the results of RCTs with the use of laparoscopy, thoracoscopy, robotics and NOTES. MIS has found wide acceptance as a modality in various malignant GI, thoracic, urologic and gynaecological procedures. Studies are ongoing to evaluate the utility in breast and head and neck cancers too.

31.1 Staging Laparoscopy

Laparoscopy is often done as a standalone procedure for staging purposes, sometimes for diagnosis and taking biopsy. It is also used in assessment of resectability prior to taking up of a definitive procedure. USG and cytology can be combined for staging purposes and consequently better treatment decisions can be taken. Laparoscopy is mostly utilized in GI cancers in pre op evaluation of the disease, staging and thereby resectability.

SAGES (Society of American Gastrointestinal and Endoscopic Surgeons) recommends staging laparoscopy in cancers of the oesophagus, stomach, pancreas and periampullary region, liver, biliary tract, colorectum and lymphoma.

31.1.1 Oesophagus and GE Junction Tumours

NCCN is of the view that laparoscopy may have some utility in some of the patients in detection of metastatic disease which is not evident on imaging, mostly true for Siewert II and III tumours (cat 2A). Early and locally advanced GE junction tumours also have the option of undergoing a stag-

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ing laparoscopy prior to definitive management. No RCTs have been conducted to demonstrate benefit with laparoscopy but several retrospective studies have shown change of management decisions and unnecessary laparotomies could be avoided in a significant number of patients [1, 2].

SAGES: Use of staging laparotomy is warranted in cases of ca oesophagus who are candidates for a curative surgery. Even in cases a curative resection cannot be done, this procedure can be used for the placement of an enteral tube, for facilitating nutrition for patients planned for neoadjuvant chemotherapy. Staging laparoscopy is also helpful in T3 and T4 adenocarcinomas of the gastro-oesophageal junction infiltrating the anatomic cardia. In such cases laparoscopy can identify peritoneal metastases and rule out curative surgery. 15% of patients may present with such a scenario and in these patients, staging laparoscopy changes the management.

31.1.2 Stomach

NCCN recommends staging laparoscopy from T1b tumours or higher, given that it is not metastatic. Laparoscopy can be used alone (cat 2A) or along with cytology (cat 2B). Various other societies have also given their own guidelines for staging laparoscopy. They vary as below:

- SAGES—T3/T4 gastric cancer with no lymph node or distant metastasis as evident on imaging studies taken pre-operatively
- ESMO [3]—Any patient planned for curative surgery.
- JGCA—Only in stage II and III tumours before taking up neoadjuvant chemotherapy

Various other retrospective and prospective studies have reinforced the utility of staging laparoscopy over the years [4, 5].

31.1.3 Pancreas

The NCCN guidelines recommends staging laparoscopy in all resectable high risk and borderline resectable tumours, as evidenced by pre op imaging. In borderline cases, if neoadjuvant therapy was administered and the patient didn't undergo staging laparoscopy prior to therapy, then it is recommended prior to undergoing the surgery. Intraop USG can be used as an adjunct. High risk cases in ca pancreas are defined as—imaging shows borderline resectability, very high CA 19.9 levels, T3 and T4 tumours, significant regional lymphadenopathy, significant loss of weight and intractable pain.

Other society guidelines are as follows:

SAGES guidelines—Indications for staging laparoscopy

1. Resectable pancreatic adenocarcinoma to rule out occult metastatic disease, even when imaging shows no metastatic disease
2. Prior to neoadjuvant therapy
3. For selection of palliative treatment in patients with locally advanced disease

Japan Pancreas Society via the Clinical Practice Guidelines for Pancreatic Cancer 2016 supports performing a laparoscopic examination in the cases of resectable pancreatic cancer or locally advanced pancreatic cancer where distant metastasis cannot be ruled out.

Spanish consensus guidelines on pancreatic cancer suggests that in patients with large tumours, mostly at body and tail of the pancreas, borderline resectability on imaging and high tumour marker levels, a diagnostic laparoscopy should be considered prior to laparotomy. Even after neoadjuvant therapy, those patients with elevated Ca 19.9 without any evidence of radiological progression of disease should be evaluated with PET CT and laparoscopy.

Those guidelines are based on several retrospective and prospective studies that enforce the efficacy of staging laparotomy on change on treatment following the procedure.

31.1.4 Biliary Tract Cancers

31.1.4.1 Gallbladder

NCCN recommends staging laparoscopy for

- T1b or greater tumours.

- T1a tumours, in incidental ca GB if the cystic duct node is positive with or without margin positive resection
- GB mass is detected on imaging +/− jaundice
- Suspicion of metastatic disease on imaging not amenable to percutaneous imaging

SAGES: Recommends staging laparoscopy in known or suspected gallbladder cancer with resectable disease

31.1.4.2 Cholangiocarcinoma

NCCN recommends staging laparoscopy in any resectable tumour.

SAGES: T2 or T3 resectable hilar cholangiocarcinoma

Although most of the other society guidelines like the Japanese Society of HPB cancers and ICMR don't mention staging laparoscopy for these tumours, several studies and meta-analyses have found utility of this procedure prior to definitive surgery [6, 7].

31.1.5 Colon or Rectal Cancer

Most of the guidelines including NCCN doesn't recommend staging laparoscopy for colorectal cancer. SAGES, however, recommends staging laparoscopy for resectable liver metastasis in a resectable primary to rule out any other sites of spread. Moreover, for these patients, this procedure can provide for a better identification of other hepatic lesions if any and provide valuable information on the size, number and location.

31.1.6 Lymphoma

SAGES: Hodgkin's lymphoma originates in one nodal group and spreads in a predictable manner. Staging laparoscopy can determine the stage and location of the disease. This is important in taking decisions regarding treatment with chemotherapy.

In contrast, for non-Hodgkin lymphoma, staging laparoscopy has no such role. The only indication is for tissue diagnosis through biopsy of intra-abdominal lymph nodes where peripheral lymphadenopathy is absent.

31.2 Laparoscopic and Robotic Surgeries

31.2.1 Oesophagus and GE Junction

NCCN guidelines states that Minimally Invasive Surgery (MIS) is acceptable for surgeries for cancer of the oesophagus and GE junction. The MIS surgeries are

1. MIS Ivor Lewis oesophago-gastrectomy (laparoscopy + limited right thoracotomy)
2. MIS McKeown oesophago-gastrectomy (right thoracoscopy + limited laparotomy/laparoscopy + cervical anastomosis)
3. Robotic minimally invasive oesophago-gastrectomy

NCCN also states that open surgery is preferred over MIS if optimal surgery with MIS approaches looks challenging.

Japanese guidelines endorse use of laparoscopy and thoracoscopy as an approach to resection of ca oesophagus. ICMR guidelines don't mention MIS as an armamentarium for ca oesophagus.

One of the first high quality RCTs was first published in the Lancet in 2012. This trial recognized the short-term benefits of MIS oesophagectomy [8].

TIME trial [9] found no differences in DFS and 3-year OS for open and MIS oesophagectomy. It further supported the use of MIS techniques in surgical treatment of oesophageal cancer.

A lot of studies—retrospective, prospective and RCTs have supported the role of MIS in ca oesophagus. Studies show that it is technically feasible and safe in hands of experienced surgeons. The perioperative mortality is around 2% [8] in upfront cases, although mortality rates are somewhat slightly higher post neoadjuvant therapy [10]. In an RCT of 115 patients comprising of oesophageal and GE junction cancers, patient

receiving MIS had significantly lower rates of pulmonary infection than open oesophagectomy. In another recent RCT of more than 200 patients with cancer of middle and lower 1/3 of the oesophagus, a hybrid approach of laparoscopic gastric mobilization with open right thoracotomy resulted in fewer post op complications, especially pulmonary and similar 3 year survival as open surgery [11].

The safety of robot-assisted mediastinoscopic oesophagectomy is shown in a number of newer studies, mostly from the Oriental countries. The middle mediastinal lymph nodes can be very well accessed via a robot and it can be utilized in taking up a nodal dissection via this route [12].

31.2.2 Stomach

Treatment of ca stomach is one of the fields where MIS has been extensively used. Laparoscopic gastrectomy was first done in 1994 in Japan. JLSSG (Japanese Laparoscopic Surgery Study Group) meta-analysis [13] on 1294 patients from the period 1994 to 2003 showed Mortality—0% Morbidity—14.8% Rec rate—.6%. OS at 5 year was

- Stage IA: 99.8%
- Stage IB: 98.7%
- Stage II: 85.7%

Another retrospective study—Long-term Outcomes of Laparoscopic Versus Open *Surgery* for Clinical Stage I Gastric Cancer: The LOC-1 Study [14] compared 3630 patients with EGC (Early Gastric Cancer)—LG (Laparoscopic Gastrectomy) vs. OG (Open Gastrectomy) from the period 2006 to 2012. It showed a 5 year survival of 97.1% for LG vs. 96.3% for OG. The 3 year recurrence free survival was 97.7 vs. 97.4 and recurrence rate 2.3 vs. 2.4 for laparoscopic vs. open gastrectomies respectively. The Korean surgeons also took up a meta-analysis which showed similar results.

Since the safety and efficacy was ascertained by the above meta-analyses a lot of RCTs have been taken up to answer various research questions regarding utility of MIS in various clinical scenarios. The Korean Laparoendoscopic Gastrointestinal Surgery Study Group (KLASS) has since then taken up nine clinical trials. The Chinese Laparoscopic Gastrointestinal Surgery Study Group (CLASS) has also taken up trials in the lines of KLASS group. Two RCTs in Japan and another two RCTs are going on for Ca stomach in Holland also.

KLASS group of trials:

- KLASS 01 [15]—This Korean trial was undertaken for stage I gastric cancer. The objective was to assess if laparoscopy assisted distal gastrectomy was safe vs. open distal gastrectomy. It was a Phase 3, multicentre, open label, prospective RCT conducted at 13 university hospitals. They had a strict criteria for the surgeons to participate in the study. The participating surgeons should have had an experience of completion of 50 cases each of LADG and open gastrectomy, with each surgeon's institution having a case load of at least 80 such surgeries every year. Both ITT and per protocol analysis were done since there was a lot of crossover among the groups. The morbidity rate for open vs. laparoscopic was 19.9% vs. 13%. This trial concluded that LADG is technically safe for the treatment of stage I gastric cancer. It also had lesser wound complications. Recently the long-term outcomes of the KLASS 01 trial have been published and it shows similar OS in the laparoscopic and the open group—94.2% vs. 93.3%.
- KLASS 02 [16]—This trial aims to compare outcomes between laparoscopic distal gastrectomy (LDG) vs. Open Distal Gastrectomy (ODG) for T2–T4a Ca stomach. The accrual has been completed but the results have not been published yet.
- KLASS 03 [17]—It was a phase II trial whose objective was to ascertain the safety and feasibility of laparoscopic total gastrectomy (LTG). The conclusion was that laparoscopic total gastrectomy is feasible and safe for proximal stage I cancer of the stomach
- KLASS 04—This trial is ongoing for comparison of pylorus preserving vs. distal gas-

trectomy taken laparoscopically for early gastric cancer at middle 1/3 of the stomach.
- KLASS 05—This trial is ongoing for comparison of laparoscopic proximal gastrectomy vs. laparoscopic total gastrectomy for upper 1/3 early gastric cancer
- KLASS 06—This trial is ongoing for comparison of laparoscopic total D2 gastrectomy vs. open D2 gastrectomy
- KLASS 07—This trial is ongoing for assessment of QOL of lap assisted distal gastrectomy vs. totally lap DG

ROBOT trial—This is a phase II trial for comparison of morbidity and mortality for Robotic Gastrectomy (RG) vs. Laparoscopic Gastrectomy (LG) of cT1–cT3 tumours

SENORITA trial [18]—This is a phase III trial that compares stomach preserving *surgery* with sentinel lymph node basin dissection vs. standard gastrectomy taken via laparoscopy in early gastric cancer patients and aims to verify whether the former achieves similar oncologic outcomes and improved quality of life

CLASS trials:

- CLASS 01 [19]: It is a randomized controlled trial comprising of advanced gastric cancer patients where laparoscopic and open routes were undertaken for distal gastrectomy with D2 lymphadenectomy. It compared morbidity and mortality head to head among the two arms. Like the Korean trials, here also the participant surgeons had to be eligible for the study. Only those surgeons who have done at least 50 open and laparoscopic D2 distal gastrectomies in institutions where 300 gastrectomies for patients with AGC annually are done were eligible for participation in the trial. There was no difference between the groups on intra op complications, post op morbidity and mortality. The lap to open conversion rate was only 4.5%.
- CLASS 02 [20]: This trial is similar to the KLASS 03 trial. The results have not been published yet.
- CLASS 04 trial aims to evaluate the safety and feasibility of laparoscopic splenic hilar node dissection with preservation of the spleen.

Other Chinese RCTs on ca stomach are also ongoing.

Japanese trials: They are taken by two groups in Japan—The JLSSG (Japanese Laparoscopic Surgery Study Group) and JCOG (Japanese Clinical Oncology Group)

- JCOG 0703 [21]: It is a prospective phase II study concluded that there is no difference in long-term outcomes for laparoscopic-assisted distal gastrectomy vs. open in stage I ca stomach.
- JCOG 0912 [22]: It is similar to KLASS 01. The results have not been published yet.
- JCOG 1401 [23]: It is similar to KLASS 03 or CLASS 02 trials. The only difference being it is a non-randomized trial but seeking an answer to the same research questions as the above-mentioned trials. The results have not been published yet.

In Japan, a single-institution phase III trial opened in April 2018 that randomizes patients with resectable gastric cancer to either laparoscopic or robotic gastrectomy [24]

Holland: Two RCTs are ongoing in the field of laparoscopic gastrectomy.

LOGICA trial [25]: This ongoing trial compares laparoscopic vs. open gastrectomy for gastric cancer in terms of outcomes.

STOMACH trial [26]: This ongoing prospective randomized, multicentre trial aims to compare open gastrectomy vs. minimally invasive gastrectomy for gastric cancer in patients who had undergone neoadjuvant therapy.

Currently, the JGCA (Japanese Gastric Cancer Association) guidelines places distal gastrectomy taken via the laparoscopy route as one of the options for clinical stage I ca stomach, but only with the minimum experience of the surgeons that landmark trials like KLASS 01, JCOG 0703 and JCOG 0912 included. They also state that laparoscopic total gastrectomy may lead to a higher risk of post op events in the first year of performance. This statement was given prior to the publication of results of the KLASS 03 trial, so they have termed this procedure as investigational.

On the lines of JGCA, the KGCA (Korean Gastric Cancer Association) also says that laparoscopic surgery is acceptable for early gastric cancer. But these guidelines too were laid before the results of KLASS 01, KLASS 02 and KLASS 03 trials were available.

ESMO guidelines states that with development of techniques for prediction of lymph node involvement, those tumours with no nodal involvement should be operated laparoscopically, whereas those with predicted positive nodes should undergo open surgery.

SAGES states that although open gastrectomy with lymph node harvest of at least 15 remains the standard surgical treatment for ca stomach in theWest, given the benefits of MIS, they encourage expanding indications for this approach.

31.2.3 Pancreas

MIS has not been extensively utilized for ca pancreas as for ca stomach. Laparoscopic pancreaticoduodenectomy (LPD), although described first over 20 years ago by Gagner et al. has not gained widespread use [27]. In contrast laparoscopic distal pancreatectomy has gained wide acceptance. However, in the recent years, even laparoscopic pancreaticoduodenectomy has gained ground.

Several non-randomized studies have compared the operative and oncologic characteristics of open and laparoscopic pancreaticoduodenectomy. Like in most MIS procedures, the time taken for the surgery was significantly prolonged compared to open procedures but intra op blood loss and duration of stay was significant. Conversion to open surgery ranged from 9 to 30%. Studies have reported that the number of lymph nodes harvested is similar or even significantly higher in laparoscopic approach compared to open pancreaticoduodenectomy. Even R0 resection rates don't differ significantly among the two approaches.

In comparison with pancreaticoduodenectomy, there are only a few studies on laparoscopic total pancreatectomy. They conclude that it is feasible and safe with satisfactory oncologic outcome.

A large meta-analysis of 29 studies showed superior outcomes for laparoscopic distal pancreatectomy in terms of haemorrhage, time to oral alimentation and length of stay in the hospital. There was no significant difference in safety profile and morbidity. Data on oncologic parameters was limited [28].

A recently concluded prospective observational study comparing minimally invasive distal pancreatectomy (MIDP)—Laparoscopic or Robot-assisted vs. open distal pancreatectomy (ODP) for pancreatic ductal adenocarcinoma (PDAC)—DIPLOMA study, showed comparable survival for both open and minimally invasive routes, even though R0 resection favoured MIDP vs. ODP (67% vs. 58%), but other parameters were in favour of the open group—resection of Gerota's fascia (31% vs. 60%) and lymph node retrieval (14 vs. 22) for MIDP vs. ODP. The results pave the way for an RCT to confirm oncological safety of MIDP [29].

Parenchyma sparing resections: Parenchyma sparing approaches are employed mainly in the management of serous cystadenoma, neuroendocrine tumours, branch duct IPMN and solitary renal cell carcinoma metastasis. This procedure is limited to tumours of size <4 cm. Although this procedure does not require reconstruction, it leads to higher postoperative pancreatic fistula rates, which was around 36.7% in a systematic review.

Robotic surgery: In 2003 Melvin et al. [30] reported first robotic distal pancreatectomy and by Giulianotti et al. [31] reported first robotic pancreaticoduodenectomy. As the use of robotic surgery increased, newer studies have shown promising results. Many a times, robotic surgery has shown better results in terms of conversion rate and duration of surgery, when compared with laparoscopy and open procedures. On the down side, robotic procedures have a significant learning curve.

Long-term results of 130 patients of laparoscopic pancreaticoduodenectomy for pancreatic and periampullary cancer from a tertiary care hospital in South India showed 5-year survival of close to 30% and median survival of 33 months. Conversion to open procedure was done in only

one case. The mean operating time was 310 ± 34 min. It was concluded that RCTs are needed to establish the advantages of LPD [32].

An RCT was taken up in the same hospital as the above prospective study with 64 patients, 32 in each group—the PLOT trial (pancreatic head and periampullary cancer laparoscopic vs. open surgical treatment trial). The results showed significantly longer median duration of stay in the hospital at the postoperative period for open vs. lap pancreaticoduodenectomy—13 vs. 7 days. Although time taken for surgery was more in the group that underwent laparoscopic resection, bleeding was more for open procedures (mean 401 vs. 250 ml). Lymph node retrieval and R0 rate showed no difference. The open and laparoscopic groups did not differ in parameters such as gastric emptying time and postoperative pancreatic fistula rates. Complication rates were similar in terms of Clavien Dindo classification. Only a single death was recorded in each of the groups [33].

Another RCT-LEOPARD-2 (Laparoscopic versus open pancreaticoduodenectomy for pancreatic or periampullary tumours) [34] has been published recently. In the study, laparoscopic pancreaticoduodenectomy had more procedure related mortality than open surgery, although this was not statistically significant. Clinically meaningful recovery of functions was similar. In light of these unexpected findings, safety concerns were raised, even when trained and experienced surgeons working in centres performing 20 or more pancreatoduodenectomies annually performed the surgeries. This trial dampens the enthusiasm for MIS for pancreaticoduodenectomy offered by the previous RCT.

NCCN guidelines mention that there is an increasing role for laparoscopic distal pancreatectomy. They have quoted two meta-analyses and one prospective study in support of laparoscopic resection. It is also mentioned that MIS pancreaticoduodenectomy is a viable option. In unresectable cases, NCCN has endorsed laparoscopic gastrojejunostomy ± FJ insertion, based on two RCTs that showed that 20% patients had GOO who didn't undergo prophylactic gastro jejunostomy. Laparoscopic celiac plexus block can also be used.

Japanese guidelines on pancreatic cancer do not support laparoscopic pancreatectomy out of clinical trials. Laparoscopic distal pancreatectomy for the treatment of pancreatic cancer has been approved by health insurance in Japan, but the significance and safety should be examined by further accumulation of cases.

31.2.4 Colorectal Cancer

Jacobs reported the first case of technical feasibility of laparoscopic colectomy in 1991. Technical approaches range from intracorporeal procedure, where no additional incisions are required, to extracorporeal, hand assisted, laparoscopic-assisted techniques or SILS (Single Incision Laparoscopic Surgery). For rectal cancers in addition to laparoscopic and robotic surgery, newer procedures like TEM (Transanal Endoscopic Microsurgery)/TAMIS (Transanal Minimally Invasive Surgery) and TaTME has garnered much interest in the recent years.

As with minimally invasive surgery in the other organs, laparoscopic surgery has gained a strong foothold for colon and rectal cancers. In addition to the benefits associated with MIS, minimally invasive techniques, especially robotic surgery has the benefit of reaching up to areas inaccessible to conventional open surgery. This enhanced visualization of the pelvic structures and accessibility aids in nerve sparing procedures and going in the correct plane with minimal blood loss and lesser complications. Furthermore, the advent of TaTME has also addressed the need for better visualization at the pelvis by combination of endoscopic and laparoscopic techniques.

Barcelona trial, published in 2002, was one of the first trials to directly compare the outcomes between laparoscopic and open colectomy for carcinoma of the colon. There were 219 participants in the study—111 in the laparoscopic vs. 108 in open. Laparoscopic group recovered better with shorter time for return to function. Although laparoscopic group fared better for the short-term outcomes, perioperative mortality rates were not significant. The laparoscopic group fared better in terms of probability of can-

cer related survival ($p = 0.02$), mostly due to differences in patients with stage III tumours. In 2008, the long-term results were published and the results were still better for the laparoscopic group [35, 36].

Another trial, the COLOR trial was a non-inferiority trial that compared laparoscopic colectomy vs. open colectomy. Primary objective was to compare the disease free survival at 3 years. The non-inferiority boundary was pre-specified at 7% difference between the groups. This was a larger trial with 1248 patients. A number of parameters like resection margin positivity, resected lymph node number, rates of morbidity/mortality were comparable among groups. The difference in DFS after 3 years was 2.0% which was well below the pre-determined non-inferiority boundary of 7%. There was a small difference of 2.4% in overall survival after 3 years with open colectomy faring better [37, 38]. The COST trial also showed similar local recurrence rates and DFS for both laparoscopic and open surgeries [39]. Similar outcomes were reported in an RCT taken up in Australia and NZ.

The UK MRC CLASICC trial recruited 794 patients of colon and rectal cancer combined (526 laparoscopic-assisted vs. 268 open). No difference was seen in the long-term outcomes. Laparoscopic resection had higher positivity rates but it did not lead to higher rates of local recurrence. This trial concluded that laparoscopic-assisted colectomy for cancer is at par with open surgery in scale of oncological parameters and preservation of quality of life. Long-term outcomes of patients who underwent laparoscopic abdominoperineal resection or anterior resection for rectal cancer were similar to open surgical resection [40–42].

The COREAN trial from South Korea included patients of post neoadjuvant chemoradiation therapy in carcinoma rectum at the mid and lower portions. cT3N0-2M0 cancers located at middle and lower 1/3rd portion of the rectum were included after neoadjuvant CT-RT. 1:1 randomization was done to segregate the patients to open or laparoscopic surgery. Both arms had 170 patients. Various parameters like TME specimen surgical quality assessed via naked eye, retrieved lymph node number, involvement of the circumferential resection margin and morbidity in the perioperative period were similar among the two groups. Certain short-term parameters like recovery of bowel function were better for the laparoscopic group. They concluded that post neoadjuvant CT-RT, short-term benefits of laparoscopic surgery, equivalent quality of oncological resection and safety for lower 2/3 rectal cancer make it a better surgical approach [43].

The COLOR II trial, published in 2013, was a non-inferiority phase 3 trial for rectal cancer that compared laparoscopic and open surgery. They concluded laparoscopic surgery was safe and margin parameters of the resected specimen were equivalent to that of open surgery but provided the patients are carefully selected and the surgery is done by experienced surgeons. Recovery was better in the laparoscopy group [44].

The ACOSOG Z6051 Randomized Clinical Trial was undertaken to compare the quality of resected rectal specimen for laparoscopic vs. open approaches. Assessment was done by gross pathologic and histologic evaluation. In contrast to the equivalent clinical outcomes that were shown by the above-mentioned trials in ca rectum, pathologic evaluation did not show non-inferiority. Successful resection rate for laparoscopic approach was 81.7% vs. 86.9% for open cases. Negative circumferential radial margin was observed in 87.9% laparoscopic resection and 92.3% in open resection group. Non-inferiority for laparoscopic resection couldn't be proven [45].

Also in ALaCaRT RCT, equivalent pathologic outcomes could not be shown. A number of oncological factors were taken as primary end point for labelling the surgical resection specimen as adequate. Non-inferiority boundary was taken at 8%. Successful resection was deemed only if it met all the following criteria: (1) Satisfactory TME specimen (2) A clear CRM of $\geq$1 mm and (3) Distal resection margin clearance of $\geq$1 mm. The pathologists were blinded to the route of surgery. Among patients with T1-T3 rectal tumours, laparoscopic surgery couldn't be proven non-inferior to open surgery for successful resection. These findings did not support the routine use of

laparoscopic surgery albeit high overall quality of surgery [46].

Although there was no doubt that laparoscopic surgery did improve the short-term outcomes, it was to be seen if the short-term benefits that laparoscopy provides are relevant when open surgery is optimized in the setting of an enhanced recovery protocol. To answer this question, The EnROL (Enhanced Recovery Open Versus Laparoscopic) trial with 208 patients was undertaken. They concluded that if skilled surgeons operate in the setting of an enhanced recovery protocol, fatigue and other perioperative outcomes were similar in both groups, but length of hospital stay was significantly reduced in the laparoscopic group [47].

From the above trials, it is now clear to us that even though short-term clinical outcomes with laparoscopic surgery are excellent, there is still doubt on the long-term oncological outcomes given that both the trials that compared the pathological specimens of open vs. laparoscopic rectal surgery have termed laparoscopic specimens "inferior" to open resected specimens. Given the confines of the pelvis and limited manoeuvrability of laparoscopic instruments, it is quite understandable. So, robotic surgery, with 540 degrees rotation, 180 degrees of articulation and 7 degrees of freedom seemed enticing.

Robotic surgery: Given that surgeons experienced in laparoscopic surgery have a short learning curve [48] and that robotic TME may attenuate the long and steep learning curve of laparoscopic TME, [49] there has been a keen interest in robotic rectal surgery. Some studies state equivalence of robotic to laparoscopic surgery [50] whereas it is seen in various meta-analyses that robotic surgery has less conversions to open than the laparoscopic surgery while cost and longer operative times have been a concern [51–53]. ROLARR trial was a multicentric RCT which sought to find out if the conversion rate in robotic surgery for rectal cancer is better than laparoscopy as the primary outcome and various pathologic and short-term surgical outcomes as the secondary outcome. Contrary to the outcome that was expected, risk of conversion to open laparotomy did not differ in the robot-assisted group compared with laparoscopic group, and there was no statistically significant differences in secondary clinical outcomes [54]. Although robotics find a special place in rectal cancer and lot of research is there related to it, its role in colon cancer is still not established. Although robotic surgery can be done, it confers no special advantage to the surgeon, except in some cases where greater manoeuvrability is required due to anatomical constraints.

SILS (Single Incision Laparoscopic Surgery): SILS has been described for colon carcinoma. Although right hemicolectomy is technically less challenging, left colon and transverse colon cancer resection has been problematic. It is technically feasible in small tumours, lean patients and more useful for segmental resection and right hemicolectomy [55–58]. The oncological safety of SILS has not yet been proven although a few studies show equivalence of SILS to conventional laparoscopic techniques. SILS has not gained ground in the management of ca rectum due to difficulties with instrument movement, rectal transection and challenge of double stapling of anastomoses intracorporeally.

Endoscopic techniques: These include TEM (Transanal Endoscopic Microsurgery), TAMIS (TransAnal Minimally Invasive Surgery) and TaTME techniques. They can be clubbed under NOTES for colorectal surgery. The first endoscopic transanal surgery was done by Buess in 1983 [59]. Clancey et al., in a meta-analysis, showed better oncological outcomes with endoscopic transanal surgery rather than with traditional transanal excision methods.

TEM/TAMIS: The principles of both these techniques are essentially same. They only differ on the type of ports and equipment used. TEM uses a highly sophisticated unit with specialized instruments whereas TEMIS uses existing conventional laparoscopic ports and instruments. Both of these techniques have several advantages over conventional transanal excision. Conventional transanal surgery uses rigid instruments and specialized retractors whereas TEM/TAMIS uses camera and endoscopic/laparoscopic instruments which gives superior manoeuvrability for making full thickness rectal wall

resections. Again, rigid instruments can give a good vision with good instrument manoeuvrability only up to 10 cm whereas surgery is possible on TEM/TAMIS platform till 15–20 cm. Since it has the drawback of excising only the primary tumour without addressing the lymph nodes, it is suitable for only those patients whose nodes are clinically free or whose nodes need not be addressed.

ASCRS (American Society of Colon and Rectal Surgeons) and various other surgical societies recommend TEM/TAMIS only in the following situations:

- Tumours occupying <40% of the circumference of the bowel lumen
- Mobile lesions
- Polypoid lesions
- Lesions not associated with lymphovascular invasion
- T1N0 lower rectal lesions which can be accessed via the anal route
- Tumours below the peritoneal reflection of the rectum
- Well-differentiated or moderately differentiated lesions

Transanal TME (TaTME): It combines the principles of TEM, TME and sphincter salvage surgery. It basically addresses the problems of

- Inability of TEM/TAMIS to address lymph nodes—mesorectal fascia
- Difficult access pelvic areas which is impossible to reach via standard laparoscopic instruments, especially in male patients, patients with a high BMI and low rectal cancer, which often results in open surgery

It has most commonly two teams operating simultaneously—One through the transanal route for full thickness resection of the rectal wall. Another team mobilizes the rectum laparoscopically and ligates the inferior mesenteric vessels and addresses the corresponding lymph nodes. Also, pelvic node dissection is possible in case the surgeon decides to do so with this approach. Here sphincter salvage surgery is better performed due to a magnified field and subsequent better delineation of the surgical planes. It also gives better visualization of the pelvic nerve fibres, which gives the theoretical advantage of better bowel and bladder functions [60].

Although the guidelines represent the best possible treatment strategy based on high quality evidence, it is encouraged that the patients are recruited into a clinical trial over accepted or standard therapy.

31.2.5 NCCN Guidelines on Minimal Access Surgery on Carcinoma of the Colon and Rectum

Colon—Laparoscopic surgery is an option in cases where the polyp specimen couldn't be removed en bloc, non-assessable margins or the tumour shows unfavourable histology. Here, resection of the colon with concomitant lymphadenectomy is to done. Laparoscopic surgery is appropriate for curative and palliative surgeries of the colon. In fact, laparoscopic surgery is preferable given better short-term outcomes in palliative settings.

Rectum—Although studies associate laparoscopy to similar or better short- and long-term outcomes when compared to open surgery, it is also shown that laparoscopy leads to higher rates of CRM positivity and unsatisfactory TME. So, in rec MIS is considered based on the following principles:

- Surgeon experienced in performing MIS with TME.
- Open surgery is preferred in threatened or high risk circumferential margin based on imaging. Laparoscopy is not preferred in this setting
- Not indicated in cases of acute bowel obstruction or perforation from cancer.
- MIS is not considered where thorough abdominal exploration is required.

Robotic surgery for colorectal cancer: The laparoscopic vs. robotic surgery studies have mostly been observational cohort studies.

Although on the brighter side it is associated with lesser loss of blood, shorter return of bowel function, shorter postoperative stays and lesser complications and SSI (Surgical Site Infection), on the down side it results in longer operating times and is more expensive.

31.2.6 NCCN Criteria on Transanal Excision

- The tumour should occupy less than 30% of the bowel circumference
- Tumour size should be less than 3 cm
- Margin of more than 3 mm should be achieved clear from the tumour
- The tumour must be mobile and free from the surrounding structures
- The tumour should be within 8 cm of the anal verge
- Only T1 tumours are eligible for such a procedure
- If an endoscopically removed polyp turns out to be cancer or of indeterminate histology on final histopathology
- LVI or PNI should be absent
- Poorly differentiated cancers are excluded
- No clinical and radiological lymphadenopathy
- Tumour amenable for full thickness excision

TEM/TAMIS: For lesions confined to the rectum but beyond the scope of transanal excision, local excision of more proximal tumours is technically feasible using transanal microscopic surgery (TEM) or transanal minimally invasive surgery (TAMIS), which are newer and advanced techniques.

31.2.7 ESMO Guidelines

Colon: Laparoscopic colectomy is safe for colon cancer. It is particularly advantageous for left sided colon cancer. For right sided colonic cancers, anastomosis must be hand sewn, which requires laparotomy. So the benefit is less obvious. Laparoscopic approach is recommended if the following criteria are met:

- Surgeons experienced in laparoscopic colorectal surgery
- Lack of clinically significant abdominal adhesion due to prior major abdominal surgery
- Not presenting with locally advanced disease and/or acute bowel obstruction or perforation.

Rectum: Experience of the surgeon should be taken into account in selecting laparoscopic or open surgery. TaTME has advantages in facilitating pelvic and distal mesorectal dissection but it has not been standardized yet the technique may vary among surgeons. Although robotic surgery provides advantages for the surgeons with respect to manoeuvrability compared to conventional laparoscopy, it is still under scrutiny.

For TEM, ESMO considers it appropriate for early rectal cancers (cT1N0 without adverse pathologic characters like grade 3, LVI, PNI). cT1N0 tumours are appropriate. TEM for larger tumours should be undertaken after discussion with the patient.

TEM permits better resection than local excision. It provides satisfactory full thickness local excision of rectal tumours en bloc. Good oncological results in pT1sm1N0 rectal cancers can be expected compared with results achieved by TME, with better anal sphincter function. Tumour bed is the most common site of local recurrence. If the resection specimen shows higher pTNM following local excision, the patient should undergo TME as the standard salvage option. The value of adjuvant CT-RT in preventing local recurrence is not proven.

31.2.8 Japanese Guidelines: JSCCR 2016

The Japanese guidelines differ from the Western guidelines significantly.

EMR (endoscopic mucosal resection) and ESD (endoscopic submucosal dissection) and polypectomy are the procedures that can be done endoscopically. These techniques are considered only when there is no lymph node metastasis and the size and location of the tumour is appropriate

for an en bloc resection. Any mucosal disease (cTis/M) or tumours with slight submucosal invasion (CT1/sm1) distal to second Houston valve can be considered irrespective of size and macroscopic type.

Lateral lymph node dissection, which is not included in Western guidelines, is to be done if the tumour extends beyond the peritoneal reflection (second Houston valve) and the tumour invades the muscularis propria.

Laparoscopic surgery is considered if the surgeon is experienced and skilled. It also depends on tumour factors such as the location and extent of tumour. Patient factors like high BMI and prior laparotomy also play a role.

There is no mention regarding robotic surgery.

31.2.9 MIS in Gynaecologic Oncology

MIS has become the standard for the management of uterus confined ca endometrium. Although there had been great enthusiasm regarding the use of MIS in ca cervix, the recent LACC trial has however, dampened the enthusiasm and brought an abrupt end to the journey of MIS in ca cervix. Although there has been quite a few speculations regarding the failure of this trial, the progress of MIS will be tardy in this field nonetheless.

31.2.10 CA Endometrium

MIS is the standard for Ca endometrium. Being common in the Western world, many patients with endometrial cancer are obese and minimally invasive surgery (MIS) is especially advantageous in these patients in having better access to the tumour and reducing postoperative wound complications. Robotic surgery with 3D vision and better manoeuvrability, especially in limited space such as the pelvis can lead to better dissection.

Since the 1990s, a lot of studies were undertaken—some retrospective analyses, some prospective observational and some RCTs, which showed short-term advantages for minimally invasive techniques, along with oncologic equivalence for both the approaches. High quality evidence began to emerge post 2008, with the publication of the short-term outcomes for the largest RCT—the LAP2 trial.

In the LAP2 trial, patients of uterine carcinoma and sarcoma stages I to IIA were randomly allocated at a ratio of 2:1 to laparoscopy versus laparotomy. The surgery done was hysterectomy + salpingo-oophorectomy + pelvic and paraaortic lymphadenectomy + pelvic cytology. Initially, this study's objective was limited to comparison of complications in the perioperative period and quality of life after 8 weeks. The protocol was subsequently changed and follow-up was extended to 5 years. They set a hazard ratio of 1.4 for the primary study endpoint of non-inferiority of recurrence-free survival. The hazard ratio and recurrence rates were lower than expected. Laparoscopy had a 3-year recurrence rate of 11.4% with and laparotomy 10.2%. Identical 5-year overall survival rate was found in both arms at 89.8%. The trial concluded that the difference in cancer recurrence when laparoscopy is compared with laparotomy is small and additionally, laparoscopy group had significantly better short-term outcomes [61, 62].

The LACE trial—Laparoscopic Approach to Cancer of the Endometrium was an RCT involving multiple centres across countries with an impressive accrual of 760 women with stage I endometrial cancer with endometrioid histology. They underwent staging with total laparoscopic hysterectomy (TLH) or total abdominal hysterectomy (TAH). No difference in DFS at 4.5 years (81.6 vs. 81.3%) or OS (mortality: 7.4 vs. 6.8%) was found. This was the second largest trial to evaluate this question [63].

A subset of 361 participants were enrolled in a QOL (Quality of life) study [64]. Patients in the TLH arm had better QOL in the initial postoperative period compared with the patients who had TAH. For some patients, the improved QOL persisted up to 6 months after surgery and continued to favour TLH.

In 2012, a meticulous meta-analysis of laparoscopic procedures for early stage ca endometrium

was done by Galaal et al. This review supported the role of laparoscopy based on evidence found for the management of early endometrial cancer. They concluded that the OS and DFS are similar with laparoscopy and laparotomy for primary endometrioid adenocarcinoma of the endometrium. Laparoscopy leads to better short-term outcomes but similar rates of severe postoperative morbidity [65].

Robotic surgery with its advantages is expected to overcome the constraints of working in closed spaces in laparoscopy. Robotic is better for obese and morbidly obese patients. It is associated with lesser duration of surgery, lesser haemorrhage, better lymph node harvest and shorter duration of stay in the hospital [66]. Despite the lesser adverse event rates with robotic hysterectomy some studies point out that robotic hysterectomy turns out to be a costly affair [67, 68]. A randomized trial ($n = 99$) of robotic versus laparoscopic staging for endometrial cancer found shorter operative duration for robotic group (139 min vs. 170 min). There were no conversions to laparotomy in the robotic arm. In contrast 5 cases out of 49 cases in the laparoscopy group had to be converted open. No differences were found in amount of bleeding, lymph node retrieval, hospital stay or the length of postoperative stay. The rate of major postoperative complications showed no statistically significant difference in robotic surgery versus laparoscopy (10 vs. 22%) [69].

The outcomes do lead us to a conclusion that robotic surgery does increase the surgeon comfort as evident from the fact that it is better suited for obese patients and lesser open conversions. Although the short-term outcomes might be better, the costs associated with robotics might make acceptance for robotic surgery as a routine quite tardy. There is no high level evidence for long-term outcomes and surgical superiority for robotic surgery.

NCCN guidelines states that staging laparotomy which includes TAH + BSO + lymph node assessment may be performed either via laparoscopic, robotic, vaginal or abdominal routes, although the standard in those with uterine confined disease is to perform the procedure with minimally invasive techniques. Regarding lymph node dissection, NCCN says that when indicated, lymph node dissection is recommended so that pathologic and prognostic data is available. Clinical decisions can be based on regarding adjuvant treatment. NCCN also supports the use of sentinel lymph node staging and has laid down the principles for conducting the SLNB.

The SGO (Society of Gynaecologic Oncology) and ICMR have also issued guidelines on the lines of NCCN guidelines in support of use of minimally invasive techniques for ca endometrium and SLNB.

31.2.11 CA Cervix

The road to use MIS techniques for management of early stage ca cervix has been interesting. Prior to the LACC trial, all previously conducted retrospective studies uniformly concluded that MIS led to better short-term outcomes and equivalent oncological outcomes [70, 71]. MIS techniques, especially laparoscopy was very much in vogue since 2000 and an MIS was a standard practice in an increasing number of institutions for early stage ca cervix. Some studies found robotic surgery to be better than laparoscopy [72–74].

The LACC (laparoscopic approach to cervical cancer) trial [74] was undertaken since there was no high quality evidence to compare survival outcomes after MIS procedures vs. open radical hysterectomy among women with early stage cervical cancer [75].

This trial failed to show non-inferiority for MIS procedures. Approximately 42% of trial participants had tumours ≥2 cm; however, the authors noted that the trial was underpowered to evaluate outcomes for tumour size <2 cm or other low-risk features (no LVSI, <10 mm depth, no lymph node involvement).

In a cohort study of female patients with stage IA2-IB1 cervical cancer in whom radical hysterectomy was done, 1225 patients underwent MIS compared with 1236 who underwent open surgery; to achieve two groups with similar characteristics, the groups were weighted based on a propensity score (the probability of MIS). With a

median follow-up of 45 months, 4-year mortality rate was higher for MIS procedures—a difference of 3.8%. Subgroup analysis found an increased HR for mortality with MIS for robotic procedures, squamous cell and adenocarcinoma, and tumour size ≥2 cm; there was a trend towards higher mortality in traditional laparoscopic procedures (this was nearly statistically significant). The study was underpowered to detect a difference in mortality risk in tumour size <2 cm (HR 1.46, 95% CI 0.70–3.02) [76].

Based on the above recent data, MIS procedures for tumour >2 cm is not recommended by most authorities, although it might have some role in management of smaller tumours (<2 cm) and those without high risk features. This recommendation is also based on the fact that tumour size divided in 2 cm intervals is the most important predictor for recurrence [77].

NCCN guidelines state that given the latest evidence of significantly poor survival rates with the MIS approaches when compared to the open approach in an RCT of women of early stage cervical cancer, women should be educated about the short-term vs. long-term outcomes and the oncologic risks of different surgical procedures. For young women opting for sparing of fertility, radical vaginal trachelectomy with laparoscopic lymphadenectomy procedure (with or without SLN mapping) offers a viable option for specially selected group with stage IA2 or stage IB1 lesions. The cervix, upper vagina and supporting ligaments are also removed as with a type B radical hysterectomy, but the uterine corpus is preserved.

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Quality of Life Issue in Pelvic Cancer Surgery

32

M. D. Ray

Gynecological cancers affecting the female reproductive tract include cancers of the cervix, corpus uteri, ovary, fallopian tube, vulva, and vagina. As per the data of GLOBOCAN 2012, estimated incidence (age standardized rate) of cancers of cervix, corpus uteri, and ovary in India is 29.2 per 100,000 populations [1]. Indian population based cancer registries data has shown that the gynecological cancers are among the ten most common cancers in Indian women [2]. Majority of these women in India, like in any other developing country, belong to families with financial constraints where health and nutrition do not get the priority. In addition, social stigma and cultural differences (communication barriers, educational inequity, traditional therapies) lead to delayed presentation [3]. Advances in diagnostics and multimodality care have focused on improving the duration of life but neglected the quality of life of these patients. Disease related symptomatology, diagnostic interventions, and treatment effects could interrupt a woman's personal and social life and therefore decrease her morale to fight against cancer. Recently, this issue has drawn attention in western studies but to become a part of cancer management in low-middle income countries. This review is aimed to highlight the common disorders faced by Indian women with gynecological cancers and the importance of quality of life in multidisciplinary care.

32.1 Gynecological Cancer Care in India

Diagnosis of cancer in most of Indian families is like a curse! Several factors can be held responsible for this agony like inequity of power, income, goods, and services resulting from a combination of unemployment, poor social policies, unfair economic plans, bad politics, and booming population [4]. Poverty, illiteracy, false beliefs, and negligence towards health are certain factors contributing to delayed referral to tertiary cancer centers. Discrepancies in treatment cost between government and private hospitals make it difficult for the common man to avail the correct treatment on time. Limited government hospitals offer cancer treatment; consequently, patients greatly outnumber the manpower and resources. On the contrary, well-equipped and resourceful private hospitals are affordable only by few. Women must confront not only with anxiety of having cancer and physical discomfort, but also with cost issues, frequent hospital visits, long queues for investigations, long waiting lists in hospitals, work at home, care of children and family. India has 27 regional cancer centers, and other multispecialty hospitals providing cancer care-services. But still all these centers do not have trained gynecologic oncologists.

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32.2 Gynecological Cancer Related Morbidities

In Indian women, cervical cancer is the most common gynecological cancer, owing to high prevalence of HPV infection, poor hygiene, early marriages, early child birth, and multiparity. Lack of screening and lack of access to health care deprive them of the benefit of early detection. It occurs in women during their reproductive age and is also considered to be associated with sexual promiscuity [5]. The fear of social outcast and embarrassment makes most women bear the pain and excessive bleeding from progressive tumor growth. Advanced stage, anemia, and poor performance status further enhance the complications of curative treatment if possible. Ovarian cancer is second commonly found gynecological malignancy, more prevalent in north and east of India [2]. It is known to present at advanced stage in peri or post-menopausal group due to inconspicuous symptoms. As per the survey by Goff et al., almost 95% of women are symptomatic at presentation. These are categorized as abdominal (77%), GI (70%), constitutional (50%), urinary (34%), or pelvic (26%) symptoms with 58% of women complaining of pain [6]. Similar frequency of symptoms is noted in Indian patients also [7] but major problem is that patients do not consult appropriate clinicians for these symptoms. Most of them are managed with either home remedies or misdiagnosed as reflux disorder, colitis, or diverticulitis. Endometrial cancer was known to have lowest incidence rates from Southeast Asia and India but recently the incidence is increasing in India due to the changing lifestyle and dietary habits. Fortunately, it presents with post-menopausal bleeding and lower abdominal pain therefore usually diagnosed at early stage. However, one-fourth cases occur in young pre-menopausal women where these symptoms are not alarming [8]. Vulvar and vaginal cancers are rare genital cancers in developing countries. Predominantly affect post-menopausal women with dyspareunia, pruritus, ulceroproliferative growths, vulvar swelling, and urinary problems [9]. Despite the distressing symptoms and deteriorating general health, majority women get diagnosed at relatively advanced stage [10].

32.3 Cancer Treatment Related Morbidities

Management of gynecological cancers includes surgery, chemotherapy, and radiotherapy or combination of any of these. As obvious, combination of such therapies can further aggravate the short- and long-term toxicities as compared to a single modality. Presentation in advanced stages almost always requires administration of multimodality care for optimal outcomes such as posterior exenteration or anterior exenteration or both (Figs. 32.1 and 32.2).

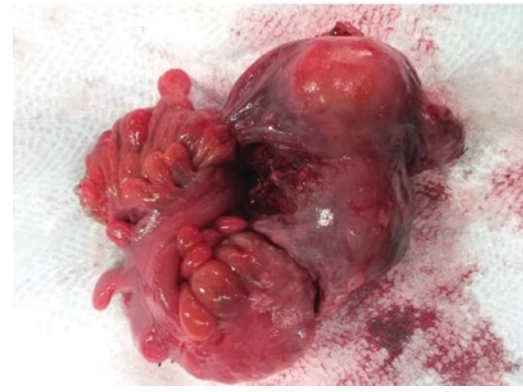

Fig. 32.1 Posterior pelvic exenteration for malignant RVF

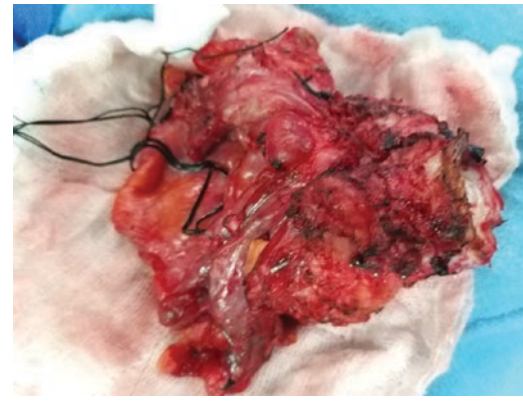

Fig. 32.2 Anterior pelvic exenteration for malignant VVF

32.3.1 Ovarian Failure

Staging in majority of gynecological cancers is surgical; oophorectomy or hysterectomy with bilateral salpingo-oophorectomy being the most commonly performed procedure. Radiotherapy and chemotherapy can also cause temporary or permanent ovarian failure depending on the oocyte pool determined by age during treatment, radiation field, and dose; chemotherapy drug regimes. Hormonal deprivation deteriorates QOL through symptoms like vasomotor symptoms, change in sleep pattern, cognitive problems, joint pain, genitourinary syndrome of menopause, and sexual dysfunction [11].

32.3.2 Sexual Dysfunction

Radical surgery disrupts the reproductive tract and results in shortened vaginal length, decreased lubrication, loss of sensation, and dyspareunia. Pelvic radiotherapy has adverse short- and long-term effects on the perineum tissues, mainly vagina and vulva. These include fibrosis, adhesions, vaginal dryness, and stenosis. Chemotherapy may cause vaginal mucositis and atrophy. All these factors impair sexual activity and negatively impact QOL [12].

32.3.3 Fertility Impairment

All the treatment modalities in reproductive age group have the potential to cause temporary or permanent impairment in fertility. This can cause emotional distress, depression, disruption of personal relationships, and poor QOL.

32.3.4 Bowel and Bladder Dysfunction

Pelvic surgery and radiotherapy can cause significant morbidity by interrupting bowel and bladder function. Bladder symptomatology may include storage symptoms (urgency, frequency, etc.), voiding symptoms (hesitancy, straining, etc.), or urinary incontinence (urge, stress, mixed). Bowel symptoms may be diarrhea, constipation, or bloating sensation [13].

Literature search has revealed studies addressing the early toxicities and tolerance to treatment in Indian patients. Not many studies have documented the incidence and type of late toxicities in treatment of gynecological cancers, likely to affect QOL. Chauhan et al. in a retrospective review of 787 cervical cancer patients treated in radiotherapy unit in Bihar noted that Stage IIIB was most common. Morbidity was not reported, however important observation was that 32% patients received post-operative therapy and merely 15% could have received adequate surgery. Conventional techniques of cobalt machine were employed in 88% of patients due to unavailability and affordability of linear accelerator [14]. This issue highlights the problems faced by patients due to misdiagnosis, additional treatment, and adverse effects. Chakraborty et al. compared treatment-related toxicities in elderly (≥65 years) vs. young (<65 years) patients of cervical cancer treated definitively with concurrent chemoradiation. Common toxicities were hematological, biochemical, and mucosal. But there was no difference in the incidence of any grade 3–4 gastrointestinal toxicities (16.7% vs. 13.3%, $P = 0.76$) or grade 3–4 hematological toxicities in these 57 patients (26.7% vs. 16.7%, $P = 0.40$) across the age category, supporting the use of chemoradiation in elderly population [15]. Sourav et al. (2013) conducted retrospective 6 years analysis of late morbidity of 260 women with endometrial ($n = 150$) and cervical ($n = 110$) cancers who underwent hysterectomy and received external RT+Brachytherapy. Most common late toxicities (LENT SOMA criteria) noticed were radiation proctitis and radiation cystitis. Of 260 patients, radiation proctitis was grade 3 in 13, grade 2 in 18, and grade 1 in 151 patients. Radiation cystitis occurred in 71 patients and 9 had grade 3 toxicity. Diarrhea, though manageable occurred in 24/260 patients. Author reasoned that morbidity be reduced by decreasing the radiation dose or changing the treatment protocol [16].

32.4 Quality of Life for Gynecological Cancer Patients

The quality, not the longevity, of one's life is what matters. QOL is a fundamental consideration for patients with cancer, as it has become the most important health concern today. The WHO defines QOL as "an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns." [17]. The concept of QOL came after the realization that medicine has become mechanistic with the only goal of eradicating the disease and symptoms and needs introduction of humanistic element into health care. Health-related QOL (HRQOL) and its determinants have evolved over decades. HRQOL encompasses the various aspects affecting health—either physical or mental. In India, almost 1.5 million people need diagnosis, treatment, and follow-up facilities at a particular time. In India, more than 70% of women usually attends cancer OPDs in locally advanced stages [18]. In such setting, clinicians are forced to serve only one motto: save the lives of as many patients, QOL issues become secondary and often not thought of! Less resources, availability, and cost of anticancer drugs and radiotherapy further grime situation. Besides all the facts and arguments, we cannot deny a woman of good quality of her remaining life with cancer. From another viewpoint, improvement in QOL can be as important as the improvement in survival from standard treatment strategies.

32.4.1 Quality of Life: Assessment

Most common problem encountered by clinicians is how to evaluate QOL in Indian population due to low level of education, limited time in overpopulated hospitals, and language and cultural barriers. Various QOL measurement tools are available that have been used in clinical trials. These tools include general health status assessment tools as well as cancer organ specific assessment tools as discussed by Andrew Bottomley [19]. Commonly employed scales are the general version of the Functional Assessment of Cancer Therapy (FACT-G) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQC30) [20, 21]. Specific subscales are available to assess QOL for cancer sites and symptoms like ovary (FACT-O) [22], cervix (FACT-Cx) [23], vulva (FACT-V) [24], FACT/GOG–NTX (Neurotoxicity) subscale [25], Brief Pain Inventory (BPI) [26], etc. These tools have been developed for western population and cannot be used uniformly worldwide. Vidhubala et al. have simplified this difficult task of QOL measurement. They validated a QOL questionnaire for Indian patients with cancer. This questionnaire comprises ten factors-psychological well-being, self-adequacy, physical well-being, confidence in self-ability, external support, pain, mobility, optimism and belief, interpersonal relationship, and self-sufficiency and independence. The tool was found to be reliable and feasible for Indian patients [27].

32.4.2 QOL Consideration: Indian Scenario (Table 32.1)

On searching PubMed on 21/07/2016 with the term "quality of life in cancers in India" and "gynecological cancers," total 380 articles could be retrieved. A considerable literature was found on QOL issue but mainly in breast cancer and head-and-neck cancer. After exclusion of other organ specific studies on QOL, total 16 studies were identified that assessed some aspect of QOL in gynecological cancers. Most of the work is centered on QOL in cervical cancer patients, particularly post radiotherapy QOL. EORTC QLQ is commonly used assessment tool though modified in local language and to suit Indian patients.

It is evident that global health and functional level deteriorated while symptoms improved posttreatment across majority of the mentioned studies. Satwant K et al. in their study concluded that the prediction model PrediQt-Cx could be used for making decision by clinicians and patients. Model is also made accessible at

Table 32.1 QOL evaluation: Indian consideration

Author	Study	Number of patients	Assessment method	Conclusion
Chandra PS et al., 1998 [28]	Psychological well-being among cancer patients receiving radiotherapy–a prospective study	70		Well-being scores decreased in dimensions of perceived family and primary group support while improved in dimensions of positive feelings, coping, social support.
Thomas et al., 2004 [29]	FACT-G: reliability and validity of the Malayalam translation	214	Malayalam version of the FACT-G	The local version of the FACT-G scale was found to be reliable and makes it possible to identify domains influencing QOL and thereby may help direct interventions to them.
Ramanakumar et al., 2005 [30]	Coping mechanisms among long-term survivors of breast and cervical cancers in Mumbai, India	52	In-depth interviews	Appropriative health seeking behavior, good general medication, and emotional support were found to be important factors for coping. An unmet need for knowledge of symptoms was identified.
Pathy et al., 2008 [31]	Palliative care in advanced gynecological cancers	64	Retrospective analysis of symptoms	The number of patients with gynecological cancers attending pain and palliative care clinics is significantly low as compared with cancers at other sites.
Kandasamy et al., 2011 [32]	Spirituality, distress, depression, anxiety, and QOL in patients with advanced cancer.	50 (11 gynecological cancers)	Visual analog scale for pain (VAP), M.D. Anderson symptom inventory (MDASI), Hospital Anxiety Depression Scale (HADS), FACT-Palliative Care (FACT-pal), and FACIT-spiritual well-being (FACIT-sp)	Spiritual well-being is an important component of the QOL of advanced cancer patients, and is closely related to the physical and psychological symptoms of distress.
Kannan et al., 2011 [33]	Assessment of QOL of cancer patients in a tertiary care hospital of South India	32 (2 gynecological cancers)	QOL questionnaire designed and Validated by Vidhubala E, et al.	80% of study population had average and below average QOL, suggesting that QOL is important as an outcome, in Addition to other clinical endpoints.

(continued)

Table 32.1 (continued)

Author	Study	Number of patients	Assessment method	Conclusion
Sau et al., 2013 [34]	Baseline demographic profile and general health influencing the post-radiotherapy health related QOL in women with gynecological malignancy treated with pelvic irradiation	147	SF-36 and FACT-G modules	Education and mental composite scores had a positive correlation while higher BMI had a negative correlation with HRQOL domains. Demographic variables affecting QOL can be detected and modified.
Parganiha A et al., 2014 [35]	Effect of hospitalization on rest activity rhythm and QOL of patients on chemotherapy.	30 inpatient (15 reproductive cancers); 26 outpatient (10 reproductive cancers); 30 control	EORTC QLQ-c30; Hospital Anxiety & Depression Scale	Hospitalization alters rest activity rhythm parameters markedly and deteriorates QoL in cancer patients.
Rai et al., 2014 [36]	Vaginal dose, toxicity, and quality of sexual life at 1 year of completion of image guided brachytherapy in cervical cancer patients.	35	EORTC Cx24; (Questions 19–24)	No correlation could be demonstrated between the radiation dose, vaginal toxicity, and its effect of the sexual quality of life.
Shankar et al., 2014 [37]	Sexual function and QOL in long-term survivors of carcinoma cervix	85	LENT SOMA scale	LENT SOMA system was feasible and will help in management to reduce the post-treatment symptoms and improve QOL.
Kumar et al., 2014 [38]	PrediQt-Cx: Post-treatment health related QOL prediction model for cervical cancer patients	198	SF-36 and FACT-G modules	The post-treatment mean global health score and symptoms score were higher while sexual activity decreased. PrediQt-Cx can be used in decision making by clinicians and patients from north India region.
Satwe et al., 2014 [39]	QOL of women with radiation therapy	35	EORTC-QLQC-30 & CX-24	QOL declined on functional and global health status scale while symptoms increased post-RT. A significant association was found between age, education and QOL.
Singh et al., 2014 [40]	QOL in cancer patients undergoing chemotherapy in a tertiary care center in Malwa region of Punjab	131 (40 genitourinary cancers)	EORTC QLQC30 version 3	QOL scoring system did not show significant improvement in all areas (except insomnia, pain, appetite loss, constipation, and financial difficulties)

Table 32.1 (continued)

Author	Study	Number of patients	Assessment method	Conclusion
Damodar et al., 2014 [41]	Reasons for low QOL in South Indian cancer patient population	104 (15 cervical cancers)	EORTC QLQC30, QLQCX24	In cervical cancer patients, physical, emotional function and in symptom scale fatigue, nausea and vomiting, pain, insomnia and in the extended symptom scale, symptom experience scale, menopausal symptoms were significantly affected.
Lewis et al., 2014 [42]	Spiritual well-being and its influence on fatigue in patients undergoing active cancer directed treatment: a correlational study	200 (37 gynecological cancers)	Functional assessment of chronic illness therapy spirituality (FACIT Sp) and FACIT fatigue scales	Fatigue during cancer specific treatment is influenced by spiritual well-being, gender, and stage of disease.
Mohanti et al., 2015 [43]	Physical, social, psychological and economic issues of Indian adult cancer survivors.	31 (2 gynecological cancers)	Modified MINI international neuro-psychiatric interview.	Survivorship issues need to be addressed in developing countries where resources and manpower are limited

http://prediqt.org [38]. Satwe et al. found presence of association between age, literacy, and QOL of patients post-RT [39]. (Table 32.1 shows the characteristics of Indian studies assessing QOL: 28, 29, 32–45.)

32.4.3 QOL Improvement: Indian Contribution (Table 32.2)

Despite the problems identified in delivering adequate health care to cancer patients, Indian clinicians have sought significant ways to alleviate the morbidity caused by treatment and therefore improve QOL of patients with gynecological cancers. Few studies have focused on the role of palliative care and symptom control in improving QOL. Information provided on the commonly encountered symptoms and their effective remedies could be of immense help to treating doctor and patients. The Japanese concept of nerve-sparing radical hysterectomy was propagated by Kobayashi in 1961 and Okabayashi [52]. The same principal and protocols of nerve-sparing technique of hysterectomy are being performed Indian patients. It not only helped in improving QOL of operable cervical cancer patients but proved beneficial also in training of gynecologic oncologists.

Alternative medicine like Ayurveda also has effective remedies for many diseases. Studies on the use of Ayurvedic drugs during chemotherapy and radiotherapy have shown reduction in treatment related toxicities. Metri K et al. explained the adverse effects of chemoradiation to result from Raktapitta (hemorrhage) or Rakta dushti (vascular inflammation) and emphasized on the efficacy of Ayurvedic medicines in relieving them [51]. These ayurvedic medicines are home-based, easily available, and safe. But these can relieve only the acute toxicities. Effect of these medicines on delayed toxicities and QOL is not known. According to recent literature, QOL improvement seems to have become an important component of cancer therapy but still appears neglected in a broad front. Major hurdle in Indian patients may be the reduced expression of problems and acceptance of them as non-curable part of cancer therapy. (Table 32.2 shows the characteristics of Indian Studies improving QOL: 31, 46–53.)

Table 32.2 QOL improvement: Indian contribution

Author	Study	Number of patients	Assessment method	Conclusion
Dave P et al., 2015 [44]	Obstructive uropathy in gynecologic malignancy and value of percutaneous Nephrostomy	25	Prospective study	80% of patients had satisfactory QOL 2 months after PCN insertion due to improvement in symptoms of uremia.
Mishra K, 2011 [10]	Gynecological malignancies from palliative care perspective	–	Review article on symptom management	Gynecology oncologist as a subspecialist has an immensely important role in assuring a good QOL to women.
Kumar and Bhasker, 2014 [45]	Development of protocol for the management of cervical cancer symptoms in resource-constrained developing countries	–	Symptoms' and medical conditions' management guidelines	Cervical cancer supportive care management protocol needs to be tested in a randomized control trial to ascertain its utility, cost effectiveness, and QALY gain.
Chhabra and Kutchi, 2013 [46]	Fertility preservation in gynecological cancers	–	Review article	Attention to long-term health and QOL for patients facing gonadotoxic therapy during their reproductive years must be incorporated into the management plan at the earliest.
Puntambekar et al., 2010 [47]	Preservation of autonomic nerves in laparoscopic total radical hysterectomy.	85.7% patients with cervical cancer of FIGO stage Ia2 and Ib1	Retrospective analysis	Nerve sparing is easier done laparoscopically. Benefit to QOL by L-NRSH technique and its long-term oncological sequelae need further evaluation.
Puntambekar et al., 2014 [48]	Nerve-sparing robotic radical hysterectomy: our technique	12 patients with cervical cancer of FIGO stage IA2 to IB1	Retrospective analysis	Technically feasible and oncologically safe procedure. Early sexual activity and bladder function recovery seen.
Gupta S et al., 2009 [49]	Role of recombinant human erythropoietin In patients of advanced cervical cancer treated "by chemoradiotherapy"	115 (58 treatment arm; 57 control arm)	Randomized controlled trial	Treatment with epoetin beta corrects anemia and is not associated with adverse effects.
Deshmukh V et al., 2014 [50]	Effectiveness of combinations of ayurvedic drugs in alleviating drug toxicity and improving quality of life of cancer patients treated with chemotherapy	15 control arm; 52 treatment arm	Randomized trial	Adjunct treatment with herbo-mineral and metallic ayurvedic drugs appears to have a significant effect on reducing the toxic side effects of chemotherapy.
Metri K et al., 2013 [51]	Ayurveda for chemo-radiotherapy induced side effects in cancer patients.	–	Review article	The simple ayurveda based solutions may act as an important adjuvant to chemo-radiotherapy and enhance the QOL.

32.5 Conclusion

In the era of multimodality treatment and precision medicine, "Quality of life" has its dedicated space. Each treatment planning must consider quality of life in their protocols since beginning. Improved QOL will motivate patients for further treatment and needed compliance. Therefore, user-friendly QOL assessment tools and refined multimodality strategies suitable for Indian population need to be incorporated in national and other cancer treatment guidelines.

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33 History and Evolution of Cytoreductive Surgery (CRS) and HIPEC for Peritoneal Surface Malignancies

M. D. Ray

33.1 Introduction

"Innovation" is a new catch phrase that has invaded medicine. It just sounds so futuristic! Surgical innovation is the aim for surgeons but the problem is under-reporting. The surgeons have been testing surgical procedures since ancient times. Since the first heart transplant in 1967 to the inception of navigational surgery and future of regenerative medicine, research is required to transfer bench side inventions to the bedside. Peritoneal surface malignancy is the best example of such innovative thinking where surgeons have translated a complex process in to a clinical reality. This innovative thinking has changed the whole treatment philosophy, where a disease which was once considered as incurable is now amenable for curative treatment.

Between 1930 and 1990, few small groups of investigators tried cytoreductive surgery (CRS), intraperitoneal chemotherapy (IP), and hyperthermia in isolation. They reported a modest improvement in survival. But, because of high morbidity and mortality (20–60%) they faced lot of criticism. Many noteworthy improvements have been made in the modern surgical arena to safely clear the macroscopic disease with the help of cytoreductive surgeries and now it is combined with hyperthermic intraperitoneal chemotherapy (HIPEC), for treatment of microscopic or minimal volume disease (Fig. 33.1). In this article we will see how the true thinking and innovative ability of a surgeon can change the disease course.

33.2 Timeline of Landmark Events in CRS and HIPEC

Peritoneal surface malignancy is the terrible progression of advanced intra-abdominal malignancies. Management of peritoneal surface malignancy, with a goal to balance the quality of life and overall survival, is difficult and it has been improving gradually over the time (Table 33.1).

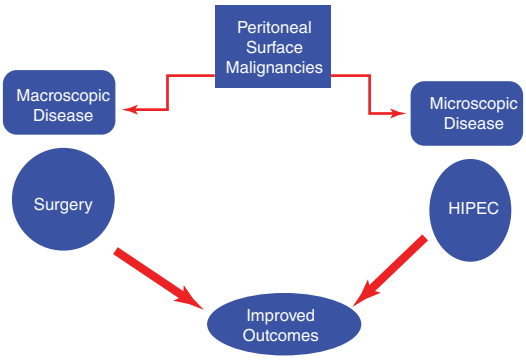

Fig. 33.1 CRS+HIPEC: a unified approach

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Table 33.1 Time line of landmark events in CRS and HIPEC

Year	Landmark event
1930s	JV Meigs describes that tumor debulking in ovarian cancer with adjuvant chemo or radiation therapy
1960s	EW Munnell and C Griffiths report improved survival in stage IV ovarian cancer patients with aggressive cytoreductive surgery to residual tumor burden <2 cm
1969	According to RT Long et al., better outcome with cytoreductive surgery on pseudomyxoma peritonei patients.
1977	J S Spratt developed a device for hyperthermic intracavitary drug delivery.
1977	J M Larkin reports on systemic thermotherapy reducing overall tumor burden
1977	J R Palta develops therapeutic infusion filtration system
1979	J S Spratt treats first patient with hyperthermic thiotepa for PMP
1980	Targeted chemotherapeutic agents for specific malignancies
1980	P H Sugarbaker investigated efficacy of technique for variety of GI malignancies
1987	Phase I trial establishes pharmacokinetic advantage of IP chemotherapy over IV chemo with cisplatin and etoposide
1990	PCI developed for quantifying peritoneal tumor burden
1995	P H Sugarbaker: formally describes technique of peritonectomy
Early 2000s	O Glehen and F N Gilly describes the completeness of cytoreduction (CC) score for measuring extent of CRS achieved
2000–2010	Modern era of CRS & HIPEC Founding dedicated societies/groups for PSM Surgical Standardization Improved peri-operative care pathways Improvement in outcomes and decrease in morbidity Introduction of protocol based treatments Modern HIPEC machines Optimization of hyperthermia and chemotherapy protocols Era of clinical trials

33.3 Cytoreductive Surgery and Peritonectomy

In 1934, Meigs suggested removal of all gross tumors as possible in ovarian cancer enhances the effects of postoperative chemotherapy, helps in relieving symptoms, and reduces complications, i.e. intestinal obstruction, perforation, ascites, etc. In 1968, Munnel published a report of 235 patients of Ca ovary. In this article she reports a significant improvement in survival of patients who underwent appendectomy, omentectomy, and resection of localized diseased peritoneum or intestinal metastases apart from total hysterectomy and bilateral salpingo-oophorectomy. Griffith CT in 1975 stressed that residual tumor of >1.5 cm after debulking surgery is associated with poor prognosis. In 1969, Long et al. reported that patients with pseudomyxoma peritonei (PMP) had significantly increased survival rates who underwent cytoreductive operations multiple times with intraperitoneal or oral alkylating agents as compared to less aggressive methods. Similarly, improved survival has been shown with aggressive clearance of mucinous deposits and resection of diseased peritoneum were found in the experience of the Memorial Sloan-Kettering Cancer Center between 1950 and 1970. Sugarbaker PH published a landmark article in annals of surgery describing peritonectomy procedure. He gave a detailed description of extent, types, and technique of peritonectomy. This article standardized the technique cytoreductive surgery including peritonectomy.

33.4 Intraperitoneal Chemotherapy and Hyperthermia

Initially Pretorius et al. conducted a trial in dogs comparing IV and IP routes of cisplatin administration. The quantity of the administrated agent detected in the urine was found to be equal despite the method of administration of the chemotherapeutic agent. Approximately half of the total administered dosage gets excreted by fourth day. On Day 4 the endothelial lining the peritoneal cavity had significantly higher (2.5–8 times) levels of drug after IP administration ($P < 0.01$). This finding further supported the hypothesis that IP chemotherapy improves the therapeutic index for treatment of peritoneal disease. Around this time, Dr Palta at the University of Missouri,

Columbia was developing a filtration system to infuse chemotherapeutic agents intraperitoneally. Among all the different methods of overall cancer cell killing in advanced stage cancer patients, the impact of hyperthermia was also explored. There were studies reporting positive results with perfusion of the visceral vasculature specifically with heated chemotherapy.

Spratt et al. designed thermal transfusion infiltration system (TIFS) to deliver hyperthermic chemotherapeutic agents into the peritoneal cavity of animals. He successfully infused large amount of chemotherapy agent under controlled temperature and did not observe any major complications or rise in core temperature of the body. In 1979, they applied TIFS to a male patient in his mid-30s and diagnosed with recurrent PMP, hence this patient was the first human to underwent TIFS with infusion of hyperthermic chemotherapy in advanced staged intra-abdominal cancers. This patient had an uneventful recovery and discharged without any complications.

In 1987, Zimm et al. from university of California conducted a phase I trial to document the antineoplastic activity of intraperitoneal cisplatin and etoposide. This study demonstrated the large pharmacokinetic advantage that exists for the IP administration of highly protein-bound drugs. This group reported that patients ovarian carcinomatosis having residual tumor size of 2 cm or less has the mean survival of more than 49 months with IP therapy.

33.5 Proof of Principle Animal Studies

Pelz et al. evaluated the response of disease peritoneal carcinomatosis in rats treated with HIPEC. They found that HIPEC reduced the weight and number of tumor implants significantly when compared to hyperthermia or chemotherapy alone (Table 33.2).

Similar study was conducted by Koga et al. in rats combining hyperthermic peritoneal perfusion with mitomycin C and reported that this may help in both therapeutic and prophylactic treatment in cases of metachronous peritoneal metastasis in carcinoma stomach post-surgery.

33.6 Evolution of Intraperitoneal Heated Chemotherapy Delivery Techniques

Various techniques have been tried by different surgeons for intraperitoneal deliver of heated chemotherapy. Hyperthermic chemotherapy administered intraperitoneally by either open abdomen technique or closed abdomen technique.

The open method also known as "The Coliseum technique" (Fig. 33.2) involves placement of a retractor apparatus to keep the abdomen open and placing a silicon plastic sheet placed over a retractor apparatus and to the skin. After such placement one incision is made over

Fig. 33.2 HIPEC is a complete team management

Table 33.2 Results on a PC (implanted 10 days before) of different treatments (four groups of six rats; IP chemotherapy was made with mitomycin C)

Treatment	Laparotomy alone	Hyperthermia 41 °C	IP chemotherapy alone	HIPEC
Weight of tumor (g)	16.4	5.9	5.7	1.8
No. of implants	68	21	16	4

the plastic sheet to access the peritoneal cavity through the small opening to form an elevated crate or coliseum to hold perfusate of the hyperthermic chemotherapy. A variation of this technique mostly used in Japan uses a device called "peritoneal cavity expander" (PCE). The closed technique (Fig. 33.3) is also similar with respect to the catheters and temperature probes but the laparotomy wound is closed in watertight manner so that the perfusion can be performed in a closed abdomen. The abdominal wall is manually agitated regularly during the procedure to keep the heat distribution uniform.

In the early 2000s, Elias et al. found that this open technique having retraction of abdomen wall edges is better for homogenous heat distribution throughout the abdomen as compared to closed technique. Subsequently, Glehen et al. conducted a survey of surgical oncologists on the best operative method for hyperthermic intraperitoneal chemotherapy. Majority of current surgeons practice open coliseum technique for HIPEC. However, there is insufficient evidence regarding which technique is better and a prospective randomized trial wound be necessary to answer this question.

33.7 Scoring Systems for Peritoneal Cancer Burden and Completeness of Resection

Tumor with peritoneal dissemination is considered as stage IV disease. A universally accepted terminology is developed to assess the tumor burden from prognostic and suitability of CRS point of view. Many groups have tried to establish this criterion for CRS and HIPEC on the basis of size and location of the tumor. In 1990, Sugarbaker and colleagues developed the peritoneal carcinomatosis index (PCI). The abdominal cavity is divided in to 13 regions and deposits divided based on size (less than 0.5 cm, 0.5–5 cm, more than 5 cm) in to three categories. The total disease burden PCI score can range from 1 to 39. The scoring is done intra-operatively by direct visualization of organ and peritoneal involvement by the surgeon.

The completeness of cytoreduction (CC score) is single most independent prognostic parameter. The CC score was first used in 2003 by Glehen and Gilly. CC-0 is no visible residual tumor after surgical debulking and deposits with largest residual tumor deposit <2.5 mm are given CC-1

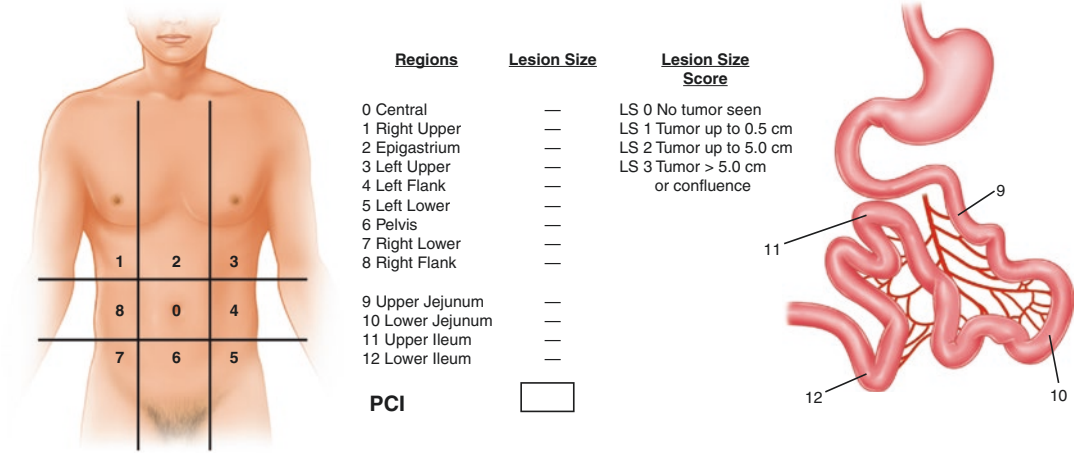

Fig. 33.3 Peritoneal cancer index (PCI)

scores. CC-0 & CC-1 (<2.5 mm) are considered as Optimal CRS and HIPEC is effective in such cases. CC-3 & -4 are considered suboptimal CRS and hence utility of HIPEC is questionable. According to a multicentric retrospective study done on patients of colorectal carcinomatosis the CC score was found to be most significant and independent prognostic factor associated with survival of these patients.

Multiple groups (Japanese, Dutch, and French) have tried to quantify the disease burden using different scales. Recently scoring systems for different site specific cancers are being introduced by dedicated groups.

33.8 Conclusion

Management of PSM is a complex and challenging task. Multiple complex interventions including cytoreductive surgery, intraperitoneal chemotherapy, and hyperthermia could be standardized due to the dedicated efforts of few surgeons over last three decades. Future efforts should focus on clinical trials to address current controversies related to patient selection, optimization of treatments and outcomes, introduction of new technologies and finally integrate CRS and HIPEC in the management of PSM.

33.9 Patient Selection and Scoring Systems

The most important determinant of CRS-HIPEC outcome is patient selection criteria. In view of heterogenous disease spectrum, varied tumor biology, different treatment approaches, and patient related factors including performance status a criterion based approach is recommended for selecting patients for CRS and HIPEC. This criterion is based on evidence generated from two decades of experience from few global centers.

Patient selection is of utmost importance and it can be divided on the basis of:

1. Patient related
2. Disease related

A patient ought to be fit to undergo a major high-risk procedure and the biology of the disease should be potentially curable by CRS-HIPEC.

33.9.1 Patients Related Criteria

1. Performance status—ECOG 0/1
2. Age
   (a) <70 years
   (b) Age <65 years with medical comorbidities in control
   (c) Selected patients >65 years of age without comorbidities, with a low PCI and a low-grade malignancy
3. BMI < 35 (Preferable)
4. Pre-operative serum albumin >3 g/dl
5. Prior systemic chemotherapy
   (a) Drug type—Platinum based, needs dose modification
   (b) Duration
   (c) Response:
      - Stable
      - Early recurrence (<6 months)
      - Progressive-poor predictor of CRS-HIPEC
6. Patients must understand the extent, the risks/benefits of the procedure and motivated to undergo the procedure.

33.9.2 Disease-Related criteria

PSM include a diverse group of cancers involving G.I. tract, peritoneum, or female reproductive organs. The biology, invasiveness, patterns of spread, and response to therapy vary widely depending on site and type of tumor. In addition, timing of peritoneal metastases—upfront synchronous or metachronous in recurrent setting can also influence treatment decisions. Various disease-related factors can influence patient selection criteria.

Organ/system of origin

In general primary peritoneal tumors (carcinomatosis, mesothelioma), PC of colorectal origin,

appendicular tumors, ovarian cancers respond well to CRS and HIPEC. Whereas outcomes with gastric, hepatobiliary, and pancreatic tumors are not very encouraging.

Volume and Extent of Disease
Next important disease related factor is burden of disease and extent of disease. Presence of extra-abdominal disease and significant intra-abdominal extra-peritoneal disease is a contraindication for CRS and HIPEC. High volume invasive disease and involvement of critical anatomical structures preclude patients' selection for CRS and HIPEC.

Pre-operatively on the basis of CT chest and CECT/MR of abdomen and pelvis the following factors predict unfavorable outcomes:

1. Multiple small bowel obstruction.
2. Larger than 5 cm tumor nodule on small bowel mesentery or serosal surfaces.
3. Involvement of root of mesentery or porta hepatis.

Treatment related Criteria
Type and extent of prior systemic or surgical therapy also influence patient selection for CRS and HIPEC. Failed multiple lines of systemic therapy, short disease free interval, chemo resistance, multiple prior surgical interventions are unfavorable factors for successful CRS and HIPEC.

33.10 Scoring Systems for CRS & HIPEC

Peritoneal Carcinomatosis Index (PCI) This scoring system was developed by Paul Sugarbaker to quantify volume of disease in different quadrants of abdomen based on tumor or lesion size. PCI can predict resectability and prognosis (Fig. 33.3).

CCR scoring is devised to score extent of macroscopic tumor clearance. Surgeon should be able to predict CCR score prior to proceeding with cytoreductive surgery (Tables 33.3 and 33.4).

33.11 Prognostic Scoring Systems

Since the CRS/HIPEC is associated with significant morbidity and mortality, extra efforts are put in to develop methods to filter out selected patients who may derive better outcome of the procedure. There are three systems for scoring have been devised for this purpose which includes many prognostic factors.

The Prognostic Score This was first formulated by Verwaal et al. for colorectal carcinomatosis patients and it uses the equation given below [3].

$$\text{Prognostic Score} = 0.592\text{C} + 1.875\text{R} + 0.448\text{D} + 0.487\text{H} + 0.343\,\text{Re}$$

Table 33.3 Completeness of Cytoreduction (CCR) Score. Jacquet and Sugarbaker [1]

Stage	Description
CCR 0 No residual	No peritoneal seeding esposed during the complete exploration (complete cytoreduction)
CCR 1 < 2.5 mm	Diameter of tumor nodules persisting after cytoreduction (complete cytoreduction)
CCR 2 > 2.5 mm < 2.5 cm	Diameter of tumor nodules persisting after cytoreduction (incomplete cytoreduction, moderate residual disease)
CCR 3 > 2.5 cm	Diameter or a confluence of unresectable tumor nodules at any site within abdomen (incomplete cytoreduction, gross residual disease)

Table 33.4 Peritoneal Carcinomatosis scoring system

Classification	Abdominal regions	Tumor measurements	Scoring/staging	Prognostic implications	Studies
PCI	13	0—No deposits 1—Less than 5 mm 2—5 mm to 5 cm 3—More than 5 cm or confluent	Region wise scoring is done and totalled to a maximum score of 39.	Predictive of survival and cytoreducibility in colorectal cancer	van der Vange 2000, [2] Verwaal 2004 [3]
Gilly staging	NA	– Less than 5 mm – 5 mm to 2 cm – More than 2 cm	No disease (stage 0) One part of the abdomen—less than 5 mm (stage 1) Less than 5 mm but diffuse (stage 2) 5 mm to 2 cm nodules (stage 3) More than 2 cm nodules (stage 4)	Significant survival differences between stages 1 and 2 and stages 3 and 4	Jacquet and Sugarbaker 1996 [1]
Japanese Research Society for Gastric Cancer	NA	NA	P0—No deposits P1—Deposits near stomach P2—Few deposits in distant peritoneum/ovary P3—Multiple deposits in distant peritoneum	P3—Low survival	Gilly 1994 [4]
Dutch SPCI	7	None <1 cm 1–5 cm >5 cm	Scores from each region ranging from 0 to 3 totalled up-to maximum 21	High SPCI scores has worse results with CRS/HIPEC	Goere 2015 [5]

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemoperfusion, *NA* not applicable, *PCI* Peritoneal Cancer Index, *SPCI* Simplified Peritoneal Cancer Index

In this equation "C" is carcinoma of colon (C51 if colon cancer, otherwise 0) and "R" is carcinoma of the rectum (R51 if rectal cancer, otherwise 0). For moderately/well differentiated tumor and poorly differentiated tumor "D" is taken as 1 and 2, respectively. If the tumor has signet-ring cell histology, then "H" is taken as 2 otherwise 1 in the absence of signet cells. Another variable "Re" represents regions of the abdomen affected and it can be 1–7. The regions can be right and left subphrenic area, subhepatic space, stomach, pelvic region, right and left lower abdomen, omentum, transverse colon and mesentery, etc. Verwaal et al. [3] was the first to report that apart from volume of the disease, the regions inside abdomen which contains the disease and removal of whole disease is also important in order to achieve good outcome. He also reported that more than five regions involvement in abdomen result in poor overall survival so does rectal carcinoma, signet cell, or poorly differentiated histology.

33.12 Peritoneal Surface Disease Severity Score (PSDSS)

Esquivel et al. [6] and Pelz et al. [7] developed the score for carcinoma appendix and colon cancer. This scoring system has tumor histology, symptoms of the patients, and PCI detected in cross section imaging done pre-operatively. According to

this score carcinoma colon and carcinoma appendix has 4 and 5 stages, respectively.

33.13 Colon and Rectal Peritoneal Carcinomatosis (COREP)

Cashin et al. [8] developed a third scoring system based on laboratory studies for colon and rectal peritoneal carcinomatosis (COREP). This scoring system uses change and elevation of various tumor markers, i.e. CA-125, CA-19.9 and CA-15.3, etc. and based on that it recognizes patients who have life expectancy of less than a year. These are the patients who are not likely to draw better outcome from major procedure like CRS/HIPEC.

Preferable patients for CRS and HIPEC based on scoring systems

1. Low PCI
   (a) Colorectal cancer: PCI < 15.
   (b) Gastric cancer PCI < 6.
2. Predicted CC Score-0/1.
3. Less than three intraoperative anastomoses.

Absolute contraindications for CRS and HIPEC

- Extra abdominal disease.
- Significant extraperitoneal disease, such as more than three liver metastases.
- Large retroperitoneal lymph nodes.
- Infiltrative tumor deposits at root of mesentery and porta hepatis.
- Unknown primary tumor.

Relative Contraindications for CRS & HIPEC

- Grade 3 adenocarcinoma (including signet-ring cells and PMCA).
- Synchronous peritoneal carcinomatosis after diagnosis of primary adenocarcinoma.
- Frozen pelvis secondary to a rectal cancer recurrence.

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34 Management of Common Complications of CRS and HIPEC

M. D. Ray

Certain malignancies can have metastases limited to peritoneal cavity notably ovary, colon and pseudomyxomas. Other malignancies of stomach, GIST, mesotheliomas can also have the similar presentations. The revolutionary idea of treatment of the peritoneal carcinomatosis was initiated by Dr Paul Sugarbaker in the 1970s and 1980s. He received good amount of the opposition from the contemporaries initially but as the results matured into good success, the procedures of cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) are now becoming standard of care for the peritoneal carcinomatosis. The procedure is extensive, long and associated with complications. CRS and HIPEC often involves massive surgical procedures. Intraperitoneal chemotherapy is also given at the end of the surgical procedure. The aim of the procedure is complete removal of macroscopic disease. The key lies in the proper selection of the patients and the proper postoperative management of the complications as they arise.

As reported in different large series the overall morbidity ranges from 22 to 34% and mortality from 0.8 to 4.1% [1–3].

With the increasing experience the morbidity and the mortality rates have decreased. The "learning curve" effect is very much there [4]. In the subsequent pages, the complications, the risk factors for the complications and their management have been discussed in brief.

The complications can be grouped as

1. Intraoperative
2. Postoperative
   (a) Gastrointestinal
   (b) Pulmonary
   (c) Hematologic
   (d) Others: urinary, wound

34.1 Intraoperative Complications

Due to dense adhesions of the previous surgery, there is a fairly good chance of inadvertent bowel injury which can range from serosal injuries to full thickness enterotomies. Precautions need to be applied during the dissection. As the dissection is done with high voltage cautery there might be thermal injury to the gut also. Key is to remain cautious enough to avoid these problems and vigilant enough to close the enterotomies and the serosal tears as and when they are found.

Diaphragmatic injuries are not uncommon. They occur during dissection of the diaphragmatic peritoneum as the cautery is at high current. Any diaphragmatic injury happening should be repaired properly there at that time only. Another important complication which can occur

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during the diaphragmatic peritoneum dissection is injury to the hepatic veins especially the right hepatic vein. It can cause severe bleeding. Prevention is the key. One should not dissect below the inferior phrenic veins which is the location of the RHV. Another site of injury is the injury to the posterior hepatic veins while doing the peritonectomy over the IVC. Being cautious at these places is paramount. Injury to portal vein or CBD may occur during dissection of the peritoneum at the hepatoduodenal ligament.

Another organ prone to injury during the peritonectomy is urinary bladder. The peritonectomy at the bladder should start at the urachus and cautiously the whole bladder peritoneum should be removed. Any injury to the bladder requires layered repair with maintenance of the Foley's catheter for prolonged period in the postoperative period. Ureteric injuries can also occur especially when the disease burden is high in the cul de sac.

During dissection the ureters should be identified and looped initially so as to prevent injury. Alternatively ureteric stents may be placed preoperatively to prevent any future injury to them.

Inadvertent vascular injuries can also occur especially in the pelvis. Cautious dissection is warranted.

Fluid losses are very common during the procedure due to development of large raw surface areas. There is extensive loss of fluid proteins which leads to fluid shifts. Anesthesiologist role is very important. They should maintain the good fluid intake which may at time reach up to 200–240 ml/h. Urine output of 1–1.5 ml/kg/h should be maintained. Albumin infusions may be given as required.

Thus most of the intraoperative complications are avoidable and easily rectifiable with thorough vigilance.

34.2 Postoperative Complications

1. *Gastrointestinal Complications*

   The procedure of CRS and HIPEC may involve multiple resections and anastomosis. The reported incidence of the Grade III/IV morbidity associated with this procedure is 4.5–19% in different series [5–7]. Previous surgical adhesions add to the difficulty of dissection added onto by the distorted anatomy. Intraperitoneal chemotherapy may alter the healing process.

   The anastomotic leakage and bowel perforation are the commonest complications and occur due to some inadvertent bowel mechanical injury going unnoticed during dissection, focal heat injury during chemotherapy instillation or non-healing of anastomosis. Non-healing of the anastomosis entails faulty technique and may be delayed healing. Debate lingers on whether the anastomosis be done before or after the HIPEC. Trials have not supported either practice and results of both the practices remain same [8]. We follow the practice of doing anastomosis after HIPEC as we are exclusively following the open technique of HIPEC. Once again the role of meticulous dissection is to be emphasized as well as properly using the ball tip cautery.

   Other complications can be biliary fistulas, pancreatic fistulas, chyle leak and gastric stasis. Gastric stasis and prolonged ileus are not uncommon but they are self-limiting usually and simply require Ryle's Tube aspiration.

2. *Pulmonary Complications*

   Pulmonary complications are common sequelae of any abdominal procedure. With the extensive surgery of CRS and add on HIPEC the incidence is bound to be higher. The reported incidence of grade 3/4 pulmonary complications is 10–16% [9, 10]. The risk of pleural effusions is high especially when postoperative chest tubes are not used. Pneumonia is also not uncommon. Both of these complications are better prevented. We routinely use postoperative chest tubes especially when there is some diaphragmatic injury. The training of the patient for the incentive spirometry should start in the preoperative period. Early ambulation is the key to success. We routinely ask our patients to start with breathing exercises in the preoperative period along with steam inhalation and the practice continues in the postoperative period

also. A better glycemic control and good fluid management are warranted for the prevention of these complications.

3. *Hematologic Complications*

These complications are quite common with a wide rage reported from 4 to 39% [11, 12]. Neutropenia in the postoperative period is associated with a reported mortality of 0–60%.

These complications are dependent upon the agent used, the dilution used, the duration and the temperature. For example, mitomycin C is classically associated with neutropenia. Oxaliplatin has higher platelet toxicity. Cisplatin is especially reno-toxic. The reporting of these adverse events is variable in literature and may be under reported.

Whether splenectomy is protective towards hematologic malignancies remains controversial. Some studies [13] confirm this association but others [12] refute the hypothesis.

4. *Others*

Other complications include the urinary tract infections, renal insufficiency (~4%) and venous thromboembolism (~5%) [14]. Deep venous thromboembolism and resultant pulmonary embolism can sometimes be fatal. We routinely use prophylactic low molecular weight heparin along with pneumatic stockings in the postoperative period.

Wound complications involve incisional hernias and wound infections. These complications are expected to be more common in view of longer incisions and previous surgeries. But at our institution we have experienced these complications to be pretty less.

5. *Mortality*

Mortality has been reported varyingly amongst different series from 0.8 to 6% [15, 16]. The mortality has been seen to be higher in CRS and HIPEC for the gastrointestinal malignancies than the ovarian malignancies. This has been ascribed to the higher number of visceral resection and anastomosis in case of GI malignancies. In the unpublished data from our institute we had an overall mortality rate of <2% with majority of the malignancies being ovarian.

34.3 Factors Contributing to the Complications

1. *Patient Factors*
   (a) *Age*: National Surgical Quality Improvement Program (NSQIP) database [17] has shown that age >60 years is independently associated with death and the incidence increased 0.6% per year after 50 years of age so do the other complications of venous thromboembolism, bleeding and respiratory complications.
   (b) *Hypoalbuminemia*: A level of <3 g/dl is associated with higher morbidity and mortality [17].
   (c) *Performance status*: Undoubtedly poor performance status is going to have higher complications rate.
   (d) *Obesity*: These overweight patients are more prone to develop venous thromboembolism. A study reported higher late readmission and late urinary tract infection rates [18].
2. *Operative factors*
   (a) *Peritoneal Carcinomatosis Index (PCI)*: Most consistent and independent factor predicting morbidity and mortality [2]. A PCI of more than 17 for colorectal, PCI > 12 for stomach and a PCI > 24 for pseudomyxoma peritonei is predictive higher morbidity and mortality [16].
   (b) *Bowel Anastomosis*: Studies have shown that postoperative complications are more common when bowel anastomosis is required at the time of CRS and HIPEC [17].
   (c) *Diaphragmatic involvement*: Patients with diaphragmatic involvement have higher operative time, higher pulmonary complications, higher bleeding and higher postoperative mortality [19]. The mortality at 90 days is higher in patients who have undergone diaphragmatic resections.
   (d) *Surgeon and institutional experience*: There is clear learning curve in the CRS and HIPEC procedure. One study reported that the severe morbidity decreased from

30% after first 70 procedures to 10% in the next 70 procedures with reduction in ICU stay, blood transfusions and operating times [20].

34.4 Conclusion

CRS and HIPEC for disseminated peritoneal carcinomatosis is an extensive procedure with a potential for high morbidity and mortality. Patient selection is paramount. A multidisciplinary team should take the decision for the procedure. The management of the complications starts in the preoperative period starting from patient selection and respiratory exercises and goes on into the postoperative period. The learning curve effect is very evident with morbidity and mortality decreases with very increasing case number. The limited available data has suggested that independent effect of HIPEC is small and the majority of the postoperative complications are related to the abdominal surgery itself.

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35 Surgical Safety for the Team Performing CRS and HIPEC

M. D. Ray

CRS + HIPEC, in contrast to surgeries for solid tumors, exposes health care workers to two distinct toxins:

1. Excessive surgical smoke
2. Cytotoxic drugs

35.1 Excessive Surgical Smoke

"Surgical smoke" refers to smoke generated upon transmission of energy to cells during surgical procedures. Electrosurgical instruments are used extensively in CRS, especially during peritonectomy, thereby generating inordinate amount of smoke. This smoke is primarily constituted of water vapor, but also contains organic compounds (e.g. benzene, toluene, formaldehyde, cyanine hydroxide, aromatic hydrocarbons) and inorganic compounds (CO, CO_2, NO_2, SO_2)—exposure to which has been known to present with varied symptoms including but not limited to headache, irritation of the eyes or respiratory tract, and nausea [1, 2]. This smoke has been known to contain ultrafine particles, measuring 0.01–200 microns in diameter, in concentrations comparable to that of passive cigarette smoking [3]. Microorganisms such as bacteria, mycobacteria, fungi, and viruses have also been identified in surgical smoke (Table 35.1). The cornerstones of safety measures against excessive surgical smoke are [4]:

(a) Ventilators,
(b) Smoke evacuators,
(c) Surgical masks,
(d) Eye protection.

Ventilation has to be maintained with a slightly higher pressure in the operating room as compared to the surroundings. It is imperative that ventilation should be continuous throughout the procedure. In modern operating rooms, it is typical to find HEPA (high efficiency particulate air) filters with airtight door closures and the same has to be modified in older ORs.

Table 35.1 Possible risks associated with electrosurgical smoke [5, 6]

Respiratory	*Skin and eyes*
Airway inflammation	Dermatitis
Sneezing	Lacrimation
Coughing	*GIT*
Throat irritation	Colic
Hypoxia	Nausea
Asthma	Vomiting
Pulmonary congestion	Hepatitis
Chronic bronchitis	*Other systems*
Emphysema	Weakness
Cardiovascular	Anemia
Cardiovascular dysfunction	Headache
	Dizziness
	AIDS

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Smoke evacuation devices like the Buffalo filter must have the following components: an absorbent HEPA type filter, a suction unit, and a for smoke evacuation, a disposable rigid tube. The smoke evacuator device must be available throughout the procedure. The suction filters once used have to be disposed of as hazardous material with standard precautions as taken for other items used in the OR and have to be changed frequently as advised by the manufacturer.

The standard surgical mask used in most OR by the operating team cannot protect the wearer from exposure to surgical smoke. Masks should fit well on the nose and mouth and should consist of a high-power filtration mechanism. This recommendation is based on the fact that they have the ability to offer high filtration of smaller particles and protect against solid and non-volatile liquid particles.

Routine use of eye protection also is recommended in the form of goggles or shields that act as mechanical barrier for contaminants and splashes.

35.2 Cytotoxic Drugs

Health hazards of exposure to chemotherapeutic drugs cannot be impressed upon enough. In addition, International Agency for Research on Cancer (IARC) has declared commonly used chemotherapeutic drugs in HIPEC as group 2A (cisplatin, doxorubicin) and group 2B (mitomycin C) carcinogens.

As per an article by Kyriazanos et al. [4], safety guidelines for administration of HIPEC are:

1. *Preparation of operating room (OR) and personnel*
   - All personnel should be sensitized about the risks posed by this procedure and precautionary measures. They should receive practical training to combat hazardous situations such as drug spillage.
   - Safety notices should be placed at multiple spots. The access to OR should be restricted to essential personnel and the OR entrance should be labeled appropriately.
   - Those participating in the CRS and HIPEC should be subjected to routine and regular health checks. Routine recommendations suggest that pregnant females should be excluded from such procedures.
2. *Use of personal protective equipment (PPE) during HIPEC*
   - PPE comprises face masks, goggles, gloves, protective gown, and overshoes.
   - High-power filtration masks are recommended. They should be changed every 2 h.
   - Routine use of eye protection also is recommended in the form of goggles or shields that act as mechanical barrier for contaminants and splashes.
   - Use of two gloves on each hand and changing gloves every 30 min are advisable. This confers a protection as air acts as an effective barrier. Long gauntlets (elbow-length) covering both hands as well as arms are to be used. The outer glove should cover the extend of the cuff of the surgical gown.
   - Surgical gowns should consist of closed fronts with the ability to knot at the sides in an aseptic manner, long sleeves covering till the wrists made of preferably elastic water repellent material and fitting enough to be watertight. Any part of the gown if drenched or damaged, should be immediately changed as soaked fabric on skin is known to exhibit excellent absorption.
   - Closed shoes which are easy to clean are to be used. Overshoes or special shoes are to be used exclusively by the OR personnel in the direct working area.
3. *Handling of the chemotherapy during HIPEC*
   - Chemotherapy drugs should be prepared and transported in containers preventing leaks and spills.
   - Smoke evacuation system should be used during the HIPEC phase to reduce airborne contaminants caused by aerosols.
   - Keeping in mind the possibility of spills from the surgical field onto the floor, towels

with impervious back should be placed on the floor all around the surgical table.
- Since body fluids, blood samples, tissues are considered contaminated 48 h after last chemotherapy, items used in OR must be considered as biological hazardous material and must be disposed of accordingly as per hospital protocols.

4. *Management of surgical spills*
   - Policies and procedures should be predefined to avoid spills by the OR administration team and should be strictly followed to prevent them.
   - A team consisting of surgeons, nursing staff, technical team should be constituted and designated as spill management teams to ensure proper management of any possible mishappenings.
   - Immediate containment and cleaning of any surgical spill is imperative.
   - Literature defines a large spill as a drop of more than 5 g or containing 5 mL of pure drug.
5. *Handling of waste after HIPEC*
   - Chemotherapy containing wastes should not be considered lightly and a policy for its management should be predefined by each hospital based on its quantity and type of waste production along with available management system and resources for disposal. This has to be followed strictly.
   - The collected contaminants should be properly labeled and stored for transport and disposal. The team should have adequate and up-to-date knowledge of the regulations and protocols in their country and adhere to it.

As CRS+HIPEC has become the new standard of care for certain types of malignancies, more centers are now adopting this technique. One must adhere to the safety guidelines, including the formulation of new policies as and when required and following predefined procedures for the safe handling of cytotoxic wastes and potentially contaminated items in the operating room.

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Role of HIPEC in Pseudomyxoma Peritonei and Appendicular Tumor

36

M. D. Ray

36.1 Introduction

Pseudomyxoma peritonei (PMP) is a relatively rare disease with a characteristic accumulation of mucinous fluid in the peritoneal cavity. Over time, this mucinous material fills the entire peritoneal cavity and presents as "jelly belly" at laparotomy. The definition of PMP has long been a matter of debate. PMP was vaguely used to describe mucinous ascites and diffuse involvement of peritoneal lining with mucinous implants. The present review describes the definition, classification, clinical features, and treatment modalities of PMP.

36.2 Origin and Definition of Pseudomyxoma Peritonei

The term "Pseudomyxoma peritonei" was first put forth by Werth in 1884 to describe the ovarian mucinous carcinoma. However, since Frankel described a similar clinical entity in 1901, in association with a benign cyst of the appendix, there was a lot of controversy in PMP's origin [1].

PMP predominantly originates in the appendix in men. The controversy exists in women where either the huge ovarian masses can be the primary site of origin or a small appendiceal tumor is the primary [2].

Various researchers have attempted to clarify the origin of PMP using immunohistochemistry and molecular genetics techniques. The pattern of cytokeratin expression differs in PMP associated with ovarian (CK7 + and usually CK20 +) and appendicular primaries (CK20 + and usually CK7-ve, similar to non-PMP appendiceal mucinous tumors) [3, 4]. Ronnett et al. [3] employed differential IHC expression to identify the origin of PMP in females. Most ovarian mucinous neoplasms stain positive for CK 7,18,20, CEA, and Human alveolar macrophage 56 (HAM 56). In contrast, most colorectal cancers are CK20 and CEA positive but CK7 and HAM56 negative. In 13 cases of PMP, appendiceal mucinous adenomas, and ovarian tumors, the same patents were immunostained with these antigens.

From a clinical viewpoint, if the appendix theory of origin was correct, sex distribution should be similar, as the appendicular tumors in females are unlikely to be pathologically different from those in males. Similar male vs female distribution is seen in four published case series. Although the Mayo Clinic series had a higher female proportion, it is because a number of them are likely ovarian in origin, as suggested from the evidence [5].

This question becomes more complicated with increasing case reports showing colorectal,

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gastric, gallbladder and biliary, small intestinal, urinary bladder, pulmonary, breast, breast, fallopian tubal, and pancreatic in origin, in addition to appendiceal and ovarian tumors. Except colorectal, these other histologies are rare and constitute less than 5%. Since mucinous adenocarcinoma of any origin can present with clinical, radiological, and surgical features similar to colorectal or ovarian primary in females, this may lead to the perception that PMP is more common in females.

The term PMP is used to indicate a slowly progressive disease process usually, but many clinicians use this term in any condition with peritoneal mucin accumulation, ranging from benign mucinous cystadenoma to invasive mucinous adenocarcinoma arising from any intra-abdominal organ. This vague description commonly grouping different tumors with different biologic behaviors leads to difficulty in diagnosing and managing this condition.

A pathological study published by Ronnet et al. is often quoted in the literature [6]. In this, cases were categorized into Disseminated Peritoneal Adeno Mucinosis (DPAM) and Peritoneal Mucinous Carcinomatosis (PMCA). DPAM group includes patients with lesions having pools of acellular/extracellular mucin with scant epithelium having little atypia or mitosis. There could be an associated appendicular mucinous adenoma. PMCA group contains more cellular mucinous lesions with carcinomatous features, with or without the evidence of an associated mucinous adenocarcinoma primary. DPAM has better survival than PMCA. To illustrate the term "Pseudomyxoma Peritonei" uniformly, Sugarbaker and colleagues suggested that this should strictly be applied to a pathologically and prognostically uniform group of patients with benign histology, frequently associated with appendiceal mucinous adenomas [7]. Peritoneal carcinomatosis cases, even with abundant mucin, are not included in this PMP definition.

Even though PMP is not aggressive biologically, in terms of the absence of invasion or metastasis, the progressive intraperitoneal space-occupying nature of the disease can compromise the nutritional function and result in death. The median OS with PMP is around 6 years, with 53–75% 5-year OS. Sugarbaker and his colleagues [7] have reported a significantly better survival by combining aggressive surgical cytoreduction with intraperitoneal chemotherapy. Though PMP is generally considered a benign entity, its strong persistence and progression over time reflects aggressive behavior, justifying it to be called a borderline malignant condition [1].

36.3 Clinical Features

With the advancements in radiology, preoperative identification of PMP is increasing. However, there is a scarcity of reports with large patient populations in the literature to define the clinical presentation because of the rare incidence.

Esquivel et al. [8] in one of the most extensive PMP series with perforated appendiceal adenoma, most common presentation was reported as a suspected acute appendicitis (27%). The most common diagnosis was made in women during workup of an ovarian mass (39%). The second most common presentation is with increasing abdominal girth (23%). New-onset hernia was the presentation in 14% cases, with most being inguinal hernias. They opined that consideration of appendicitis, ovarian mass, abdominal distension, and new-onset hernias as features of this condition, can help in diagnosing it.

36.4 Preoperative Workup

With increasing availability of cross sectional imaging like good quality CT scans with combinations of oral, rectal, and intravenous contrast, PMP is suspected based on few pathognomonic features. "Compartmentalization" of relatively spared small bowel in the central abdomen with a large "omental cake" is seen in most scans in PMP cases. "Scalloping of liver surface" by mucinous deposits is another characteristic fea-

ture. Small bowel usually shows normal luminal calibre without any obstructed segments. The normal flow of peritoneal fluid can result in this pattern of distribution of mucin. Initial seeding occurs in areas of relative stasis, with eventual filling up of the abdominal cavity. Imaging features predominately show pressure effects. PMP can extend into the pleural cavity or hernial orifices [9]. Gradual involvement of small bowel and mesentery by mucinous tumor masses follows the progressive encasement of the rectosigmoid and stomach.

A broad spectrum of these radiological appearances and previous surgeries can also alter the appearances and increases the complexity of interpretation. At present, Ultrasonography and Magnetic Resonance Imaging does not add much to the information obtained on a good quality CT scan. However, with advances in technology and dynamic small bowel assessment, MRI can prove to be helpful in the future.

Obtaining relatively acellular material on image-guided biopsy makes the interpretation difficult. Measurement of CA 125 in women and CEA in both sexes may lead to erroneously marking them as advanced ovarian or colorectal primaries.

Upper and lower gastrointestinal tract investigations, if performed, will be normal. Few clinicians only can encounter more than a handful of cases in their careers because of the rare incidence. A number of patients are often misdiagnosed and managed as irritable bowel syndrome for years before arriving at a definitive diagnosis. Women are more likely to have imaging for nonspecific abdominal symptoms to address the suspicion of ovarian cancer. Men are far more likely to present with advanced disease with years of history of nonspecific abdominal symptoms before the diagnosis.

The significance of tumor markers is not well established in PMP. In these patients, CA-125 is commonly elevated, even in males with appendiceal primary. Higher levels can predict likely failure of complete cytoreduction. Marker tests help in the follow-up of patients with elevated levels to detect recurrence and progression.

36.5 Treatment

The management of PMP continues to be controversial due to the scarcity of level I scientific evidence. Such evidence is also likely to be unavailable ever in view of rarity and heterogeneity of the condition.

Both systemic chemotherapy and radiotherapy have little role to play in the management of PMP. Targeting radiotherapy is not possible given the broad field of tumor involvement with interspersed viscera. Achieving sufficiently high doses for therapeutic efficiency is nearly impossible.

These tumor cells are low grade, and PMP is a borderline malignancy. Low grade and the poor blood supply limit the efficiency of systemic chemotherapy in disease control. Sufficient high doses to achieve tumor control result in serious adverse effects. Few reports indicate the benefit of platinum-based chemotherapy regimens, and there is a possibility that the tumors in those reports are of ovarian origin rather than PMP.

36.5.1 Surgical Management of PMP

Surgical debulking of the tumor and peritonectomy procedures are two approaches in surgical management.

The widely practiced traditional approach is debulking. During laparotomy, mucous and tumor are removed as much as possible by combining blunt dissection and limited visceral resections like omentectomy, hysterectomy, oophorectomy, colectomy. Debulking provides the patient with a symptom-free interval before the disease eventually recurs. Repeat laparotomies addresses symptomatic recurrences, and with each episode, it becomes less effective and dangerous. Morbidity increases due to intra-abdominal abscesses, entero-cutaneous fistulas, anastomotic leaks. Complete removal of tumor is not possible due to tumor cell entrapment in bowel adhesions, small bowel or critical structure involvement, or progressive malignant transformation like the adenoma–carcinoma sequence.

The alternative surgical approach is complete cytoreduction. Since these tumors are minimally invasive and spread along the peritoneal surfaces, Sugarbaker described six peritonectomy procedures for the complete removal of tumors based on disease location and progression. With an increasing understanding of the disease, Sugarbaker further defined the role of Hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC) [7].

Peritonectomy involves stripping parietal peritoneum and resection of stasis sites to remove tumor laden visceral peritoneum to achieve complete cytoreduction. Ball tipped monopolar handpiece with the electrosurgical generator on pure cut at high setting is used for evaporation of small tumor nodules. To facilitate vision and to protect the operation theater environment, a smoke evacuator is used.

36.5.2 Peritonectomy Procedures for Complete Cytoreduction

A liberal midline laparotomy extending from xiphoid to symphysis pubis is necessary for required exposure (Fig. 36.1). A careful and diligent examination of the abdominal cavity is performed. Assessment of disease-free small bowel is critical before one proceeds further, especially if complete cytoreduction needs a gastrectomy (Fig. 36.2). Before performing any irreversible high-risk procedures, the possibility of achieving complete cytoreduction should be carefully evaluated. Sugarbaker [7] proposed six peritonectomy procedures, which are usually performed during cytoreduction:

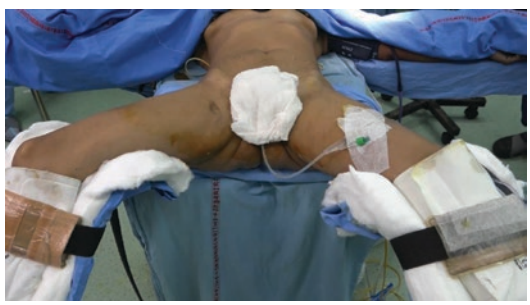

Fig. 36.1 Position of the patient during CRS+HIPEC

1. Greater omentectomy and splenectomy
2. Left Hemi-diaphragmatic peritonectomy
3. Right Hemi-diaphragmatic peritonectomy
4. Lesser omentectomy and cholecystectomy
5. Distal gastrectomy (antrectomy)
6. Pelvic peritonectomy with resection of the rectosigmoid

The anterolateral parietal layer of peritoneum is also stripped. A single patient may not require all six peritonectomy procedures. Right hemicolectomy removes the disease concentrated around the ileocecal area. Gastric branches of gastroepiploic arcade are ligated during greater omentectomy. Left gastric artery is the main or only vessel supplying the gastric remnant after excising the disease in the gastric antrum area (with or without antrectomy). In few cases, with disease involving the left gastric artery, total gastrectomy with esophagojejunostomy.

These complex surgical procedures in a patient suitable for complete cytoreduction require considerable operative time of 8–10 h depending upon the surgeon's expertise and experience.

36.5.3 Intraperitoneal Chemotherapy

The surgical strategy in gastrointestinal tumors is to operate well beyond the tumor, keeping a clear tumor-free margin. Though the surgical excision is quite effective to address the macroscopic disease in PMP, it is almost impossible to achieve microscopic clearance. Microscopic remnant warrants adjunctive treatment for eradication. Intra-abdominal mucinous tumors are relatively resistant to oral or intravenous chemotherapy. The peritoneal/plasma barrier, the relatively low blood supply to the tumor, and the "slow-growing" nature of such tumors contribute to the chemoresistance. Sugarbaker proposed strong arguments in favor of intraperitoneal chemotherapy usage, especially intraoperatively, after removing all macroscopic disease, total adhesiolysis, and the surgeon having access to the entire abdomen to ensure delivery [7].

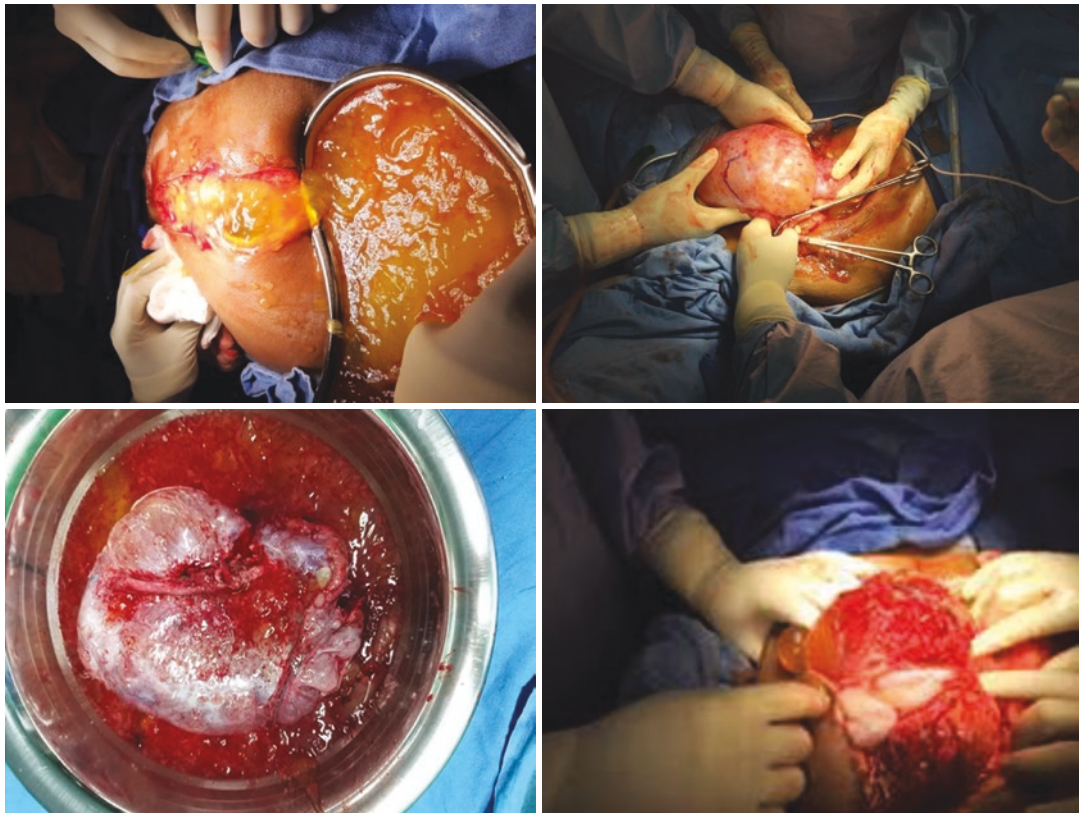

Fig. 36.2 Jelly like mucinous material in pseudomyxoma peritonei

Intraperitoneal chemotherapy's rationale is that direct exposure of cancer cells and small volume disease to high concentration chemotherapy can result in disease eradication by direct effect. Chemotherapy drugs enter the tumor cells by diffusion and can thereby penetrate only 2–3 mm into the nodules. One should understand that intraperitoneal drug delivery in the context of gross residual disease or multiple adhesions is futile exercise. In these situations, the observed small benefit could be attributed to systemic drug absorption.

36.5.4 Hyperthermic Intraperitoneal Chemotherapy

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) aims to deliver high dose intraperitoneal heated chemotherapy regionally with minimal systemic effects in patients with no/minimal residual disease. A high dose of heated (to around 107 °F or 40–42 °C) chemotherapy solution is circulated throughout the abdomen to kill any residual microscopic cancer cells (Figs. 36.3, 36.4, and 36.5). Hyperthermia has cytotoxic and histotoxic properties. It results in massive tissue damage on prolonged exposure apart from generation of heat shock proteins, altered cellular thermoregulation in cancer cells. Potential thermal enhancement of cancer cell killing property of few chemotherapy agents is identified in animal studies. Most common drugs used in appendiceal mucinous neoplasms are mitomycin C at 10–12.5 mg/m^2, oxaliplatin at 460 mg/m^2, cisplatin, and 5-FU, individually or in combination regimens [10, 11].

HIPEC is a complex and morbid procedure. An increase in postoperative fistula complications and leak rates, especially in the colorectal anastomosis was documented by Sugarbaker [7]. Grade 3,4 neutropenia is seen in around 5% of

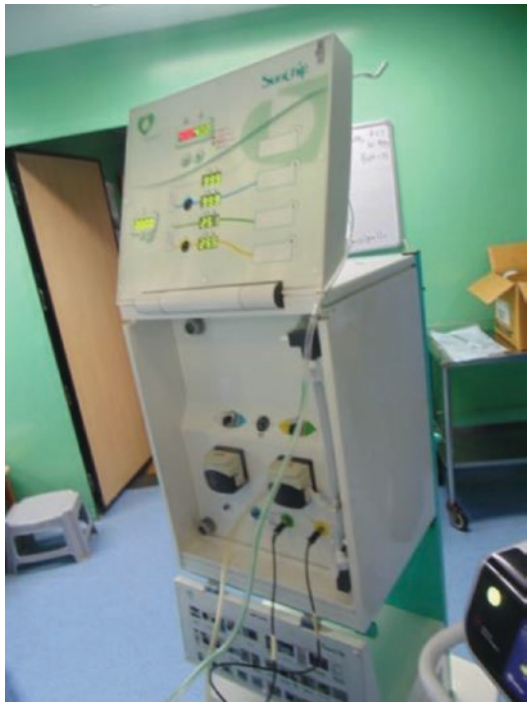

Fig. 36.3 HIPEC machine

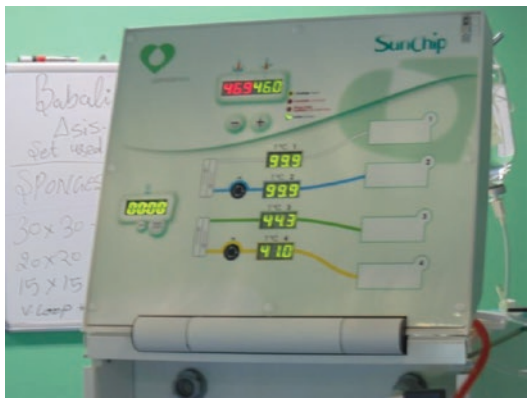

Fig. 36.4 HIPEC machine showing optimum temperature (41 °C)

cases in the second week after surgery. It may be complicated by infections. Early identification of neutropenia with administration of appropriate antibiotic, antifungal agents, and granulocyte colony-stimulating factors use early in the course can improve outcomes. Isolation can prevent secondary infections. Good supportive care is crucial to avoid mortality.

Careful patient selection is crucial to have acceptable morbidity and mortality. Over course

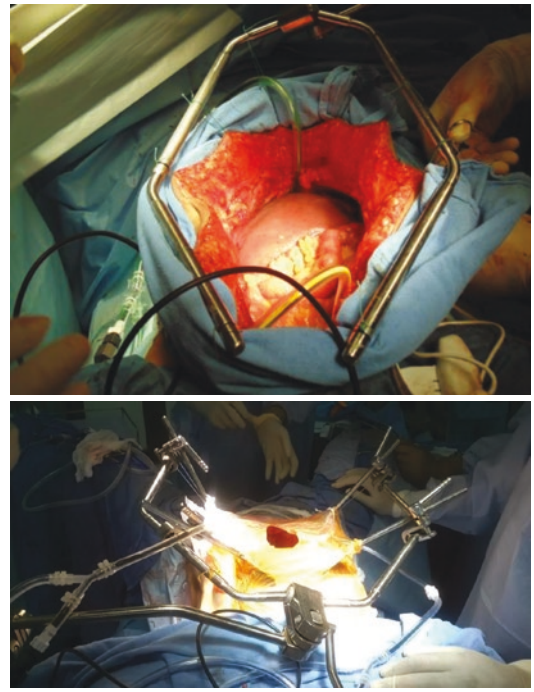

Fig. 36.5 Semi-open technique of HIPEC

of time, disease progression is seen in many patients and may eventually succumb, despite aggressive conventional surgery.

Recent literature indicates that the achievement of optimal cytoreduction with intraperitoneal chemotherapy prolongs disease-free survival, even beyond 10 years in few. However, careful patient selection is essential. It predominantly involves diligent, thorough clinical assessment, and good quality cross-sectional imaging. A recommendation of CRS with HIPEC in patients with aggressive disease must be made in context of age, general condition, and wishes of the patient. Risks and benefits should also be looked in context of the experience and outcomes of the treating unit. It may not be always possible to predict accurate findings before surgery. It is essential to inform relatives and patients about the possibility of abandoning surgery if any unexpected findings are identified. Jacquet and colleagues [12] identified two radiological findings that predicted incomplete cytoreduction in their retrospective study. They were: (a) segmental small bowel obstruction, (b) Greater than 5 cm deposits on the small bowel jejunal, proximal ileal mesentery. Focal small bowel stenosis could

indicate an invasive component, likely of mucinous adenocarcinoma.

36.6 Summary

PMP is an unusual condition, although of "borderline malignant potential," it is universally fatal. The definition of PMP has been a matter of debate. Inclusion of heterogeneous pathologic conditions with a shared clinical presentation of mucinous ascites under the blanket term PMP is vague. Different authors have used different definitions of PMP in various reports. To identify a more homogenous group representing PMP, Sugarbaker proposed that the name "pseudomyxoma peritonei syndrome" should strictly be applied to a pathologically and prognostically uniform group of patients with benign histology, which is frequently associated with appendiceal mucinous adenomas. Mucinous adenocarcinoma cases are not included in this definition. Optimal treatment is complete cytoreduction by complex surgical peritonectomy procedures and intraperitoneal chemotherapy. Mortality and morbidity rates are high for cytoreduction and HIPEC. The rare incidence and high treatment morbidity suggest that management should be undertaken in high volume centers to optimize outcomes.

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CRS and HIPEC for Management of Malignant Mesothelioma

37

M. D. Ray

Mesothelioma is a neoplasm of serosa lined organs, including pleura, peritoneum, pericardium, and tunica vaginalis of testis [1]. The most common site is visceral pleura, followed by peritoneum. The typical presentation of malignant peritoneal mesothelioma (MPM) is a diffuse and extensive form of serosal spread in the abdomen with rare extra-abdominal metastasis, affecting pleura or lymph nodes. Mesothelioma is associated with industrial pollutants and mineral exposure, most commonly to asbestos. The incidence of mesothelioma has reached its peak in several countries given the marked decline in harmful asbestos for several decades, but still, in countries like India, Russia, China, and Brazil, the peak of incidence is yet to come [2]. Other risk factors include prior radiation therapy, simian virus 40 (SV 40), pancreatitis, and exposure to organic chemicals and other mineral fibers [3].

MPM presents with vague, nonspecific abdominal symptoms. So, it is difficult to diagnose early. The most common initial complaint is abdominal distension (30–80%). Abdominal pain is the second most common symptom, which is usually diffuse and nonspecific. The patients may also present with early satiety, weight loss, nausea, new-onset hernia, etc [4].

In a patient presenting with weight loss, abdominal distension, and sarcopenia, malignant ascites or peritoneal malignancy is suspected, and a detailed workup is needed [5].

There is no diagnostic imaging modality of choice for MPM. On computed tomography (CT), MPM is seen as an irregular enhancing heterogeneous soft tissue mass with irregular margins. MPM usually appears as proliferative and pushing rather than infiltrating lesion. The absence of primary tumor site identification with lymph nodal involvement helps differentiate MPM from other intra-abdominal malignancies. In newly diagnosed patients, ascites is found in 60–100% of cohorts. Other findings may be an omental mass, mesenteric nodules, peritoneal thickening, diaphragmatic deposits, scalloping of viscera like the liver, spleen, etc. None of the tumor markers are specific to diagnose MPM, but CA-125 and mesothelin can be used during surveillance and follow-up [6].

The definitive diagnosis of MPM is made by pathologic evaluation. Ascitic cytology maybe sometimes inconclusive due to a smaller number of malignant cells in ascites. Due to the variable expression of specific tumor markers, the diagnostic accuracy increases with solid tumor biopsy specimens. Such samples are obtained by CT/ultrasonography or diagnostic laparoscopy guided biopsy. In the case of pleural effusion, the thoracic spread is evaluated with thoracoscopy.

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Pleural effusion fluid cytologic analysis may be used as an adjunct.

According to WHO, subtypes of MPM include epitheloid, sarcomatoid, biphasic/mixed histology. The commonest is the epithelioid subtype and carries the best prognosis among all other histological variants. Others have a relatively poor prognosis. For final diagnosis, most of the time, immunohistochemistry is required with a panel of markers like EMA (epithelial membrane antigen), calretinin, CK 5/6 (cytokeratin 5/6), WT-1, mesothelin [7]. The current recommendation suggests using two mesothelioma markers and two carcinoma immunostains (Carcinoma embryonic antigen, Ber-EP4, LeuM1, Bg8, TTF-1, B72.3) for the diagnosis [8, 9].

MPM has limited hemo-lymphatogenous spread potential and remains confined to the peritoneal cavity in most cases. Nodal involvement is rare. Even the suspicious appearing nodes during surgery are pathologically negative. Twenty to twenty-eight percent of patients undergoing cytoreductive surgery have lymph nodal metastasis. TNM system was proposed in 2011 based on the peritoneal spread (T), Nodal spread (N), distant metastasis (M). T stages of 1,2,3,4 correspond to PCI scores of 1–10, 11–20, 21–30, and 31–39. Stage I disease includes T1N0M0, stage II includes T2-3N0M0, and stage III includes T4N0M0 with any T/N with distant metastasis (M1) disease. The corresponding 5-year survival for stage I, II, III, is 87%, 53%, and 29% [10].

Given the rare incidence of MPM, there is a lack of high-quality RCT data guiding the management strategies. Based on most of the retrospective data, there are established consensus regarding cytoreductive surgery and intraperitoneal chemotherapy as standard of care [11]. As peri-operative intraperitoneal chemotherapy, most institutes use hyperthermic intraperitoneal chemotherapy (HIPEC). A meta-analysis of 20 studies that included 1047 MPM patients, treated with CRS-HIPEC showed that among 67% of patients achieved a complete or near-complete cytoreduction before HIPEC, 5 year survival was 42%. In the experienced institutions, operative mortality ranges from 0 to 8%, and morbidity, including severe life-threatening complications, consists of 10–45%. Median overall survival (OS) without defined treatment has been observed up to 5–12 months from diagnosis. With CRS-HIPEC, median survival has improved significantly up to 38–92 months. Even in recurrent scenarios, a median OS of 54 months could be achieved with CRS-HIPEC [12].

But, given all said and done, not all patients are appropriate candidates for CRS-HIPEC. Alternatively, systemic chemotherapy with pemetrexed with/without cisplatin has shown a median survival of 13.1 months and 8.7 months. Replacing cisplatin with carboplatin has demonstrated similar efficacy.

No TKI has shown many promising results in improving progression-free survival (PFS)/OS in MPM. Tremelimumab, a monoclonal antibody, has shown some promise as second-line therapy after treatment failure with traditional chemotherapy with a median PFS of 6 months.

So, till now, histologic subtype, grade, peritoneal carcinomatous index (PCI), completeness of cytoreduction (CC) score, lymph node metastasis, and HIPEC with cisplatin are among the identified predictive factors for overall survival in patients with MPM [13]. In one study, the median OS was 6 months in patients with lymph node metastasis compared to 59 months in node-negative patients. Cisplatin gives better 1-, 2-, 3-years survival compared to Mitomycin C. Median OS was 40.8 months in the Cisplatin arm and 10.8 months in the Mitomycin C arm.

37.1 Conclusion

MPM is a rare disease of serosa lined organs. With the evolution of treatment options, CRS-HIPEC evolved as first-line therapy in select cases. While systemic chemotherapy is useful in a few cases, further research is needed to understand the molecular pathways and discover therapeutic targets and agents.

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The Role of CRS and HIPEC in Ovarian Cancer

38

M. D. Ray

The incidence of ovarian cancer is increasing in the Indian population and is approaching the incidence of Ca Cervix. Presently greater than 80% of patients present with advanced stages (Stage III and IV), i.e. with the peritoneal carcinomatosis and distant metastasis, respectively.

To date, the contemporary standard treatment of choice is optimal cytoreduction, even in stage IIIc onwards if feasible, followed by systemic chemotherapy. Despite all efforts, more than 75% of patients have a recurrence and thereby having poor long-term outcomes. The median survival of the cohort is 36–39 months. The theory behind the recurrence is the development of a clone of resistant malignant cells over time. However, most of the epithelial ovarian cancer is chemosensitive.

The basic treatment with optimal CRS (cytoreduction surgery) and HIPEC (Hyperthermic Intraperitoneal Chemotherapy) has been developed with time, which sounds scientific and logical. As the disease burden of ovarian carcinoma is usually confined to the peritoneal cavity [1], the recurrence even does not cross the boundary usually. It spreads beyond in only 3–5% cases. Therefore, after complete cytoreduction with diseased peritonectomy and visceral resection, HIPEC may destroy all the microscopic disease and thereby may decrease the chance of relapse [2]. This combined treatment modality may provide long-term recurrence-free survival and overall survival with acceptable morbidity [3].

So, CRS and HIPEC may be used as (1) first-line therapy (primary CRS-HIPEC), (2) interval CRS-HIPEC, and (3) secondary CRS-HIPEC [4].

Even it may be applicable in palliative settings to reduce symptoms due to intractable ascites or due to high disease burden.

This chapter will review the role of CRS and HIPEC in ovarian cancer in the light of current literature and evidence.

38.1 What Is Optimal Cytoreduction in Stage III and IV Ovarian Cancer

The optimal cytoreduction in ovarian carcinoma includes the following steps: (1) Ascitic fluid/peritoneal wash for cytology, (2) Hysterectomy with bilateral Salpingo oophorectomy along with the adnexal mass excision, (3) Bilateral pelvic lymphadenectomy, (4) Para-aortic lymphadenectomy, (5) Total greater omentectomy, (6) Lesser omentectomy with the removal of omental bursa, (7) Disease-limited peritonectomy, i.e. pelvic, subdiaphragmatic, parietal, or total peritonectomy, (8) Resection of the small bowel (Figs. 38.1 and 38.2), (9) Visceral resection (if involved) including liver parenchyma (Fig. 38.3) and splenectomy (Fig. 38.4). The biopsy from fol-

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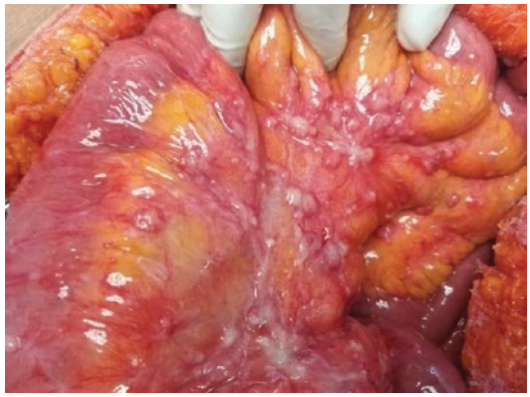

Fig. 38.1 Mesenteric deposits in Ovarian Carcinomatosis

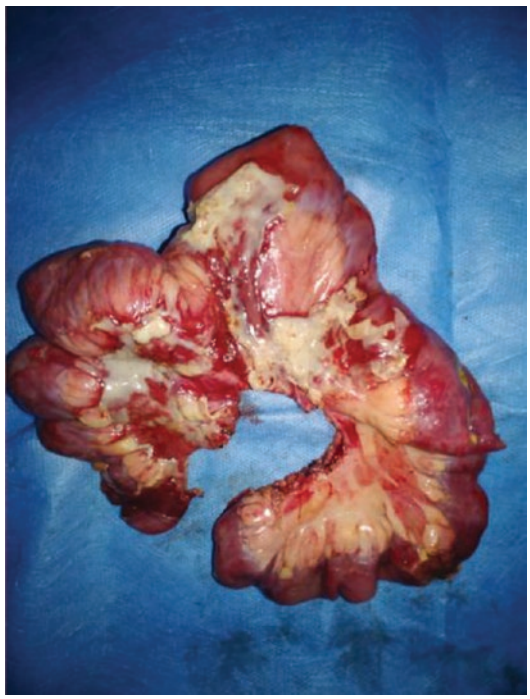

Fig. 38.2 Resected diseased bowel loop

lowing regions should be taken in absence of gross disease: both sides of pelvic peritoneum, urinary bladder peritoneum, pouch of Douglas, bilateral parietal peritoneum, bilateral subdiaphragmatic peritoneum, mesenteric peritoneum, suspected bowel serosal deposits, or any site of adhesion, etc. (Table 38.1)

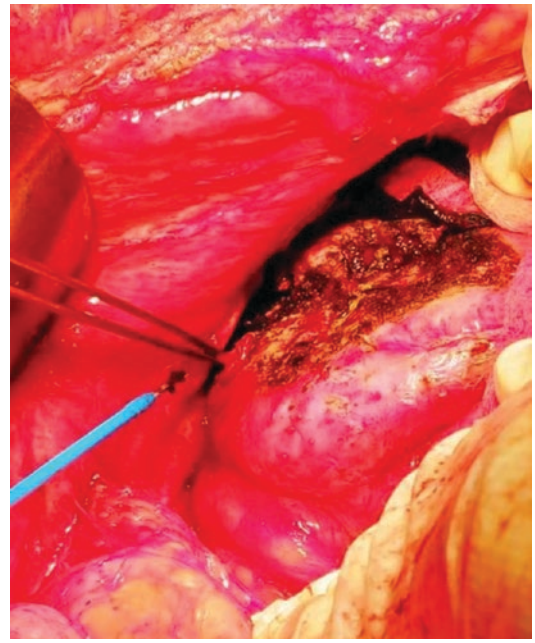

Fig. 38.3 Partial resection of involved liver

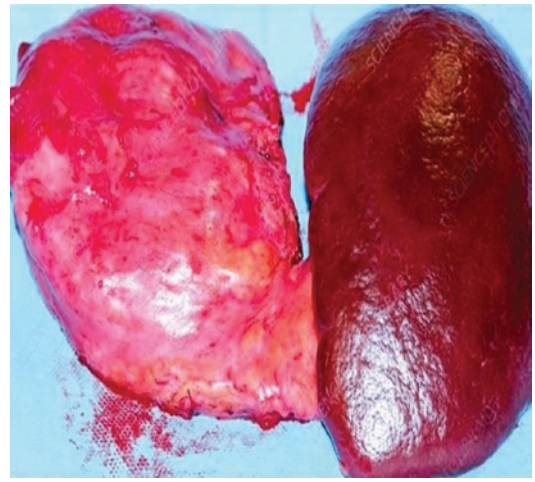

Fig. 38.4 Removal of spleen with the disease at hilum

Sometime distal gastrectomy, right hemicolectomy, and/or anterior resection are also performed as pyloric antrum, ileocecal junction, and rectosigmoid junctions are involved by the disease because of being relatively immobile part of the gut [5].

Table 38.1 The Chart of Peritonectomy procedure

	Parietal	Visceral
Right upper quadrant	Right hemidiaphragm, Morrison's pouch	Glisson's capsule, cholecystectomy, ligamentum teres, pont hepatique
Left upper quadrant	Left hemidiaphragm	Splenectomy
Central quadrant	Greater omentum, lesser omentum, lesser sac peritonectomy	
Bowel	Mesentery	Stomach, small and large bowel resection
Pelvis	Bladder, pouch of Douglas, sidewall peritoneum	Hysterectomy, bilateral Salpingo oophorectomy, anterior resection (if required)
Miscellaneous	Umbilicus, paracolic gutters	

38.2 The Rationale for CRS in Ovarian Carcinoma

The earliest evidence from a review of 112 patients by Griffiths et al. supports the benefit of cytoreduction surgery for ovarian cancer [6]. In this study, the authors showed that survival time was inversely proportional to residual lesions size under 1.6 cm. Cytoreductive surgery improves survival for lesion smaller than 1.6 cm.

A subgroup of Gynecologic Oncology Group (GOG) by Hoskins et al. showed optimal cytoreduction with <1 cm remnant lesion reflected longer survival than those who had residual disease >1 cm among 294 patients. This study of GOG recommends that the residual tumor implants size should be <1 cm in optimal debulking [7].

Presently, optimal cytoreduction denotes no macroscopic residual disease after cytoreduction.

A meta-analysis of 53 studies of 6885 patients by Bristow et al. concluded that optimal CRS followed by platinum-based chemotherapy showed an independent improved prognostic variable for survival ($P < 0.001$) [8].

So, the goal of CRS should be no visible or palpable tumor left behind even after doing diaphragmatic resection, splenectomy.

The spread of the disease in the upper abdomen suggests aggressive tumor biology. We know in cancer that "Biology" is the King. "Selection of case" is queen and the "techniques of the surgery" are prince and princess.

38.3 Primary versus Interval CRS

Primary CRS is the gold standard in ovarian carcinoma even in stage IIIc onwards to date because on the passage of time resistant clone develops and which is the culprit for relapse even after systemic chemotherapy!

But it is also the fact that in approximately 30% of patients, primary CRS may not be optimal in stage III and above disease. Also, there are no valid criteria for neoadjuvant chemotherapy. It is also noted that in 30% of patients, in whom upfront CRS is not possible, laparotomy becomes futile.

So, in which cases one should think about NACT? As per our institutional protocol, NACT is offered in the following clinical scenarios. It includes Leuven's selection criteria too [9].

1. Patient age > 70 years.
2. ECOG >2.
3. Large mass (>3 cm) involving porta hepatis.
4. Large mass (>3 cm) at the root of the mesentery.
5. Involvement of liver or splenic parenchyma.
6. Upper abdominal extensive disease burden with gross ascites.
7. Two or more organs resection and/or two or more resection anastomosis of bowels.
8. Studded mesentery.
9. Extensive bowel serosal deposits or bowel wall infiltration.
10. Bulky nodal disease in pelvis and retroperitoneum. Figures 38.5 and 38.6 depict the

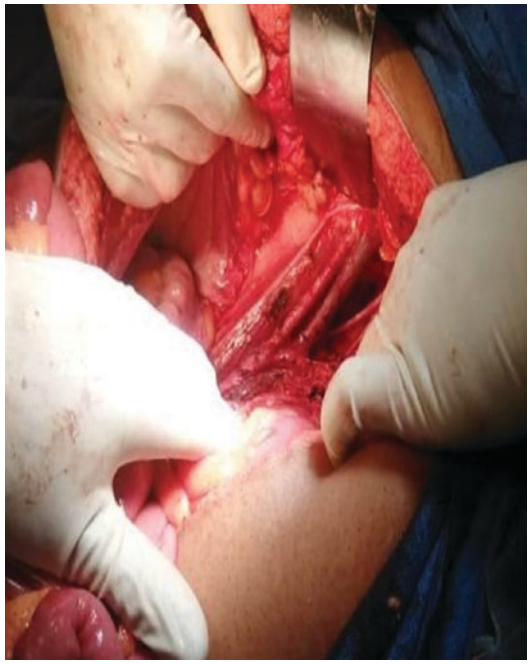

Fig. 38.5 Pelvic nodes dissection

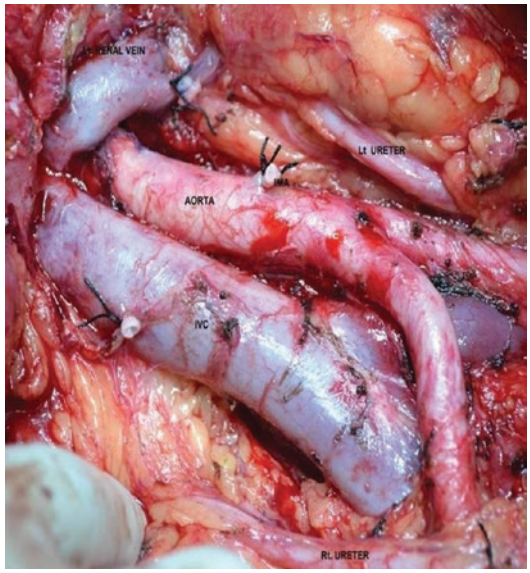

Fig. 38.6 Retroperitoneal lymph nodes dissection

intra-operative images of pelvic and retroperitoneal node dissection, respectively.

If we review some literature we can see.

Based on the retrospective data, previously it was believed that primary surgery was the treatment of choice. Data from Japan (Seiya Sato et al) showed that a single attempt of debulking surgery does not make significant changes in survival, in a case of newly diagnosed advanced ovarian cancer [10]. Although primary surgery can be considered in the case of early-stage cancer with minimal disease. Another treatment option is neoadjuvant chemotherapy (NACT) followed by interval debulking surgery. This treatment protocol is suitable for unresectable disease and medically unfit patients. Recent evidence suggests that NACT is superior to primary debulking surgery.

Nishicho et al conducted a noninferiority trial comparing NACT followed by interval debulking surgery with primary debulking surgery [11]. According to them, NACT is not a superior treatment option. Potential side effects of chemotherapy and the development of resistance are the major issues related to NACT. The precise role of NACT in epithelial ovarian cancer is yet to be established. A multicenter randomized clinical trial is required to establish the role of NACT in epithelial ovarian cancer. Other treatment options are immunotherapy, and molecular targeted therapy, although the role of this treatment modality still to be established.

If surgery is at all possible, post-surgical issues like morbidity, hospital stay, quality of life are very important aspects. On the other hand, NACT may down-stage the disease, and interval cytoreduction may be optimal but the question of recurrence persists yet. As per Bristow et al. in 2006, the chance of development of chemoresistance of cancers increases with the passage of chemotherapy. Nevertheless, even after debulking the recurrence risk is high! So, what would be the solution? It's like a carpenter saw, which cuts both the way. If we look back at our institution (All India Institute of Medical Sciences, New Delhi, India) data, PDS and NACT-IDS were feasible in 40–45% and >80% patients, respectively (significant difference). But the recurrence rate was comparable in both groups. Overall survival is not different between the two groups. Completeness of the cytoreduction of ovarian tumor is considered the most important prognostic factor. As most of the patients of Ca ovary present in advanced disease, hence performing CRS may be difficult at times.

38.4 Overall Completeness and Applicability of Evidence

In a noninferiority trial by Nishicho et al, only stage IIIc and stage IV patients were enrolled, so the evidence of this study is not widely applicable. Most of the patients had extensive disease. Sixty-one percent of the patients had a metastatic lesion >10 cm, and 189 patients had an extrapelvic tumor <5 cm in diameter. In the EORTC 55971 trial, overall survival was significantly improved with primary debulking surgery (PDS) in comparison to NACT followed by interval debulking surgery (IDS). In stage IV disease longer survival duration was noticed with NACT followed by IDS than PDS alone. Although in some centers PDS is the standard treatment protocol for stage III and IV ovarian cancer, and NACT is an alternative treatment option for bulky stage III/IV disease. The advantage of NACT over PDS is that NACT increases the rate of completeness of cytoreduction surgery, but fails to improve the overall survival. Which patients are likely to be benefited from NACT is still not defined, and further studies are required for validation. Patients may be selected for NACT based on Leuven's selection criteria (Vergote et al.), [9] although this selection criterion needs further validation.

38.5 CRS for Recurrent Ovarian Cancer

Surprisingly more than 75% of ovarian carcinoma cases recur. However, most of these cases are platinum-sensitive disease. In recurrent ovarian cancer, many studies had evaluated the role of CRS. A study by Munkarah et al demonstrated survival of 44–60 months who had undergone CRS and had no residual disease, whereas survival of 35 months noticed for those patients, who received chemotherapy alone [12].

A meta-analysis by Bristow et al. [8] found a statistically significant recurrence-free survival in patients with complete CRS ($p = 0.019$) [13]. Patient selection has the utmost importance, as the recurrent ovarian cancer is a heterogeneous disease. Presence of symptomatic ascites, peritoneal disease, early relapse before 6 months, and patients with poor performance status are least likely to be benefited from CRS. In a retrospective study (AGO desktop study), 267 patients were recruited with recurrent ovarian cancer. All patients underwent CRS. This study revealed that the completeness of cytoreduction is the only predictive factor for prolonging survival.

The Role of HIPEC in Ovarian Cancer If we look back the history of using HIPEC at various time points, we can see the evolution. In our Institution Prof N K Shukla and Prof SVS Deo used to put hot saline and monitoring the abdominal temperature by temperature probe along with covering the opened abdomen in different ways. I mean to say pioneer of this technique always proved "make the most whatever you have"!!

Mulier et al. established the fact that HIPEC can be used along with upfront CRS or along with interval cytoreduction. HIPEC can be used with consolidation CRS in patients with complete response after NACT. It is broadly used along with secondary cytoreduction (in recurrent Ca Ovary).

A meta-analysis suggested that HIPEC for primary and recurrent ovarian cancer showed significant survival benefit.

Study conducted by W J Van Driel et al. [10] in stage III epithelial ovarian cancer showed that interval CRS and HIPEC increases overall survival and recurrence-free survival compared to surgery alone, with minimal side effects (OV HIPEC trial).

38.6 How Does HIPEC Act? Pharmacokinetic and Molecular Pathway

Heat increases chemotherapy drug penetration into tissue up to 5–6 mm. Heat itself has antitumor effects and it increases the cytotoxicity of chemotherapeutic agents. Intraoperatively heated drugs (41–42 °C) were distributed equally in the abdominal cavity. Owing to the plasma peritoneal barrier, there is less systemic absorption of

drugs and thereby it causes less systemic adverse effects like less nephrotoxicity, less nausea, vomiting, etc. Hyperthermia increases platinum sensitivity by reducing the mechanism of drug resistance in both sensitive and resistant cell lines. Heat increases the intracellular accumulation of cisplatin and increase cisplatin and DNA adduct formation in tissues up to 3–5 mm depth. The time elapses during HIPEC (30–90 min) allow removal of small cancer nodules from surfaces including bowel serosa and mesentery up to 2.5 mm (CC_1).

Morbidity and mortality associated with HIPEC were elaborated elsewhere.

The major limitation of HIPEC procedure lies in its high morbidity, mortality profile, and long learning curve.

Reported morbidity and mortality in a high-volume center are 6–48% and 0–10%, respectively.

HIPEC methodology and different regimens have been discussed in different chapters of this handbook. In short, the most commonly used drugs are Cisplatin, Oxaliplatin, Mitomycin C, and Doxorubicin.

For beginners, Cisplatin is a drug of choice with a dosage of 70 mg/m^2 or 40–55 mg/liter of normal saline perfusate for 1 h at 41–43 °C. Cisplatin in HIPEC is active in both platinum-sensitive and resistant cell lines.

38.7 Conclusions

Though there are many criticisms for HIPEC in ovarian carcinoma, still there is a strong rationale for using CRS-HIPEC in upfront, interval, consolidation, or secondary settings. HIPEC may not cure the disease completely but it increases recurrence-free survival and overall survival in a selected group of patients. HIPEC in a high-volume center does not have increased significant morbidity and mortality as compared to CRS alone. Peritoneal carcinomatosis index (PCI), age, grade of tumor, and aggressive tumor biology, etc., are the prognostic factors. The role of HIPEC should be evaluated with large-volume, multicentric randomized control trials (RCT). Every well-equipped center should start the HIPEC modality always as a research protocol basis. And lastly, the inference is "Patients selection is the queen behind the success of the King (Surgeon) without any doubt".

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39 CRS and HIPEC for Peritoneal Metastasis from Colorectal Cancer

M. D. Ray

39.1 Introduction

The management of colorectal cancer peritoneal metastases is evolving. Traditionally, patients with limited liver or lung metastases were only considered as candidates for metastasectomy. However, patients with metastasis limited to the peritoneum were found to have improved clinical outcomes with metastasectomy [1]. Although systemic therapy significantly prolongs survival in patients with metastatic colorectal cancer, patients with PM demonstrated inferior outcomes. In the last 20 years, the recent advances in the form of CRS followed by HIPEC significantly prolonged survival in patients with colorectal peritoneal metastases with even cure reported in a selected group of patients [2].

39.2 Clinical Presentation and Diagnosis

CRC ranks third in terms of incidence worldwide. Approximately 5–10% of CRC patients present with peritoneal metastases (PM) during treatment for primary cancer, whereas the incidence of PM is about 15–30% in patients with recurrent disease, which generally leads to death within weeks or months. Apart from having a poor prognosis, the quality of life of these patients with PM is significantly impaired due to ascites and small bowel obstruction [2, 3].

In the early phase of PM, patients are usually asymptomatic. The small volume PM is difficult to diagnose; therefore, regular follow-up with clinical examination and imaging is necessary. In high-risk cases, the use of contrast enhanced computed tomography (CECT) of abdomen or magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT) is warranted to rule out PM. Diagnostic laparoscopy may also be required in certain patients. The selection of these investigations should be decided on case-to-case basis where there is a high index of suspicion for PM [1, 2].

39.3 Treatment Options for CRC Peritoneal Metastasis

Systemic chemotherapy is the standard treatment for colorectal PM. Over the last 20 years, the combination of CRS and HIPEC or early postoperative chemotherapy (EPIC) has significantly improved the prognosis of patients with colorectal PM. However, this treatment is suitable for only selected group of patients with good performance status, limited peritoneal disease, and in the absence of extraperitoneal disease [2].

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39.3.1 Systemic Chemotherapy

Systemic therapy consisting of combination of agents along with targeted therapy has been the mainstay of the treatment strategy for colorectal PM. Survival with traditional chemotherapeutic agents 5FU and leucovorin rarely exceeds more than 12 months. The chemotherapeutic agents including oxaliplatin, irinotecan, cetuximab, and biologic agents like bevacizumab and panitumumab have significantly improved survival in patients with metastatic colorectal cancer. Various studies have shown better survival from 19 months to 22 months with these new novel agents in metastatic CRC. However, the patient population in these studies included those with hepatic or pulmonary metastasis which is a favourable group as compared to PM [4, 5].

The subset analysis from CAIRO and CARIO 2 study showed reduced efficacy of currently used standard chemotherapy and biologic agents in patients with colorectal PM. This is because PM behave differently to systemic chemotherapy as compared to metastases elsewhere [4, 5].

39.3.2 Role of CRS and HIPEC

The majority of the evidence for CRS and HIPEC in colorectal PM is from retrospective studies from a single institution or from multicentric prospective studies. The median survival in these studies varies from 12 to 62 months which are very encouraging for future research in this field [2, 6].

The main aim of surgery is to remove all the macroscopically visible disease by CRS followed by treating residual and/or microscopic invisible disease by HIPEC (Figs. 39.1 and 39.2). It is essential that all tumour deposits (> 2mm) should be removed becauae of limited thickness (<3mm) penetration by chemotherapeutic drugs in tumour tissue. HIPEC should be performed immediately after surgery in order to prevent peritoneal adhesions leading to the formation of tumour sanctuary by trapping the tumour cells [7]. Figure 39.1 shows low anterior resection specimen, which has been removed during CRS in our institution. Diversion loop ileostomy was performed

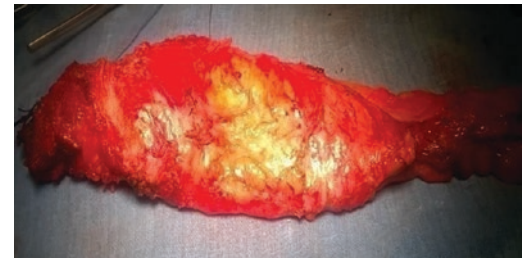

Fig. 39.1 Total mesorectal excision specimen B

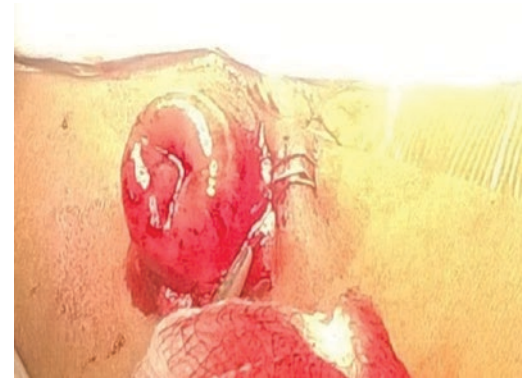

Fig. 39.2 Loop diverting ileostomy

(Fig. 39.2). HIPEC tubing was placed after optimal CRS (Fig. 39.3). The benefit of the CRS-HIPEC over the systemic chemotherapy (5-FU or leucovorin-based) was confirmed in a phase 3 randomized study. Veerwal et al. randomized a total of 105 patients in 2 arms. In one arm, patients were treated with standard systemic chemotherapy (5-FU and leucovorin-based) with or without palliative surgery. In the second arm, aggressive CRS with HIPEC was done followed by the systemic chemotherapy regimen. After a median follow-up period of 21.6 months, there was a significantly improved median survival (p-value = 0.032) in the experimental arm (22.3 months) as compared to the standard therapy arm (12.6 months). The median survival was also found to be significantly better (p-value <0.0001) in patients with macroscopically complete CRS (R1) as compared to those with limited or extensive residual disease (R-2a, R-2b). This survival advantage was confirmed after longer follow-up of 8 years. The authors concluded that cytoreduction surgery followed by HIPEC significantly improves survival in patients with

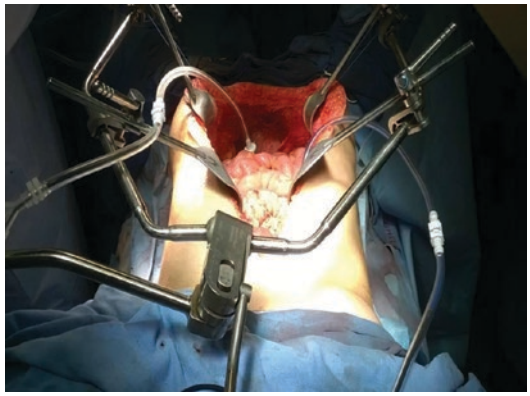

Fig. 39.3 HIPEC tubing placement after retracting the parietal abdominal wall

colorectal PM. However, patients having six or more regions of PM and grossly incomplete CRS had a poor prognosis [6, 8]. The major criticism of this trial was that modern chemotherapeutic agents were not used. Hence, it failed to conclude if the achieved survival benefit was from CRS and HIPEC both or CRS alone.

It is impossible to separate the effects of CRS and HIPEC in the currently available literature. Recently, Desoineux et al. reported that although the surgery is highly efficacious in patients with colorectal PM, the benefit of HIPEC is questionable [9]. Therefore, the French study group had randomized the patients in Prodige 7 trial and we are eagerly waiting for its results [10]. The abstract has been published in "Journal of Clinical Oncology" on seventh June 2018. Prodige 7 (NCT 00769405) is a prospective randomized multicentre phase III trial, in which patients with histologically proven CRC and isolated peritoneal dissemination with peritoneal carcinomatosis index ≤25 were included. The study aims to evaluate the magnitude of benefit conferred by HIPEC after a complete CRS. After a complete CRS, the patients were randomized intraoperatively to receive HIPEC or not [10]. The overall survival (OS) was the primary endpoint, whereas relapse-free survival (RFS) and toxicity were considered for secondary endpoints. In this study, François Quenet et al. concluded that CRS alone showed satisfactory survival results in PC from colorectal cancer. There was no added benefit of HIPEC with oxaliplatin on OS.

39.4 Concerns with CRS and HIPEC in the Modern Era

Due to lack of standardization in the methodology of HIPEC, type and doses of chemotherapeutic agents used, and good results observed with EPIC, there is still a debate for and against the use of HIPEC worldwide [1, 2]. There are two main methodologies currently used worldwide for HIPEC: mitomycin-C for 60–90 min at 41 °C with the closed-abdomen technique and the other with oxaliplatin for 30 min, at a homogeneous temperature of 43 °C with an open-abdomen technique [11].

Most of the centres have recently switched agents for HIPEC in CRC-PM from mitomycin to oxaliplatin. Oxaliplatin and mitomycin-C are both alkylating agents, interfering with DNA-synthesis and DNA-metabolism. There is limited systemic absorption of both agents owing to large molecular weight. The toxicity profile and the tissue penetration abilities are also comparable. There is a paucity of data from randomized studies comparing oxaliplatin and mitomycin-C but the available literature suggests equal antitumour efficacy. The advantages with oxaliplatin over mitomycin-C include the absence neutropenia and the need for shorter perfusion time (30 min) [3].

The use of bidirectional intra-operative chemotherapy which includes intravenous infusion of 5-FU and leucovorin followed by intraperitoneal oxaliplatin is common for PM from CRC [12].

Currently, there is no evidence to support the prophylactic resection of omentum or ovaries which are considered at risk for harbouring the tumour cells. Theoretically, people who use HIPEC after CRS assume that HIPEC will take care of micrometastasis at these potential sites [3].

CRS-HIPEC is considered as a procedure having high morbidity and mortality. Good patient selection, meticulous surgical technique, and optimum perioperative management have significantly decreased the morbidity and mortality. Numerous studies report morbidity rates of 23–45% and mortality rates of 0–12% [13].

Patient selection is a very important aspect for the planning management of these patients. Eligibility criteria for CRS and HIPEC are Eastern Cooperative Oncology Group (ECOG) performance status of less than 2, age below 70 years, no extra-abdominal disease, controlled medical comorbidities, non-obstructive bowel disease with no bulky unresectable clinical or radiological PM. The absolute contraindications include poor general condition, presence of extraperitoneal metastases (except up to 3 easily resectable liver metastasis), and diffuse PM. Relative contraindications include subacute obstruction due to bowel involvement, peritoneal disease progression after systemic chemotherapy, and the presence of >3 resectable or any unresectable liver metastases. These metastatic lesions are not absolute contraindications, if they are fewer than 4 and if they are easily resectable [13, 14].

39.5 Conclusions

The patients with colorectal PM have poor prognosis despite recent advances in systemic therapy. Optimal CRS and HIPEC significantly improve survival in patients with PCI < 20 and should be considered as the standard of care. Further large scale randomized studies are warranted to clearly establish the role of CRS and HIPEC in colorectal PM.

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The Role of HIPEC in Gastric Cancer

40

M. D. Ray

40.1 The Burden and Presentation

Gastric adenocarcinoma ranks fourth in terms of incidence and second in terms of mortality worldwide according to GLOBOCAN 2012 data. However, it accounts for the third position in incidence in the Indian subcontinent. In some of the Asian countries where national screening programs are implemented (South Korea and Japan), majority of gastric cancers are detected in the early stages. However, in countries without any screening programs, patients present with advanced-stage disease. Patient with early-stage gastric cancer gets cured with surgery alone. In locally advanced disease, we need to give chemotherapy (neoadjuvant or adjuvant) or chemoradiation in addition to surgery for achieving a cure. Despite multimodality management for gastric adenocarcinoma, a high percentage of patients experience recurrence with a 5-year overall survival rate of 24.5% and 40–60% in Europe [1] and in Asia [2], respectively.

The peritoneal dissemination caused by seeding of carcinomatous cells from primary tumor constitutes the most important cause of treatment failure and is the commonest root of spread. The presence of macroscopic peritoneal carcinomatosis confers a dismal prognosis with only 3–6 months of median overall survival [3].

40.2 The Pattern of Recurrence

Different studies have been performed to describe the pattern of metastasis in gastric cancer in surgically resectable disease after curative resection. However, the results are not consistent due to heterogeneity in the studies. However, a study of >1100 patients having metastatic or recurrent gastric cancer found peritoneal and liver metastases in 46% and 30% of the patients, respectively [4]. Various other studies reported a recurrence in the range of 30–62% of patients with peritoneal recurrence alone or in combination with visceral metastasis. Peritoneal involvement confers a poor prognosis. Jo et al. study observed that stage IV patients having peritoneal metastasis had poorer survival than the early disease (7.5 months versus 14 months) and a higher mortality rate (hazard ratio = 2.026, p-value = 0.004) [5].

40.3 Selection of Patients for Cytoreduction and HIPEC

The advanced disease at risk can be divided into four groups (Table 40.1).

The first group are those who present with parenchymal metastasis. They are usually treated

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Table 40.1 Distribution of the advanced gastric cancer

Group	Features	Management
Group 1	Parenchymal metastasis or non-regional nodal metastasis	Chemotherapy, best supportive care, palliative resection, rarely curative resection
Group 2	Surface deposits on bowel, mesentery, and omentum without parenchymal metastasis	Primary surgery ± neo/adjuvant therapy ± HIPEC or palliative therapy
Group 3	Cytologically positive malignant cells in ascites or peritoneal lavage	Primary surgery ± NEO/adjuvant therapy ± HIPEC
Group 4	T3/T4 primary lesion, without above features	Primary surgery ± Neo/adjuvant therapy ± HIPEC

with palliative intent except for few exceptions. The second group are those with surface deposits on bowel, mesentery, and omentum without parenchymal metastasis. They may be diagnosed with pre-operative imaging when they are planned for chemotherapy followed by surgical reassessment if operable. They may also be detected on surgical exploration, due to poor sensitivity of pre-operative imaging in detecting small peritoneal deposits. The third group are those with only cytologically positive malignant cells in ascites or peritoneal lavage, without any features of the first or second group. The fourth group are associated with T3 or T4 primary gastric cancers, who have a higher risk of peritoneal recurrence. The treatment of the second, third, and fourth groups has been tried with cytoreduction and hyperthermic chemotherapy in recent years with varying results.

40.4 The Strategies for Management of Peritoneal Disease

The patients with gastric cancer peritoneal metastases have a dismal prognosis as compared to those with systemic metastasis. The systemic chemotherapy improves median survival in systemic metastases by 7–10 months in contrast to only 3–4 months in peritoneal disease [6].

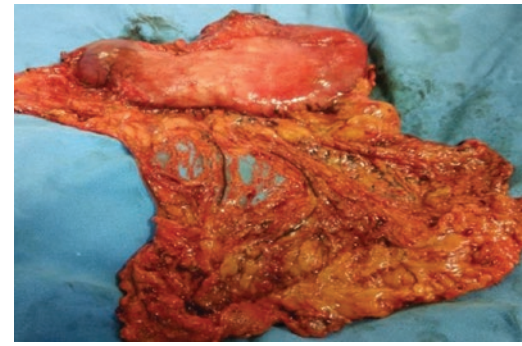

Fig. 40.1 Carcinoma stomach with omental metastasis (Peritoneal Carcinoma Index 6)

Similar to other disease sites, the primary requirement for proceeding to HIPEC is the ability to completely cytoreduce and thus patients with extensive inoperable peritoneal metastasis are not candidates. Besides, those located at unresectable sites of peritoneal metastasis, e.g. porta hepatis or extensive small bowel serosal deposits, root of mesentery are poor candidates for CRS and HIPEC (Fig. 40.1). Patients having hematogenous metastases along with peritoneal disease are less likely to be benefitted. Careful patient selection is key to good outcome. HIPEC may optimally be used during gastric resection with lymphadenectomy [7, 8].

40.5 Randomized Studies

Eleven randomized studies have been completed which included patients for prophylactic (with no peritoneal metastasis) HIPEC or therapeutic (with peritoneal metastasis) [9–19]. All studies in prophylactic or therapeutic settings have shown results of a variable degree of improvement in survival with HIPEC. Those with higher peritoneal carcinomatosis index (PCI) have a higher chance of early recurrences. A complete cytoreduction gives a better recurrence-free survival.

40.6 Meta-Analysis

A recent meta-analysis by Desiderio et al. of 11 RCTs and 21 non-randomized studies consisting of 2520 patients was analyzed. In patients with no peritoneal carcinomatosis (prophylactic group), the OS rates between the HIPEC and control groups favor the HIPEC group at 5 years (risk ratio [RR] = 0.82, *p*-value = 0.01). However, it was observed that there was no difference in the 3-year OS (RR = 0.99, $P = 0.85$) but a prolonged median survival of 4 months in favor of the HIPEC group was observed. HIPEC led to a higher complication rate for both groups of patients with (RR = 2.15, $P < 0.01$) or without (RR = 2.17, $P < 0.01$) peritoneal carcinomatosis. Anastomotic leak rates were similar between the two groups. This study concluded that there was a survival advantage in HIPEC arm, used as a prophylactic strategy, and suggested that patients having disease burden, limited to malignant ascites and regional nodes were more benefitted than the others. The completeness of cytoreduction has been proven to be a major prognostic factor for survival [20].

40.7 The Ongoing Trials

GASTRICHIP is a prospective, multicentric phase III randomized study aimed at evaluation of the effects of HIPEC with oxaliplatin on patients with T4a, N+, and M1 gastric cancer. The enrolled patients will be treated with perioperative systemic chemotherapy and curative radical gastrectomy. Per-operatively, after completion of the surgery, patients will undergo randomization. Endpoints in this ongoing study are overall survival, 3- and 5-year recurrence-free survival, and site of recurrence, morbidity, and quality of life. The number of patients to be randomized was calculated by statistical methods to be 306 [21].

The PERISCOPE II aims to compare the OS between patients with gastric cancer with limited peritoneal disease and/or tumor with positive peritoneal cytology treated with palliative systemic chemotherapy, and those patients treated with gastrectomy, CRS, and HIPEC after NACT. It will determine the safety, tolerability, and feasibility of gastrectomy combined with cytoreduction and HIPEC using oxaliplatin in combination with docetaxel after systemic chemotherapy. These data are a prerequisite for the safe conduct of future HIPEC studies in patients with gastric cancer [22].

40.8 Conclusions

Prophylactic HIPEC decreases peritoneal recurrence and improves survival. Those with gross peritoneal disease, a complete cytoreduction is essential before proceeding to HIPEC, and complete cytoreduction with HIPEC may improve overall survival with increased recurrence-free survival. There are no statistically significant increased incidence of surgical morbidities including anastomotic leaks following HIPEC. Also, it does not increase mortality significantly as well.

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Rule of Six for CRS and HIPEC and Institutional Experience

41

M. D. Ray

We, on the basis of our experience for the last 4 years, tried to develop a standard protocol as *'RULE OF SIX IN HIPEC'* for the better understanding and management of this challenging procedure. This rule may help for the better outcomes of HIPEC procedures, practised as six indications, six rationales, six criteria of patient selection, six contraindications, six advices before HIPEC, six steps of checking before CRS, six assessments for NACT, six steps of surgery, six mechanisms of action, six important complications, six advices in discharge, six important points to be clarified still [1].

1. *Diseases to be considered under PSM:* Worldwide six common indications for CRS and HIPEC. But in carcinoma appendix with pseudomyxoma peritonei and mesothelioma CRS and HIPEC have been the standard of care. These malignancies are enumerated as follows [1]:
   (a) Carcinoma appendix with pseudomyxoma peritonei
   (b) Mesothelioma
   (c) Colorectal cancer
   (d) Ovarian cancer:
      - Primary CRS + HIPEC
      - Interval/consolidation CRS + HIPEC
      - Secondary CRS + HIPEC
   (e) Gastric cancer with peritoneal dissemination only
   (f) Peritoneal sarcomatosis
2. *RATIONALE:* Six reasons are proposed in literature for CRS and HIPEC to be considered in a patient [2].
   (a) In vast majority of the cases the disease is confined to the peritoneal cavity for a long time.
   (b) Even in recurrent cases, disease remains confined to peritoneal cavity only.
   (c) Intraperitoneal administration of chemotherapy results in high peritoneal to plasma ratios for peak concentration of chemotherapeutic drugs.
   (d) The higher peritoneal concentration improves penetration of cytotoxic agent in tumour microenvironment.
   (e) Less than 2–3 mm or smaller tumour deposits have significantly higher chemotherapeutic drug exposure from IP administrations as compared to IV.
   (f) Avascular tumours are exposed to higher drug concentration with IP chemotherapy with less systemic toxicity.
3. *PATIENT SELECTION:* Six criteria of patients selections [3].

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(a) Good performance status ECOG1 and ECOG 2 with optimization.
(b) Mentally and physically fit for extensive surgery.
(c) Clinically, radiologically, and biochemically the disease is low burden and resectable.
(d) No haematogenous and extra-abdominal disseminated metastasis.
(e) Good renal function to clear the nephrotoxic chemotherapeutic drugs.
(f) Age < 65 years with PFT (FEV1 > 1–1.5lts), non-smoker with complete blood counts, kidney function tests and liver function tests within normal limit.

4. *CONTRAINDICATIONS:* The following are the six contraindications for CRS + HIPEC [4, 5].
   (a) Poor performance status, i.e. ECOG ≥3.
   (b) Patients is not willing for extensive surgery.
   (c) Signs and symptoms of active peritonitis and sepsis.
   (d) Clinically and radiologically high burden disease involving porta, root of mesentery, diffuse serosal deposits, disease burden not amenable for optimal cytoreduction.
   (e) Compromised liver, renal, and respiratory function.
   (f) Age > 70 years with cardiovascular compromise.
5. *PREOPRETATIVE THERAPY*: There are six indications for neoadjuvant chemotherapy (NACT) before CRS + HIPEC when [3].
   (a) Imaging suggestive of high tumour burden where upfront optimal CRS is not feasible.
   (b) Tumour ≥3 cm around porta hepatis or around root of mesentery.
   (c) Intrahepatic metastasis or extra-abdominal disseminated disease.
   (d) Where bowel resection is required more than 1.5 m due to extensive serosal or intraluminal involvement.
   (e) Possibility of ≥2 small bowel anastomosis after CRS.
   (f) Extensive Retroperitoneal Lymph Nodes [Included a few criteria of Leuven for NACT in Ca ovary].
6. *OPTIMIZATION:* Patients to be optimized preoperatively by six ways before CRS and HIPEC [6].
   (a) High protein diet
   (b) Maintenance of hygiene
   (c) Regular ½ hour to 1 hour mild to moderate physical exercise.
   (d) Incentive spirometry 200 times per day
   (e) Haematinics to optimize haemoglobin
   (f) Adequate hydration 2.5–3 litres of liquids inclusive of water per day to keep the renal function normal
7. *PREOPERATIVE ADVICE*: Six preoperative advices for the patients to be followed at home prior to surgery [5, 7].
   (a) Liquid diet 1 day prior to CRS and Nil Per Orally (NPO) since night before surgery.
   (b) Bowel preparation with PEGLAC if required with early morning bowel wash through ano-rectum.
   (c) Stop oral hypoglycaemic drugs 2 days prior and anticoagulant 4 days prior.
   (d) DVT prophylactic started 12 hours prior to surgery, i.e. LMWH and continue prophylactic dose 6 hours after surgery along with intermittent pneumatic compression.
   (e) Aprepitant (3 tabs pack antiemetic) 125 mg at evening before surgery and 80 mg early morning with sip of water and 80 mg day after surgery through nasogastric tube.
   (f) Essential drugs like Eltroxin, Antihypertensives to be taken in the early morning.
8. Advantages of HIPEC [2].
   (a) Single time application for locoregional control of microscope disease.
   (b) Drug delivery is under anaesthesia, thereby better compliance.
   (c) Superior distribution and better penetration of chemotherapeutic drugs.
   (d) Better tolerated by patients under GA.
   (e) Less systemic toxicity due to plasma peritoneal barrier.
   (f) Short Duration 30–90 Minutes Only

Six common drugs used in HIPEC [8].

Drug	Dose	Molecular Weight
1. Cisplatin	60–70 mg/m^2	300
2. Oxaliplatin	360–450 mg/m^2	397
3. Mitomycin-C	15–20 mg/m^2	334
4. Doxorubicin	15–20 mg/m^2	500
5. 5-FU	250–450 mg/m^2	130
6. Melphalan	50–70 Mg/m^2	35

(Paclitaxel: though ideal for PSM as MW-854 and AUC 1000 but it is heat liable and not effective with hyperthermia)

9. *INTRAOPERATIVE ASSESSMENT:* Six intra-op assessments of disease [1, 3].
   (a) See the overall disease burden at primary site.
   (b) See the involvement of bowel, bladder and its extension.
   (c) See root of mesentery and small bowel involvement.
   (d) Exclude the liver and spleen parenchymal involvement.
   (e) Subdiaphragmatic burden involvement of diaphragm.
   (f) Exclude involvement of porta hepatis and Superior Mesenteric vessels.
10. *TUMOUR IMPLANTATION MECHANISMS*: Six mechanisms [2, 5].
   (a) Free intraperitoneal tumour emboli as a result of full thickness invasion of bones wall by tumour cells.
   (b) Leakage of malignant cells from transected lymphatics channel.
   (c) Dissemination of cancer cells from surgical trauma as a result of dissection at narrow margin.
   (d) Blood clots which may remain at peritoneal cavity may contain viable malignant cells.
   (e) Fibrin entrapment of tumour emboli on traumatized peritoneal surface or subperitoneal soft tissue.
   (f) Tumour promotion of these entrapped cells through the growth factors involving wound healing.
11. *SURGICAL TECHNIQUE FOR PERITONECTOMY*: Six basic steps of peritonectomy [9].
   (a) Proper exposure of abdomen, parietal peritonectomy, keeping posterior rectus sheath intact.
   (b) Greater omentectomy and splenectomy if required.
   (c) Left upper quadrant peritonectomy, i.e. stripping of peritoneum from left hemidiaphragm.
   (d) Right upper quadrant peritonectomy, i.e. stripping of peritoneum from right hemidiaphragm and capsule of liver and subdiaphragmatic space.
   (e) Lesser omentectomy, removal of omental bursa with cholecystectomy.
   (f) Pelvic Peritonectomy the Peritoneum below the Pelvic Brim Including Pouch of Douglas and Bladder Peritoneum
   (g) Apart from this antrectomy, anterior resection or right limited hemicolectomy done as these sites (pyloric antrum, ileocecal junction, and rectosigmoid junction) are non-mobile and less peristaltic.
12. *Just before HIPEC:* Checklist [1].
   (a) Complete haemostasis—most important
   (b) Complete cytoreduction
   (c) Patients stability
   (d) Drug dose as per Body Surface Area or Normal Saline/Litres
   (e) Placement of inflow and outflow catheter and temperature probe. Inflow catheter should be away from anastomotic site/sites.
   (f) Drug to be delivered only when inflow and outflow temperature would be in between 41 and 43°C.
13. *MECHANISMS FOR HIPEC*: Six mechanisms of action of HIPEC [5].
   (a) Heat increases chemo drugs penetration into tissue up to 5–7 mm.
   (b) Heat itself has antitumour effects and it increases cytotoxicity of chemotherapeutic agents.
   (c) Intra-operatively drugs and heat (41–42°C) distributed manually to all surfaces in abdominal cavity.
   (d) Owing to plasma peritoneal barrier, less systemic absorption of drugs and thereby

less systemic adverse effect like less nephrotoxicity, less nausea, vomiting.
(e) Hyperthermia increases platinum sensitivity by reducing the mechanism of drug resistance.
(f) The time elapses during HIPEC (30–90 min) allows removal of small cancer nodules from surfaces including bowel serosa and mesentery.

14. *Effect of HIPEC on Immune Microenvironment*.
(a) *Surface molecular expression:* Heated tumour cells increase the surface expression of MHC class I, making the tumour cells more sensitive to lysis by CD8+ T (T cytotoxic) cells.
(b) *Expression of HSPs:* Heated tumour cells release heat shock proteins (HSPs) which are heterogeneous group of molecular chaperones with various functions. It activates natural killer (NK) cells and antigen presenting cells (APCs). HSPs contain potential tumour antigens, and APCs take up the HSP antigen complex and cross present the antigen to CD8+ T cells.
(c) *Exosome production:* Heated tumour cells release exosomes, containing potential antigens and antigen presenting cells (APC). They take up the antigen and cross present the antigen to CD8+ T cells.
(d) *Direct effect on immune cells:* Immune cells, such as NK cells, CD8+ T cells, and dendritic cells (DC), in the tumour also get activated by the hyperthermia.
(e) *Tumour vasculature:* Increases the permeability of tumour vasculature. Changed vasculature within the tumour may help immune cells mobile.
(f) *Immune-cell trafficking:* Improving immune-cell trafficking between the tumour and draining lymph nodes.

15. *MORBIDITY AND MORTALITY*: Six common morbidities [4].
(a) Paralytic ileus with nausea and vomiting—most common
(b) Lymphocele formation
(c) Anastomotic leak
(d) Surgical site infection with wound dehiscence
(e) Derangement of renal function and respiratory tract infections
(f) Enterocutaneous Fistula (Mortality worldwide 0–10%)

16. *Six Important Questions to be answered still* [5].
(a) Greater understanding of mechanism of hyperthermia and its interaction with CT agents at molecular level.
(b) In combination with surgery it remains a sensible theoretical option. It could be delivered without significant additional morbidity.
(c) Ideal agents: What all could be more beneficial?
(d) Ideal duration of perfusion and ideal temp of perfusion.
(e) Ideal methods open, close, semiclose which one?
(f) Unexpected Morbidity and Mortality to Be Clarified?

Institutional Experience

Introduction: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has become the treatment of choice for resectable peritoneal carcinomatosis (PC). Morbidity associated with the procedure in perioperative period affects the quality of life and also increased rates of complications. These question the cost-effectiveness of the procedure; therefore, selection of the patients and preoperative optimization are warranted to improve outcome. We analysed our cohort and wish to share the experiences.

Methods: Ninety-seven, CRS/HIPEC procedures, performed in patients of intraperitoneal visceral malignancies with peritoneal involvement during the period 2015–2017, were examined in prospective analysis. Type of primary cancer, ECOG status, peritoneal cancer index (PCI), completeness of cytoreduction (CC), duration of hospitalization, postoperative morbidity, mortality were reviewed. Morbidities were graded according to Clavien–Dindo classification.

Results: All of the ninety-seven patients (100%) underwent a secondary CRS/HIPEC. The median age was 57 years (range, 25–65) and included 30.00% males and 70.00% females (M:F 1:2.34). Majority (90.91%) were performance status ECOG 1 and the remaining were ECOG 2. Median PCI was 14 (8–25). Completeness of cytoreduction score of 0 and 1 (CC-0/1) was achieved in all patients, with CC -0 IN 90.09% and CC-1 in 9.91% cases. The mean operating time for CRS was 581 min (range, 172–874) and for HIPEC was 50.54 min (range, 60–90). Median intensive care unit (ICU) was 2 days (range, 1–8 days), and mean hospital stay was 7 days. Total four patients succumbed in the postoperative period. One patient died 8 hours postoperatively all of a sudden, most probably due to pulmonary embolism. One patient died on 6th post-operative day on the day of re-exploration because of intestinal obstruction and sepsis. One patient expired on 3rd post-operative day due to massive myocardial infarction and fourth one on 8 th post-operative day because of post-splenectomy bacterial peritonitis and sepsis. Overall 30-day morbidity after repeated CRS/HIPEC was 21% where 5.32% patients developed Clavien–Dindo major complication (IIIb and IV). Nausea and vomiting were the most common postoperative events in early postoperative period, followed by paralytic ileus in 9.09%, whereas deep venous thrombosis developed in 10.09%, and subacute intestinal obstruction in 5.45% cases in late (21–30 days) postoperative period. Most common cause of readmission was subacute intestinal obstruction (9.09%), which were managed conservatively. Median disease-free interval between first CRS/HIPEC and peritoneal recurrence was 19 months (range, 8–32). Median disease-free survival of 17 months (range, 5–25). After a median follow-up of 11 months (range, 2–25), all patients are alive with disease ($n = 7$) or disease free ($n = 48$) under chemotherapy. Two of our patients required repeated CRS+ HIPEC in follow-up period.

Conclusions: In experienced centres, CRS and HIPEC can be performed with acceptable morbidities and mortality. Perioperative and postoperative outcomes can further be improved by proper patient selection and quality care with team approach.

Keywords: Cytoreductive surgery, HIPEC, peritoneal involvement, PCI, Clavien–Dindo classification. Optimizing perioperative outcomes after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+ HIPEC) in a tertiary care centre.

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42 HIPEC, HITHOC, and Technique: How we Do it?

M. D. Ray

42.1 Introduction

Previously, peritoneal disease was considered terminal and systemic chemotherapy was offered for palliative intent while palliative surgery only had a role in symptomatic relief. With the advent of cytoreductive surgery (CRS) in the early 1990s, it is now the accepted treatment modality for a subset of patients with peritoneal carcinomatosis from pseudomyxoma peritonei, appendiceal adenocarcinoma, and mesothelioma and has also showed promising results in selected patients with ovarian, colorectal, and gastric cancer [1]. The purpose of CRS is to resect all macroscopic disease through peritonectomy and involved viscera followed by intraperitoneal chemotherapy by targeting residual microscopic disease through provision of a high intraperitoneal concentration with lower systemic toxicity [2]. If CRS is complete, the more provocative procedure hyperthermic intraperitoneal chemotherapy (HIPEC) is performed in the same setting [2, 3]. HIPEC improves both quality of life and survival [4]. These treatments are based on the concept that when disease is limited to the peritoneal cavity, it is still considered locoregional. The comprehensive CRS approach was described by Dr. Sugarbaker [3] in 2007. Evidence for hyperthermia is based on accelerated cell death at 41–43 °C in experimental settings [5]. The additive toxic effects of HIPEC have also been documented in the literature [6]. Interval CRS and HIPEC resulted in longer recurrence-free and overall survival among FIGO stage III epithelial ovarian cancer than surgery alone and did not result in excessive side effects [7]. It also offers a significant survival benefit to patients with recurrent epithelial ovarian cancer, especially in patients with complete CRS [8]. There is no randomized controlled study or feasibility study demonstrating the efficacy of hyperthermic thoracoabdominal chemotherapy (HITAC) over HIPEC however. Erasmus et al. [9] reported that chemotherapeutic drugs were also absorbed from the pleural cavity like the peritoneal cavity. In the case of HITAC, the intrapleural concentration of chemotherapeutic drugs was persistently high compared to plasma. The current study is focused on the technical aspects and feasibility of HIPEC and HITAC in ovarian cancer patients. It does compare HIPEC alone with HIPEC and HITAC. Cognizant of the beneficial effects of HIPEC in selected patients with ovarian cancer, the same strategy was applied through HITAC in patients with thoracic involvement. This is the first study of its kind in the Indian patient population.

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42.2 Materials and Methods

This is a retrospective study of three prospectively selected patients with ovarian carcinoma and metastatic pleural effusion treated with CRS and HITAC after neoadjuvant chemotherapy. The aim was to describe the technical aspects of the surgery with brief descriptions of the postoperative outcomes and treatment-related morbidities on follow-up.

42.3 CRS Technical Aspects

For CRS, a midline laparotomy extending from the xiphoid process to symphysis pubis was performed to provide greater exposure of the abdomen. Bilateral pelvic and retroperitoneal lymph node dissection with total omentectomy were done routinely as a part of CRS in ovarian cancer apart from total hysterectomy and salpingo-oophorectomy. Regarding peritonectomy, we do not routinely practice total peritonectomy in all cases. Selective peritonectomy was performed in the region(s) macroscopically affected by the tumor. Total peritonectomy was performed in two cases in the present study, which had gross peritoneal disease. Total peritoneal stripping in continuity is a technically demanding procedure, hence in the current study, we followed the split technique, which involves stripping and removal of the entire peritoneum in five parts: right subdiaphragmatic peritoneum along with Glisson's capsule, left subdiaphragmatic peritoneum, right and left parietal wall/paracolic gutter peritoneum, and pelvic peritoneum. Peritonectomy was performed by holding and lifting the peritoneal edges with multiple artery forceps (Fig. 42.1).

Surgical dissection was performed using monopolar diathermy with a sharp tip and diathermy settings at 30 coagulation spray mode although many surgeons prefer ball tip diathermy in pure cut mode. Additional visceral organ resection (colectomy, coloproctectomy, splenectomy, gastrectomy, appendicectomy, cholecystectomy, liver resection, and small bowel resection) may be performed, depending upon the involvement. Whenever bowel resection is required, we prefer resection anastomosis before HIPEC. Bowel edema, erythema, and other hyperthermic chemotherapy-induced changes due to HIPEC at the edges of the bowel wall may become a constant threat for anastomotic leaks. For diaphragmatic peritonectomy, access and exposure of the diaphragmatic peritoneum were of utmost importance. Adequate exposure was obtained with the Omni-Tract surgical retractor and the liver was completely mobilized, except at the area of the hepatic veins and the suprahepatic inferior vena cava. For full-thickness large solid deposits involving the diaphragm, we performed full-thickness diaphragmatic resection in two cases of the present study. In another case, partial resection of the hemidiaphragm was created for HITAC. Full-thickness resection of the diaphragm and the subsequent diaphragmatic rent created are shown in Fig. 42.2. Pleural nodules were excised through the same rent in one case. The other two cases had only pleural effusion with no preoperative or intra-operative evidence of metastatic pleural deposits. Total parietal pleurectomy was not performed. We aspirated the pleural effusion in each case and dissected a few pleural deposits with electro-diathermy in one case. Thorough pleural lavage with chemotherapeutic perfusate into the pleural cavity was performed during HIPEC.

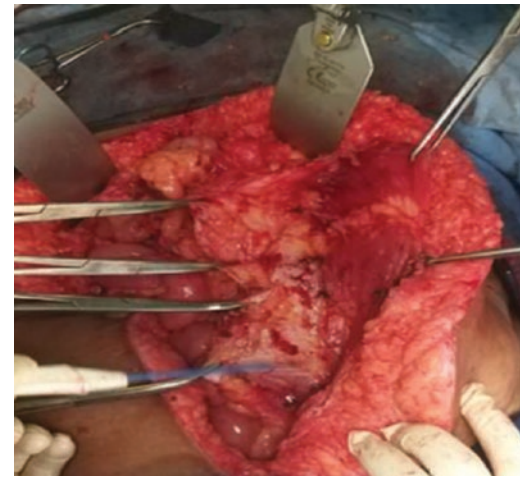

Fig. 42.1 Peritonectomy using multiple artery forceps for retraction

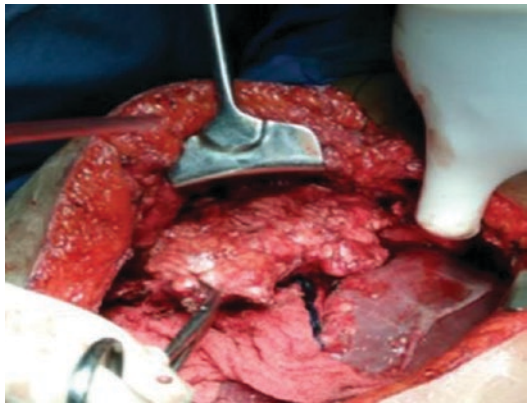

Fig. 42.2 Diaphragmatic peritonectomy with full-thickness resection of diaphragmatic deposits

42.4 The Technique of Diaphragmatic Resection

For diaphragmatic resection, one must be aware of the anatomy of the diaphragm in relation to the phrenic nerve. The phrenic nerve originates mainly from the fourth cervical nerve, but also receives contributions from the fifth and third cervical nerves (C3–C5).

The right phrenic nerve enters the diaphragm through the central tendon or inferior vena cava opening. On the right side, it courses relatively more medially throughout its thoracic course to various structures like the right brachiocephalic vein, SVC, and pericardium over the right atrium. The inferior vena cava lies medially and reaches under the surface of the diaphragm by passing through the inferior vena cava foramen in the central tendon.

The left phrenic nerve pierces the superior surface of the muscular part of the diaphragm, just to the left border of the heart.

Both nerves divide or trifurcate at or just above the diaphragm. The branches travel together into the diaphragmatic musculature, while small sensory branches supply the peritoneum over the central part of the diaphragm. The larger motor branches separate within the diaphragm into four major nerves trunks: sternal, anterolateral, postero-lateral, and crural. The nerve trunks travel partly within the diaphragmatic muscle and innervate the inferior surface covered by peritoneum. Therefore, the diaphragmatic incision has to be made circumferentially to avoid the main phrenic nerve trunks.

In the present study, we made an incision in the above-mentioned manner and excised the tumor deposits.

The patient's head end was lowered during HITAC procedures, so that the chemotherapeutic fluid can gain easy access to the thoracic cavity by free flow from the abdominal cavity.

42.5 Reconstruction of the Diaphragm after HITAC Procedure

In two cases, we had to incise approximately one-fourth of the diaphragm (Fig. 42.3). The diaphragmatic defects were repaired primarily with polypropylene 1–0 suture. In another case, the peritoneal defect was almost 50% and required reconstruction with polypropylene mesh, fixed with polypropylene 1–0 suture. In all three cases, we placed the ICD in the triangle of safety.

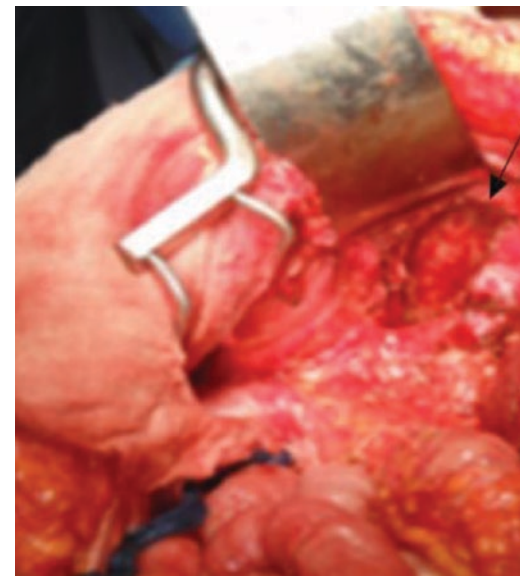

Fig. 42.3 Diaphragmatic rent after partial diaphragmatic excision (black arrow)

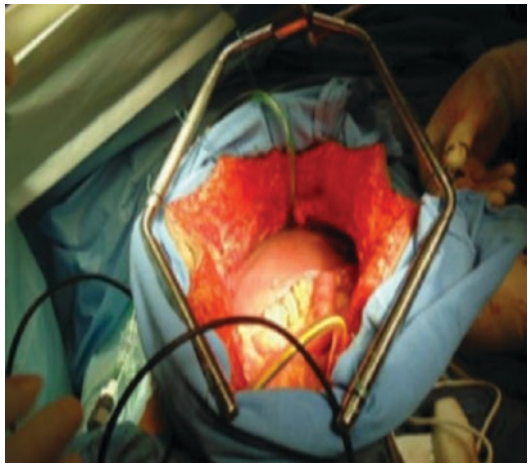

Fig. 42.4 Demonstrating the creation of coliseum for performing hyperthermic intraperitoneal chemotherapy

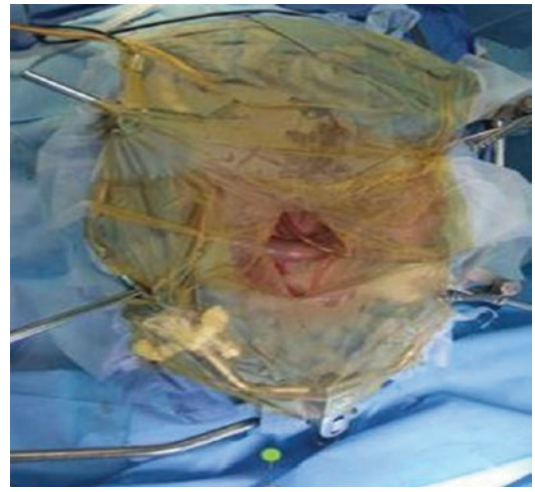

Fig. 42.5 Showing the coliseum (semi-open technique) and hyperthermic intraperitoneal chemotherapy tubes with adhesive sheet

42.6 HITAC: Technical Aspects

HIPEC was performed using the open Coliseum technique (Fig. 42.4) as described by Sugarbaker [3]. We used the Omni-Tract surgical retractor for exposing the abdominal cavity. Skin edges were suspended using interrupted polyester sutures fixed to the horizontal arms of the retractor to create an open space in the abdominal cavity, as depicted in Fig. 42.4. An avascular plane of about 2–3 cm was routinely created between the anterior rectus sheath and subcutaneous tissue so that the rectus sheath and muscle would be immersed in the HIPEC perfusate.

An adhesive plastic sheet was incorporated to prevent spillage of the chemotherapy solution and heat loss (Fig. 42.5). A slit was made in the plastic cover to allow manual access to the abdomen and pelvis during HITAC. This helped in cases of blocked tubings during HIPEC and was also used to ensure uniform distribution of the perfusate and heat by constant, intermittent manipulation of the perfusate. A specially designed wooden spatula was used for stirring the heated chemotherapy solution to ensure uniform distribution as well as heat. Elbow-length gloves were worn for manual stirring and debris removal from the HIPEC tubing ports.

In cases of ovarian carcinoma, cisplatin was used as a chemotherapeutic drug in HITAC. Apart from routine drug dosage calculation using body surface area, another method of estimation uses the approximate volume of the peritoneal cavity in liters. Dosage was calculated at 50 mg of cisplatin per liter. The chemotherapeutic solution was prepared by a resident doctor/specialized staff nurse using aseptic technique and full body personal protective equipment in a separate room adjacent to the surgical suite. The desired temperature from the inflow tube was kept in the range between 42 °C and 44 °C and out-flow was maintained at 41 °C to 43 °C. As per the literature, microscopic as well as tumor deposits up to 2.5 mm are destroyed by the synergistic effects of hyperthermia (42 °C) and chemotherapy [5]. To achieve the desired temperature in the abdominal cavity, the temperature in the heat exchanger of the machine was regularly titrated depending on the recorded temperature. During combined HIPEC and HITAC for 60 min with close intraoperative monitoring of core body temperature, hemostasis was ensured before starting. We also constantly monitored the flow rate and nature of fluid content in the tubings. The inflow tube was kept in the pelvis away from critical areas and the great vessels. The average perfusate volume was

2.30 L, depending upon the capacity of the abdominal cavity. We used a triple-layered filtration mask, tightly fit to the face. It was also desirable to have a surgical smoke evacuator work continuously under the plastic sheet during perfusion and we used this in a number of cases. After completion of the procedure, the perfusate was aspirated, hemostasis ensured, and lung expansion confirmed before closure of the pleural defect. We did not perform peritoneal saline irrigation after completion of HITAC although some surgeons prefer to do so after clearing out the chemotherapeutic solution at the end of the procedure. Ipsilateral single intercostal drainage tube would then be placed. Two soft abdominal drains, one each in the sub-hepatic region and pelvis, were routinely placed in all cases. Additionally, we also placed a suction drain in the subcutaneous cavity after mobilizing the rectus sheath as mentioned earlier and this was removed on day 3 routinely unless drainage was more than 100 mL in the last 24 h.

42.7 Intra-Operative Monitoring

The role of the anesthesiologist is crucial during CRS with HITAC because of the extensive resection and long duration of procedures. The addition of hyperthermia in HITAC presents further challenges for the clinicians so a team approach is paramount. The main concern is related to the various physiological changes that can occur during CRS with HITACe, where hyperthermia and the use of chemotherapeutic agents concurrently may affect body systems. These concerns relate mainly to major fluid shifts, respiratory, hemodynamic, renal, hepatic, hematological, and metabolic changes along with electrolyte, fluid, and thermal imbalances. The maintenance of normal physiology remains the main goal. Ventilatory strategies are also of a major concern, not only because of abdominal surgery but also from exposure of the thorax to chemotherapy drugs and hence, the need for single lung ventilation.

Preoperative assessment and optimization are thus required for optimal outcomes. A thorough history and examination is key and includes routine assessment along with evaluation of prior drug therapy including chemotherapy, analgesics, or drugs for associated comorbidities. Preoperative rehabilitation is also emerging as an important management tool because of its various beneficial aspects in enhanced recovery after surgery.

Appropriate monitoring is essential for patients undergoing CRS and HITAC. Apart from routine conventional intra-operative monitoring (electrocardiogram, non-invasive blood pressure monitoring, pulse oximeter, capnography, temperature), certain additional monitoring strategies are required for such interventions. For airway management, the conventional endotracheal tube is used routinely with oropharyngeal core body temperature probe monitoring. However, single lung ventilation is desirable in cases of pleural deposit excision. Anesthesia induction is usually done using propofol, fentanyl, and atracurium and maintained with atracurium, fentanyl, and inhalational agents like sevoflurane or desflurane in oxygen and air mixture. Based on the extent of the abdominal mass and the patient's clinical condition, ventilator strategies may require further planning.

Goal-directed fluid therapy is desirable for fluid management. Monitoring for fluid management is routinely done using urine output measurement and non-invasive methods such as cardiac output monitors for assessing the fluid status to guide management. Multimodal analgesia is required for optimal outcomes. The use of thoracic epidural analgesia with local anesthetic and opioids appears to be acceptable in the current study. Coagulopathy needs to be identified and corrected as necessary. The use of point of care tools for assessing coagulopathy remains promising. Postoperative monitoring is crucial as these patients continue to have various physiological changes for days in the postoperative period. The patient should be monitored closely for fluid balance, hemodynamic fluctuations, renal impairment, coagulopathy, and electrolyte imbalances. Such patients also need DVT prophylaxis in the postoperative period using pharmacological and/or mechanical measures.

42.8 Results

CRS with HIPEC and HITAC was performed in three patients with ovarian carcinoma and peritoneal carcinomatosis after neoadjuvant chemotherapy.

Patients were 29–46 years with a mean age of 40 years. All patients resided in urban localities and were of middle class socioeconomic status.

Patient serial number "1" is a 45-year-old female with known hypothyroidism. She underwent staging laparotomy at another institution for ovarian malignancy in December 2015 and histopathology was FIGO stage IB. The patient did not undergo any adjuvant chemotherapy. Six months later, she self-referred to our tertiary center in May 2016 with symptoms of cough, breathlessness, and abdominal distension and was diagnosed as FIGO stage IVA, recurrent ovarian carcinoma. The patient underwent chemotherapy with 6 cycles of TP (Paclitaxel/Carboplatin), 6 cycles of Gem/CDDP (Gemcitabine/Cisplatin), and 1 cycle of TP (Paclitaxel/Carboplatin). Post-chemotherapy, the patient had partial response and she proceeded with secondary CRS and HITAC as mentioned in Table 42.1. In the early postoperative period, the patient did not develop significant surgical morbidity (Clavien–Dindo grade III/IV). Following 3 cycles of adjuvant chemotherapy, the patient remains disease-free with the last follow-up on 12-02-2020.

Patient serial number "2" is a 46-year-old female with no known comorbidities nor significant family history. She initially presented to another institution with symptoms of abdominal pain, constipation, fever, and weight loss. She was diagnosed with Koch's abdomen and received tuberculosis treatment for 1 year. However, she had persistent and worsening of symptoms, so a right-sided intercostal drainage tube was placed for a right pleural effusion. Image-guided pleural biopsy was performed and histopathology was suggestive of poorly differentiated carcinoma which was immunopositive for CK7+, ER+, and focal CA125+. The patient then self-referred to our hospital. After thorough work-up, she was planned for weekly TP neoadjuvant chemotherapy followed by surgical reassessment before proceeding with interval CRS with HITAC. Details of the surgical procedure were mentioned earlier and are based on pre- and intra-operative clinical findings. Postoperative histopathology was consistent with FIGO stage IVA. In the early postoperative period, the patient developed a recurrent right pleural effusion which necessitated another right intercostal drainage tube. After delayed clinical recovery, six cycles of adjuvant TP and bevacizumab were administered to the patient. The patient is currently alive with persistent disease at the last follow-up on 13-03-2020 and is still on bevacizumab based chemotherapy.

Patient serial number "3" is a 29-year-old female with no known comorbidities, significant family history nor past medical or surgical history. She presented with a dry cough and shortness of breath for 10 months. The patient was worked-up and diagnosed with ovarian carcinoma with right-sided malignant pleural effusion (FIGO IVA). Multidisciplinary tumor board discussion advised for TP based neoadjuvant chemotherapy followed by CRS and intraperitoneal/intrathoracic chemotherapy. Post 3 cycles TP, the patient underwent interval CRS with HITAC. The procedure details are mentioned in Table 42.1 and the postoperative period was uneventful. Final histopathology reported the same FIGO stage disease because of similar tumor deposits on the pleura. Three cycles of adjuvant TP regimen were administered to the patient. At the last follow-up on 19-09-2019, the patient was alive and disease-free.

Table 42.1 The demographic and clinical details with follow-up status

Patient sl. no 1	Patient sl. no 2	Patient sl. no 3	Age (years)
45	46	29	Date of registration
08-05-2016	04-06-2018	27-06-2017	Prior surgery
Staging laparotomy	None	None	FIGO stage
IVA	IVA	IVA	NACT (cycles/ regimen)
6#TP, 6#gem + CDDP, 1#TP	12#TP	3#TP	Date of surgery
20-05-2019	08-11-2018	12-03-2018	Types of CRS
Secondary CRS	Interval CRS	Interval CRS	CRS procedure
Disease limited peritonectomy + omental cake excision + terminal ileum and limited right colon resection anastomosis	TAH + BSO + B/L PLND + RPLND + total omentectomy + pouch of Douglas and liver deposit excision	TAH + BSO + B/L PLND + RPLND + total omentectomy + right diaphragmatic stripping + selective peritonectomy	CRS duration (min)
370	410	330	Blood loss (mL)
1150	600	450	PCI
23/39	2/39	15/39	HITAC drug
Mitomycin	Cisplatin	Cisplatin	Drug dosage (mg)
30	100	100	Duration (min)
60	45	60	Temperature (°C)
42	42	42	Perfusate
Normal saline	Normal saline	Normal saline	Perfusate volume (L)
2.5	3.0	2.5	CC score
1	0	0	Comorbidity
Cl. Dindo II	Cl. Dindo III	Cl. Dindo II	Adj chemotherapy
3#TP	6#TP + Bev	3#TP	Follow-up status
Alive and disease-free	Alive with disease	Alive and disease-free	

Sl. No serial number, *FIGO* International Federation of Gynecology and Obstetrics, *NACT* neoadjuvant chemotherapy, *TP* Paclitaxel/Carboplatin, *CDDP* Cisplatin, *TAH* total abdominal hysterectomy, *BSO* bilateral salpingo-oophorectomy, *B/L PLND* bilateral pelvic lymph node dissection, *PAND* paraaortic node dissection, *CRS* cytoreduction surgery, *PCI* peritoneal carcinomatous index, *HITAC* hyperthermic thoracoabdominal chemotherapy, *CC score* completeness of cytoreduction score, *Cl. Dindo* Clavien–Dindo score, *Adj* adjuvant, *Bev* Bevacizumab

42.9 Conclusion

CRS with HITAC is a complex and evolving procedure. These are viable treatment options for cases of ovarian carcinoma with peritoneal carcinomatosis and pleural disease in the post neoadjuvant chemotherapy setting. Macroscopic disease can be removed with CRS and the remaining microscopic disease can be dealt with through HITAC to reduce thoracic recurrences. In this study, there were no life-threatening surgical morbidities. No mortality was recorded till the last follow-up. Following the technique described in this study, CRS with HITAC can be safely performed and replicated easily without additional morbidity or need for extra resources for HITAC. However, multicenter studies with larger numbers of patients and longer follow-up are warranted to establish reproducibility and acceptance of the procedure.

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Bowled out Phenomena in CRS and HIPEC

43

M. D. Ray and Manish Kumar Gaur

43.1 Introduction

Cytoreductive surgery (CRS)/hyperthermic intraperitoneal chemotherapy (HIPEC) has gained popularity in the management of peritoneal surface malignancies (PSMs). CRS/HIPEC provides measurable improvements in outcomes compared to old series and has significantly affected survival in peritoneal carcinomatosis. HIPEC aims to eradicate any microscopic residual disease through synergistic effects of higher local concentrations of chemotherapeutic agents and hyperthermia [1]. The better outcomes with HIPEC have been explained because of the optimal timing of loco-regional therapy immediately after CRS, plasma partition concept, the reversal of platinum resistance, enhanced drug penetration into tumor deposits, [2–4] and synergistic effect of chemotherapy along with hyperthermia [5].

43.1.1 Prehyperthermic Intraperitoneal Chemotherapy and Hyperthermic Intraperitoneal Chemotherapy Era Results [6, 7]

Survival of patients with PSMs:

1. Pre-CRS + HIPEC.
   - Median survival—5–11 months.
   - Three years survival—10–15%, maximum up to 30%.
2. Post-CRS + HIPEC.

- Median survival—30–92 months.
- 5% year survival—30–50%.
- Pre-HIPEC Post-HIPEC
- Pseudomyxoma 65>80%.
- Mesothelioma 25>50%.
- Colorectal Ca 30–40% 50–60%.
- Ovarian Ca 15–30% 30–90%.
- Ca Stomach 10–15% 25–30%.
- Sarcomas No such standard data still.

The key to success with CRS/HIPEC lies with proper patient selection and proper postoperative management of the patients. As reported in different large series, the overall morbidity ranges

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from 22 to 34% and mortality from 0.8 to 4.1% [8–10] and varies up to 8%.

Complication rates of venous thromboembolism (VTE) have been found to be 5% [11]. Deep-vein thromboembolism (DVT) and resultant pulmonary embolism (PE) can sometimes be fatal very surprisingly.

43.2 Patients and Methods

CRS/HIPEC has evolved as an effective treatment for patients with PSM. The complexity of these two combined procedures results in a steep learning curve for the surgeons. The quality of CRS and critical surgical outcomes are an indicator of surgical performance and quality of a CRS/HIPEC program.

All patients who underwent CRS/HIPEC in the Department of Surgical Oncology at DR BRAIRCH, AIIMS, New Delhi, India, from May 2012 to February 2019 were analyzed from a prospectively maintained database. Key CRS surgical parameters, including types of surgery, CC 0/1 rates, types of peritonectomy, ostomy rates, perioperative morbidity, and mortality were analyzed as markers of oncosurgical quality indicators.

43.3 Results

From the database, a total of 172 eligible patients' data undergoing CRS/HIPEC was included for the analysis. The patients underwent CRS/HIPEC for varieties of PSM, as shown in Fig. 43.1. Majority of patients were carcinoma ovary (50%). Overall CC 0 or 1 could be achieved in 90% of cases. The spectrum of surgical procedures included was total peritonectomy in 82 (53%) patients and the remaining had disease-specific partial peritonectomy. Resection of the colon or rectum was performed in 35 (22%) patients. Multivisceral resection, including various combinations of the small bowel, bladder, liver, spleen, and parietes, was performed in 20 patients. Overall morbidity was 30%, and Fig. 43.2 shows the spectrum of morbidity.

The most common complication was subacute intestinal obstruction followed by DVT. Most of the complications were managed conservatively. Re-exploration was required in 9 (6%) patients,

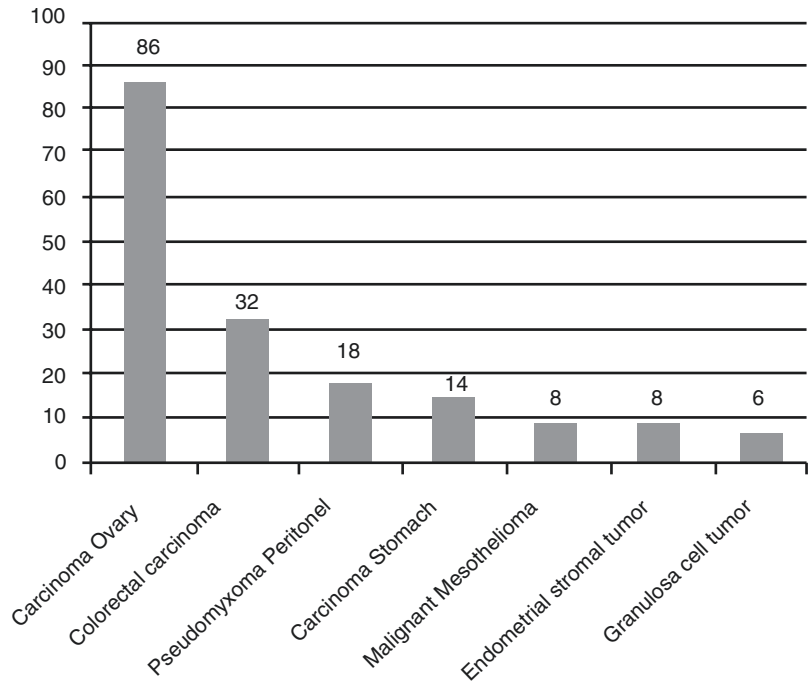

Fig. 43.1 Distribution of various indications of cytoreductive surgery/hyperthermic intraperitoneal chemotherapy in our patients

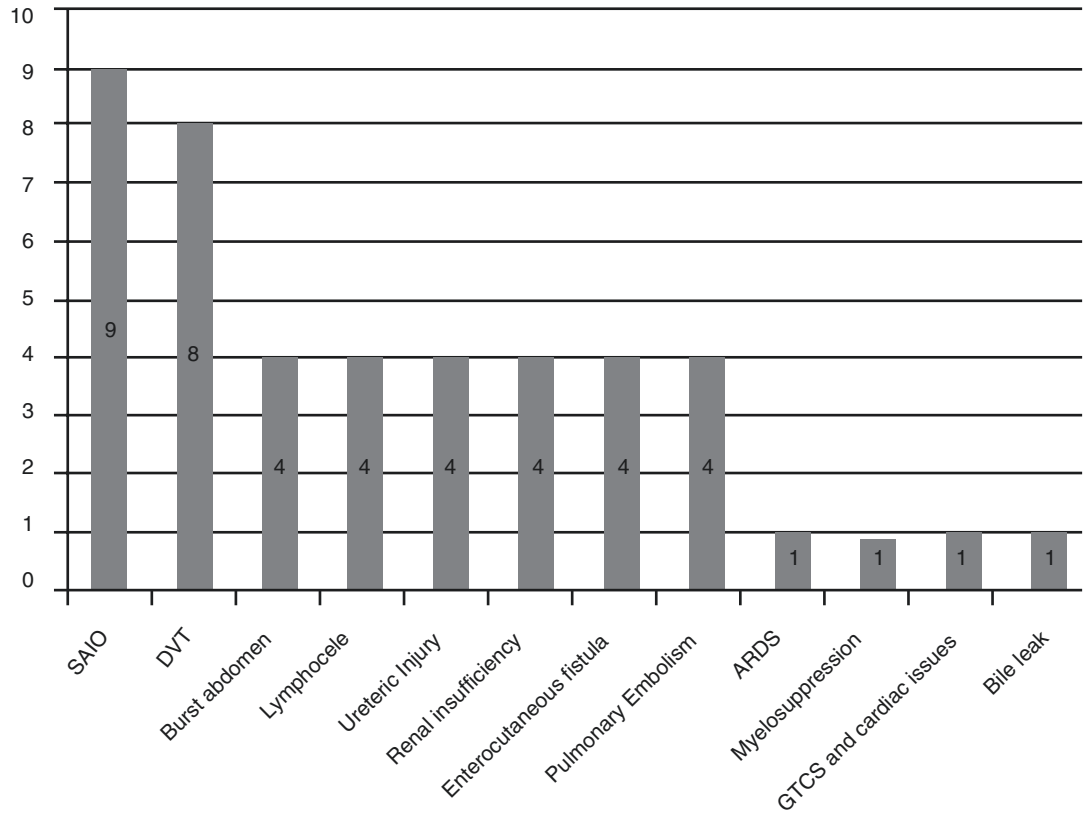

Fig. 43.2 Major morbidity profile in 172 patients

including 3 cases for bowel anastomotic leak, 2 for ureteric leak, 1 case each for bile leak, lymphocele, and intraabdominal sepsis. Two patients had postoperative acute renal failure, managed with hemodialysis and ICU care. Overall perioperative mortality was 3.4% (6/172). Major causes of mortality were acute respiratory infection, PE, and myocardial infection. The average ICU stay was 1.4 ± 1 day, and the average hospital stay was 7 ± 2 days.

Of 172 patients, 8 patients developed VTE. Of these 8 patients, 2 had sudden death after 6–8 h after surgery and that was due to PE, which we called "bowled out phenomenon." One obese patient died on the eighth postoperative day because of the sudden development of hypotension, tachycardia, and dyspnea suggestive of PE. D-dimer was positive. In cricket, a single ball can destroy every expectation of the batsman, same way this PE can take the life all of a sudden and make the surgeon stupefied despite proper selection and CRS/HIPEC without any hint any point of time.

Thereby, the question comes how to prevent this catastrophe? As there is next to nothing kind of guideline to prevent VTE in the world literature after CRS/HIPEC.

As per our experience and on the basis of pathophysiology of VTE after extensive surgery, especially after CRS/HIPEC in PSM patients, we started offering thromboprophylaxis 12 h prior to the commencement of CRS, especially in patients with (1) High burden disease, (2) Obese patients, (3) Smoker, (4) <40 years of age especially with mucinous histology, and (v) Previous history of VTE. Moreover, the same prophylactic dose is repeated 6 h after surgery and in the morning on first postoperative day. The dose of dalteparin used is 80–100 U/kg body weight subcutaneously daily for minimal 2 weeks after the discharge of the patient.

With this strategy, we see not a single patient develops VTE or even PE in the last 58 patients in our series.

43.3.1 Cytoreductive SURGERY and Hyperthermic Intraperitoneal Chemotherapy

The term CRS was advocated in 1930 by Meigs in relation to ovarian cancer surgery. Optimal cytoreduction was initially defined as the removal of all tumors except 2 cm; next, it was 1 cm tumor could be left behind maximum. Now by definition, optimal cytoreduction is no macroscopic, i.e., visible tumor should be left behind. HIPEC is to be performed only after achieving optimal cytoreduction. However, as per Paul Sugarbaker up to 2.5 mm tumor nodule (CC-1) HIPEC can be performed. The procedures are the removal of tumor along with organ involved, greater omentectomy, lesser omentectomy, removal of omental bursa, involved peritoneum, draining lymph nodes, and multiple organ resections to achieve optimal cytoreduction. No visible disease could be left behind. This surgery on an average takes 6–8 h and average blood loss is around 800 ml to 1.2 L.

43.4 Discussion

The management of peritoneal surface malignancy is a complex and challenging job. The history and evolution of CRS/HIPEC are as complicated as this procedure. In 1968, Munnel et al. reported significant improvement in survival of patients who underwent omentectomy, appendectomy, and resection of localized peritoneal or intestinal metastases in addition to total hysterectomy and bilateral salpingo-oophoerectomy. In 1987, Zimm et al. conducted a phase I trial to document the antineoplastic activity of intraperitoneal cisplatin and etoposide. The same group later reported longer survival in patients with peritoneal carcinomatosis of carcinoma ovary who received intraperitoneal therapy, with residual tumor <2 cm had mean survival >49 months. In 1975, Griffith computed tomography highlighted that residual tumor of >1.5 cm after debulking is associated with poor prognosis. It was in 1995 that Sugarbaker published a landmark article describing the extent, type, and technique of peritonectomy. In the last three decades, the procedure of CRS and process of HIPEC have been standardized globally. We already mentioned the survival benefit after CRS/HIPEC.

CRS/HIPEC often requires major surgical procedures which are long, extensive, and often associated with complications. The morbidity rates range from 22 to 34% and mortality varies from 0.8 to 6% [12, 13] These morbidities have come down as the passage of time, technique, and experience. The important postoperative complications are gastrointestinal (GI) complications, pulmonary complications, hematologic complications, renal complications, and VTE. They reported the incidence of grade III/IV GI-related morbidity is 4.5–19% in different series [14, 15]. Similarly, the incidence of grade 3/4 pulmonary complications is 10–16% [16]. Hematologic complications are quite common, with a wide ranging from 4 to 39% with neutropenia associated with mortality in the range of 0–60% [17, 18].

The reported incidence of VTE in CRS/HIPEC is 5%, but deep VTE and resultant PE can sometimes be fatal what happened in our three cases [11]. However, the prevalence and risk factors for VTE in such patients are unclear. Previous studies reported an incidence of 3–10% of all VTE events [18, 19]. Certain tumors such as hematological and metastatic diseases are more prone to develop VTE [20]. Mucin-producing cancers such as ovarian cancers, colorectal cancers, and lung cancers are likely to be associated with VTE than other solid tumors [21].

The Yang et al. study published in 2011 is the only randomized controlled trial published to date evaluating outcomes for CRS with and with-

out HIPEC. They included 68 patients of peritoneal carcinomatosis of gastric cancer, the serious adverse event rate for patients randomized to CRS alone was 11.7%, while the serious adverse event rate for those randomized to CRS plus HIPEC was 14.7% ($P = 0.839$) [22]. In a comparison of 54 patients undergoing CRS for recurrent ovarian cancer, 22 patients underwent CRS alone, and 32 patients underwent CRS plus HIPEC, with no difference in morbidity between groups (23% vs. 28%, $P = 0.453$) [23].

The pathophysiology of thrombosis in cancer is not well understood. The role of prothrombotic pathways has been investigated in the molecular biology of cancer [24]. The VTE pathophysiology is complex and involves the interplay of multiple pathways including activation of procoagulants, inhibition of anticoagulant or fibrinolytic pathways, and cytokine release [21]. CRS/HIPEC has been found to have disruptive effects on hemostatic pathways, both on the platelet and coagulation pathway [25]. Etulain et al. proposed an altered platelet response either a positive platelet response (an enhancement of inflammation) or a negative one (an inhibition of inflammation), due to expression of adhesion molecules on luminal surfaces of leukocytes and endothelial cells and secretion of various inflammatory mediators (cytokines, chemokines, nitric oxide, and reactive oxygen species) into the microenvironment. They demonstrated that platelet hemostatic function is altered negatively by higher temperatures along with variation in release of the alpha-granule contents [26].

If we review the literature, which is scanty, we find PE is one of the common catastrophes after CRS/HIPEC [27]. The way we lost three patients very unexpectedly, that is nothing but a bowled out phenomenon both for the surgeon and the next of kin of the unfortunate patients.

In the cricket world cup semifinal 2019, Virat Kohli, Rohit Sharma, and K. L. Rahul were the victims of this kind of phenomenon, unexpected, unwanted, never seen in nightmare too type!

Hence, the incidence of PE of our patients is nothing but a "*bowled out phenomenon.*"

43.5 Conclusion

The sudden PE occurring in CRS/HIPEC patients is a phenomenon unexplained. The rates are so low and underrated that no solid and conclusive data is available regarding the incidence as well as for the prevention of these dreaded complications. However, bowled out phenomenon is to watch out for in the immediate postoperative period as well as discharge too. Preventive measures do not follow any consensus guidelines but are mostly institutional based. We mobilize the patient from the first postoperative day and encourage to move as much as possible and start prophylactic low-molecular-weight heparin (LMWH) 12 h before CRS, especially in high-risk patients and advise to continue minimum 2 weeks after the discharge.

Bowled out phenomenon is fatal complication, and a good patient selection and prophylactic LMWH therapy is the best strategy to avoid it.

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44 Where Does HIPEC Stand: An Evidence Based Review

M. D. Ray and Kunal Dhall

44.1 Introduction

Peritoneal surface malignancies (PSM) were considered as terminal disease only a decade back and still majority of the tertiary health care centers in India are continuing the same tradition. The treatment was systemic chemotherapy with a palliative intent, hence, the prognosis was dismal. The peritoneal dissemination from the malignant abdominal organ is presently called "Peritoneal Metastases" (PM) rather than peritoneal carcinomatosis. These peritoneal metastases are comparatively less responsive to systemic chemotherapy [1]. The symptoms caused by peritoneal dissemination of the disease are many and they significantly affect the quality of life (QoL) [2]. In majority of cases, this disease is confined to only peritoneal cavity, so the locoregional treatment is more effective than systemic chemotherapy. Therefore, few innovative therapies like CRS and HIPEC have been introduced for treating these patients [3]. Initially the CRS was performed in carcinoma ovary and gradually in other PM too [4]. The basic principle of cytoreductive surgery is to remove all the macroscopic disease. The surgical technique of peritonectomy along with multi-visceral resection was described by Prof Paul Sugarbaker in 1995 [5]. The aim of this review is to highlight the present ideal indications of HIPEC based on available recent data across the globe.

44.2 Rationale of HIPEC

As peritoneal surface malignancies are mostly confined to the abdominal cavity even after recurrence and the fact that systemic chemotherapy is not as effective as desired owing to plasma peritoneal barrier, therefore, some form of locoregional therapy is scientifically more effective. HIPEC is the product of this scientific thought and it has become the popular treatment modality in PSM patients. The chemotherapeutic drugs used for a particular malignancy during HIPEC are absorbed through the portal system and directly go to liver and detoxified, hence, lesser systemic toxicity. Heat (41–43 °C) itself is tumoricidal and along with chemotherapeutic drugs has synergistic action and causes more penetration of chemotherapeutic agent (5–7 mm) [6, 7].

44.3 Prerequisites

To get the desirable action of intra-peritoneal chemotherapy certain prerequisites need to be fulfilled [8]. The idea behind intraperitoneal chemotherapy is that the microscopic disease

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(nodules up to 2.5 mm) may be taken care of by both heat and chemotherapy. This is because of the uniform distribution of the chemotherapeutic agents and exposure of the entire serosal peritoneal surface. Therefore, the preceding CRS should leave behind no or minimal macroscopic disease. The choice of chemotherapeutic drugs in HIPEC is very important particularly with regard to the disease to be treated. The ideal drug should be heat stable, less toxic, and cost effective, should not require conversion into its active form, and at the same time should have least systemic absorption. It should also have well-established activity against the disease being treated [9, 10].

44.4 Tumor Biology and Patient Selection

The most important aspect for the successful outcome of the challenging procedure like CRS and HIPEC is careful selection of patients. The disease biology should be considered as the king, patient selection as the queen, and our techniques as prince and princess. First and foremost thing a surgeon should take care of while selecting the patient is the biology of the tumor. Very aggressive tumor, especially in young age, e.g. signet ring cell histology in gastric and colorectal cancer, low-grade serous ovarian carcinoma where extensive disease burden including extensive mesenteric involvement or extra-abdominal involvement, etc. are warning signs for this major procedure [11].

Apart from this patient related factors like comorbidities, advanced age may compromise the intraoperative and postoperative courses. Upper abdominal extensive disease burden, extensive involvement of small bowel and its mesentery, large mass at porta and lesser omentum, hepatoduodenal ligament involvement, more than 2 bowel stenosis, mass on superior mesenteric vessels or extensive retroperitoneal lymphnodes involvement or liver/splenic parenchymal involvement suggestive of aggressive tumor biology are not amenable for upfront surgery. Neoadjuvant chemotherapy and then reassessment for CRS is a better option especially in ovarian cancer. In colorectal cancer up to 3 resectable metastases in liver with limited peritoneal metastases could be considered for CRS and HIPEC [11]. In gastric cancer, limited peritoneal metastases, peritoneal cancer index ≤6, one can go for CRS and HIPEC. Prophylactic role of HIPEC in selected cases of locally advanced carcinoma stomach showed good survival results.

No imaging modality is ideal for PSM. CECT abdomen and pelvis are the most commonly used modality despite certain drawbacks like low detection rate of subdiaphragmatic disease burden, transmural infiltration of bowel, or mucinous tumors. In such cases, MRI is better modality. Sometimes PET CT is an option particularly when the disease is beyond the abdomen and in recurrent settings but it is not routinely recommended for the assessment of PSM because it overestimates the disease in atleast 30% of cases [12].

At every step of the treatment, detailed discussion should be done with patient and relatives regarding the extent of surgery, multivisceral resection, ostomies, postoperative complications, QoL, and recurrence risks. Above all, the patient should be well-motivated as it strongly influences the outcomes of surgery and survival.

44.5 Recent Clinical Data of CRS + HIPEC

CRS and HIPEC are the most advanced treatment modality for various peritoneal surface malignancies. Apart from pseudomyxoma peritonei and malignant mesothelioma, there are no established data in support to varieties of malignancies related to peritoneal surface spread like colorectal, ovarian, and gastric cancer. The various evidenced based current indications for CRS + HIPEC will be discussed here.

44.6 Pseudomyxoma Peritonei (PMP)

PMP, a rare malignancy with widespread mucinous deposits and accumulation of mucin within the peritoneal cavity is very aptly called as "jelly belly."

The usual primary site is Appendix. Ovary and intestine are other sites of origin. Biologically, it is a heterogenous group of diseases which includes Diffuse Peritoneal Adenomucinosis (DPAM) and Peritoneal Mucinous Carcinomatosis (PMCA). Whereas DPAM is characterized by low-grade disease with abundant extracellular mucin with scanty proliferative epithelium (60–65% cases) but the most malignant type is Peritoneal Mucinous Carcinomatosis (PMCA) seen in 30–35% cases [13].

The standard of care of any form of PMP is CRS and HIPEC [14–16]. Before CRS and HIPEC the conventional treatment used to be complete removal of mucin along with appendicectomy or the organ of origin. If it was not possible, serial debulking was done. Surgery had got some role to relieve symptoms followed by systemic chemotherapy. Sugarbaker reported 5 years survival of PMP to be 86% with low-grade PMP (so-called DPAM) in 325 patients [17].

In a retrospective study of 2298 patients, both DPAM and PMCA patients underwent CRS with 89% of these patients further underwent HIPEC with mitomycin C and oxaliplatin. The median PFS was 98 months and OS was 196 months. 10 years survival was 63% and 15 years survival was 59% [18]. A French study of 301 PMP patients showed 5 years OS of 73% [19]. A prospective Dutch study of 300 patients showed a median PFS of 53 months, median OS of 130 months, and 5 years OS of 65% [20].

Pre-operative elevation of tumor markers like CEA, CA 19–9, CA-125 are the predictors for an increased recurrence risk and reduced OS after complete CRS and HIPEC [21]. The most significant prognostic factors for PMP are complete or optimal CRS, low-grade histology, and low PCI [22].

Approximately 25% patients of PMP develop recurrence after CRS and HIPEC [23]. A diffuse recurrence usually denotes an aggressive biology or resistance to intraperitoneal chemotherapy, especially when it occurs within 6 months. It is suggestive of a poor prognostic disease. CRS and HIPEC may be performed in limited disease or diffuse disease where CRS is feasible [24]. Selected patients with a second-third recurrence are also candidates for "salvage CRS and HIPEC" with favorable results [25].

44.7 Malignant Peritoneal Mesothelioma

It is a locally advanced peritoneal disease observed in a patient having exposure to asbestos and usually affect pleura (60–70%), peritoneum (20–30%), pericardium (1–2%), and tunica vaginalis (1%). It is quite rare with an incidence of 0.5–3 and 0.2–2 cases per million for men and women, respectively [26].

Diffuse peritoneal malignant mesothelioma (DMPM) has a diverse spectrum of histologies, viz. epithelioid (the most common histology accounting for approximately 75% of cases), sarcomatoid, papillary well-differentiated, low-grade (tubule-papillary), biphasic/mixed, multicystic, and deciduoid [27]. The sarcomatoid variety is an aggressive mesothelial malignancy with poor prognosis. Palliative surgery with or without systemic chemotherapy provides the median overall survival of 1 year [28, 29]. The aggressive locoregional treatment approach comprising of CRS and HIPEC has improved the survival significantly.

The largest multi-institutional experience of treating MPM with CRS and HIPEC included 405 patients. The median overall survival was 53 months (1 to 235 months), and 3- and 5-year survival rates of 60% and 47%, respectively, were observed. The epithelial subtype of tumor, absence of LN metastasis, completeness of cytoreduction, and HIPEC were independently associated with improved survival [30]. A meta-analysis of 20 publications and 1047 patients reported 1-, 3-, and 5-year survival of 84%, 59%, and 42%, respectively. Patients receiving early postoperative intraperitoneal chemotherapy [EPIC] (44%) and those receiving cisplatin intraperitoneal chemotherapy alone (48%) or in combination (44%) had an improved 5-year survival [31].

There is still no gold standard chemotherapeutic agent of choice for MPM. However,

RENAPE study has attempted to answer some of the questions by retrospectively analyzing data of 249 patients who underwent CRS + HIPEC for MPM. The overall survival is better when combination of two drugs (especially platinum-based regimen) is used as compared to a single drug [32].

Both neoadjuvant and adjuvant systemic therapy have not shown to increase survival in DMPM patients undergoing CRS and HIPEC [33]. On the other hand, adjuvant bidirectional chemotherapy (including the combination of intraperitoneal pemetrexed and intravenous cisplatin) after CRS and HIPEC have been tried but survival data is lacking [34]. The long-term survival study revealed that the survival curve reached a plateau after 7 years of optimal cytoreduction and HIPEC and the cure rate was 43.6% [35]. In recurrent DMPM, treatment with repeat HIPEC showed a survival benefit [36].

The most important prognostic factors for survival after CRS and HIPEC for MPM include histologic type, lymph node status, disease burden, proliferative index, pre-operative serum CA-125 levels, completeness of CRS, and postoperative morbidity [30, 31, 33, 35–38].

44.8 Colorectal Cancer

About 5–10% of colorectal cancer (CRC) patients have peritoneal metastasis during initial presentation [39]. Peritoneum is the sole metastatic site in approximately 5% of patients during initial evaluation. Whether synchronous or metachronous, peritoneal disease is more common in colonic cancer (10%) as compared to rectal cancer (4%). In colonic cancers, right sided colon cancers are more likely to have peritoneal dissemination in contrast to left sided colon cancers [40]. Recurrent colorectal cancer has peritoneal involvement in 20% of cases and 40% of these patients have peritoneum as the solitary recurrence site [41]. Therefore, the role of CRS and HIPEC in colorectal cancer cannot be overlooked.

The randomized trial from Netherlands reported that the median survival was 12.6 months in the standard therapy arm (systemic chemotherapy with or without palliative surgery) and 22.3 months in the experimental therapy arm (CRS with HIPEC). Macroscopically complete resection was associated with better median survival [42]. Long-term follow-up study of these patients showed that the median progression-free survival was 7.7 months in the control arm and 12.6 months in the HIPEC arm. The median disease-specific survival was 12.6 months in the control arm and 22.2 months in the HIPEC arm. The 5-year survival was 45% for those patients in whom a macroscopically complete resection was achieved [43].

A systematic review observed an OS of 20–63 months and 5-years survival rates of 17–51% for CRS and HIPEC in contrast to 5–24 months and 13–22%, respectively, for palliative surgery group [44]. The most recent meta-analysis evaluating 76 studies found pooled hazard ratios (HRs) for OS of 2.67. The patients receiving HIPEC in both oxaliplatin and mitomycin C groups had significantly better survival ($P < 0.00001$) with a morbidity rate of 33% and mortality rates of 2.8% with HIPEC [45].

The question of adding HIPEC to liver metastatectomy in patients with both peritoneal and liver metastasis has also been addressed in very few number of studies. There was no survival difference survival between patients with colorectal peritoneal metastases alone or along with liver metastases who underwent aggressive treatment. Selected patients with CRPC and LM, especially those with a low PCI and up to 3 liver metastasis may undergo curative resection [46].

The drug of choice for HIPEC in colorectal peritoneal metastasis is still a matter of debate. Mitomycin C has been used frequently but recent studies compared it with oxaliplatin. Patients receiving oxaliplatin had better median survival than mitomycin C. Subgroup analysis demonstrated an advantage of oxaliplatin in females, low-grade tumors, non-signet ring histology, and low PCI [10–15, 47]. Another comparative study

found that the overall postoperative complication rate was significantly higher in mitomycin C patients with a comparable intra-abdominal complication rate but a tendency towards more extra-abdominal complications in mitomycin C patients. GI complications were more common with oxaliplatin. It also showed no clear benefit in RFS and OS for HIPEC with oxaliplatin or mitomycin C [48].

The concept of "second look" laparotomy after definite surgery for colorectal cancer in patients considered to be at high risk for peritoneal metastasis has been advocated by some researchers. The three situations that could potentially lead to higher risk of recurrent peritoneal carcinomatosis were identified as synchronous peritoneal carcinomatosis, synchronous isolated ovarian metastases, and a perforated primary tumor [49]. The 5-year OS and DFS rates were 90% and 44%, respectively. The presence of PC at second-look surgery portends a poor prognosis [50].

44.9 Gastric Cancer

Gastric cancer with peritoneal dissemination confers a dismal prognosis with a median survival of approximately 4 months with best supportive care, and 7–10 months with aggressive systemic therapy [51].

A meta-analysis by Coccolini et al. reported that intraperitoneal chemotherapy increases 1, 2, and 3-year overall survival but not 5-year overall survival rate. It also improves 2- and 3-year mortality rates in patients with N+ disease and 1- and 2-year mortality rates in patients with T4a disease. Locoregional N+ disease in patients with advanced gastric cancer does not contraindicate HIPEC [52].

Another meta-analysis found that the use of HIPEC significantly increases the 1-, 3-, and 5-year survival rates and decreases overall systemic and peritoneal recurrence rates. This is achieved at the cost of higher morbidity in the HIPEC group which includes myelotoxicity and renal insufficiency [53]. A recent meta-analysis evaluated the effectiveness and safety of neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) combined surgery for gastric cancer peritoneal metastasis. NIPS-combined surgery yielded higher survival than NIPS alone. NIPS regimens had a higher conversion rate, higher percentage of patients with R0 surgery, less severe adverse reactions to chemotherapy, and fewer postoperative complications [54].

Desiderio et al. conducted a meta-analysis which demonstrated a survival advantage with prophylactic HIPEC. The maximum benefit of HIPEC is conferred to those with disease burden confined to positive cytology and limited nodal involvement. Larger tumors (>4 cms) and serosal involvement should be considered for prophylactic HIPEC. The completeness of cytoreduction carries a prognostic importance in higher disease burden [55].

44.10 Ovarian Cancer

Majority of patients with epithelial ovarian cancer present with stage 3 or 4 disease with involvement of peritoneum. The best possible treatment in this scenario would be complete surgical removal of all the macroscopic disease followed by systemic chemotherapy. Still, majority of these patients present with recurrent disease. CRS and HIPEC has shown a benefit in both the first line setting as well as in recurrent disease [56].

HIPEC may be used as a treatment modality for ovarian cancer as various stages, viz., as upfront treatment (primary), after neoadjuvant chemotherapy (interval), after complete response to neoadjuvant chemotherapy (Consolidation HIPEC); in patients having suboptimal surgery followed by chemotherapy and having residual disease and finally in recurrent setting after initial complete response to first line therapy (Secondary). In re-recurrent setting, it is known as Salvage CRS and HIPEC [57].

The use of HIPEC in the treatment of ovarian malignancy was first studied in patients with recurrent disease. An Italian study concluded that in patients with recurrent disease, CRS and HIPEC are a feasible and safe treatment which significantly improves survival as compared to surgery alone or surgery plus chemotherapy [58].

A French multicenter retrospective cohort study of 566 patients (which included 474 patients with recurrent disease) found that median overall survival was 45.7 months for recurrent cancer. It also showed that patients with platinum resistant disease when treated with CRS and HIPEC have similar survival as patients with platinum sensitive disease [59].

Two recent trials advocate the use of HIPEC in patients with advanced ovarian cancer in first line setting. In Netherlands, an open-label, phase 3 trial was conducted which randomly allocated patients after neoadjuvant chemotherapy with CRS alone or CRS with HIPEC. Three cycles of adjuvant chemotherapy were administered post-operatively. The median recurrence free survival was 10.7 months in the CRS group and 14.2 months in the CRS + HIPEC group. The median overall survival was 33.9 months in the CRS group and 45.7 months in the CRS + HIPEC group with no increase in higher rate of side effects [60].

Another randomized trial conducted in Korea randomly assigned HIPEC to patients who had optimal CRS. The 5-year OS was not significantly different between the HIPEC and no HIPEC arms, but for women who received neoadjuvant chemotherapy, the median 5-year OS for the HIPEC arm was 47.9% as compared with 27.7% in the control group. The trial concluded that more follow-up studies are required to critically evaluate the impact of HIPEC have in this patients receiving neoadjuvant chemotherapy [61].

44.11 Peritoneal Sarcomatosis

Peritoneal sarcomatosis is defined as intraperitoneal dissemination of sarcoma in the absence of extra-abdominal metastasis. The most common sarcomas causing peritoneal metastases are retroperitoneal soft tissue sarcomas, pelvic sarcomas (e.g. uterine leiomyosarcomas), GISTs, and desmoplastic small round cell tumors [62].

The abdominal sarcomas have a high propensity for local recurrence at the resection site as well as in peritoneum. The peritoneal spread is attributed to pre-operative spontaneous tumor embolism, intraoperative tumor embolism through shed venous blood and surgical trauma leading to intraperitoneal spillage [63]. The mainstay of treatment of peritoneal sarcomatosis has been adjuvant chemotherapy or radiotherapy without much improvement in prognosis. Recent studies show the benefits of CRS and HIPEC in such settings.

Several single institution studies showed that HIPEC does not provide a survival benefit in abdominal sarcomatosis. The largest series of 60 patients by Rossi et al. found that median local progression-free survival and OS were 22 months and 34 months, respectively, and that they are determined by histologic grading and completeness of cytoreduction [64].

Many other smaller non-randomized studies were also conducted across the globe and almost all were of the opinion that it is too early to draw conclusions about the beneficial role of HIPEC in abdominal sarcomatosis. However, a particular subset of patients with peritoneal sarcomatosis from uterine leiomyosarcomas are the potential candidates for HIPEC [65–70].

The authors of worldwide analysis issue of PSOGI concluded that the exact role of HIPEC in peritoneal sarcomatosis is yet to be determined. It is impossible to conduct a randomized trial for each etiology. The best approach would be to individualize this treatment taking into merit the age of patient, performance status, site of origin, presence or absence of extra-peritoneal metastasis, and histologic diagnosis. Thus, HIPEC should be reserved for young patients with a good performance status and without extra-peritoneal spread, with PM from an intra-abdominal primary, or from mucinous histology [71].

There is a need for standardization of the procedure, indications, and regime. Although

some researchers consider it as an investigational option to achieve better locoregional control, still optimal CRS is best prognostic factor in both primary and recurrent settings. Further large scale and randomized studies in these patients are warranted to draw definitive and reliable inferences.

44.12 Conclusion

To conclude, CRS and HIPEC are the standard of care for PMP and DMPM across the globe. In colorectal and gastric cancer, there are several phase three trials showing overall survival benefit in selected cases while there is a prophylactic role of HIPEC in gastric cancer. Three reported phase 3 trials showed positive results in ovarian cancer. (Table 44.1) Still, there is a dire need for worldwide collaboration, especially from developing countries, for research and standardization in this field to have a clinically meaningful data in the near future.

Table 44.1 Current role of HIPEC based on available data

Primary site	Indications of HIPEC	Level of evidence
Pseudomyxoma Peritonei	CC score 0/1 and irrespective of PCI and grade, limited recurrent disease	3
Malignant peritoneal mesothelioma	CC score 0/1, epithelioid histology; no lymph node disease	3
Colorectal Cancer	CC score 0/1, low PCI, absence of systemic disease except 3 resectable liver metastasis, recurrence with no systemic disease	3
Gastric Cancer	CC score 0/1; no distant metastasis	1
Ovarian Cancer	CC score 0/1; recurrent disease	2
Peritoneal Sarcomatosis	Uterine leiomyosarcomas	3//4

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