# 4 Anaesthetic Implications of Chemotherapy and Radiotherapy

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## 4.1 Introduction

The cancer burden is increasing across the globe and is expected to rise further. It is estimated that the world will need about 45 million cancer surgeries annually by the year 2030 [1, 2]. The cancer management is primarily multidisciplinary and various teams like medical oncologists, radiation oncologists, and surgical oncologists remain an integral part. Surgical intervention is required for both curative and palliative intent. Therefore, the burden of surgical interventions for cancer is also poised to increase significantly in the coming years. Upfront surgical resection is performed soon after diagnosis and offers the best loco-regional control and potential for cure. However in certain patients, based on tumour type, site, and its extent, upfront surgery is not feasible. These cancer patients receive either alone or combination of treatment modalities including systemic chemotherapy, radiation therapy to reduce the tumour bulk before surgery. Disease recurrence after initial therapy may also lead to surgical intervention. Alongside curative surgery, many patients also undergo palliative surgeries for various cancers. Thus, a large proportion of patients who undergo surgery for cancer could have possibly received chemo-radiation before they end up on the operating table.

Levels of cancer care worldwide have significant variations. In the developed world, most of the surgical burden of cancer is upon comprehensive cancer centres and tertiary level hospitals. It is therefore vital for anaesthesiologists working in comprehensive cancer centres and otherwise to have insight into the basics of chemotherapy and radiotherapy, their perioperative implications and management.

## 4.2 Concerns in the Preoperative Period Due to Cancer Therapy

The preoperative cancer treatment including radiation therapy and/or chemotherapy has an impact on various body system physiology and mandates not only its assessment but also perioperative care accordingly. Various chemotherapeutic regimens are administered based on tumour type, site, and response. These combinations of chemotherapeutic agents induce cell apoptosis by the various mechanism of drug–receptor interaction. However, the toxicity of such chemotherapeutic agents may involve all organ systems. Newer anticancer agents provide targeted therapy and differentially affect the tumour cells. Despite its preferential target on fast-growing cancer cells, still, these agents have

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a toxic effect on various body cells and functions. Radiotherapy is frequently used along with chemotherapy or alone to achieve tumour response. It causes tissue damage and death by the formation of oxygen-free radicals and causes a multitude of changes which have widespread implications on the perioperative course of the patient. The most significant among them are cardiopulmonary toxicity of chemo-radiation and airway changes induced by radiation that can directly influence the delivery of and response to anaesthesia. With the gradual adoption of hyperthermic intraperitoneal chemotherapy (HIPEC) for management of peritoneal surface disease, a new paradigm of chemotherapy and its perioperative effects has emerged that is significant to the anaesthesiologist.

## 4.3 Basic Principles of Chemotherapy

Cytotoxic chemotherapy targets the various functionality of nucleic acids, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) leading to the destruction of cells. Most of the contemporary chemotherapy regimens comprise a combination of various cytotoxic drugs in an attempt to increase the 'fractional cell kill'. Combination therapy is designed in a way so that each drug has a different mechanism of activity and works in different parts of the cell cycle. Drugs with similar resistance mechanisms and toxicity profiles are usually not grouped.

The timing of administration of chemotherapeutic agents varies and its usefulness can be achieved at various time points of the cancer trajectory. Based on the course of multidisciplinary treatment, the chemotherapy regime is labelled as:

- Neoadjuvant therapy: The therapy is administered before upfront definitive surgical intervention for the primary tumour, local or distant metastasis, or both. The intent for neoadjuvant therapy is to decrease the tumour bulk at the primary site or metastatic site for feasibility for attempting complete tumour resection. It also aims to prevent extensive or less mutilating surgical intervention like lumpectomy vs mastectomy for breast cancers.
- Adjuvant therapy: The therapy is administered after the surgical removal of the tumour mass and is aimed at managing any micrometastasis and thus preventing cancer recurrence.
- Palliative therapy: The therapy is primarily aimed at improving the quality of life and possible survival and does not assure curability of cancer.

## 4.4 Chemotherapeutic Agents

The medical management of cancer uses various chemotherapeutic agents and in various combinations. These agents have a different mechanism of action and thus are combined for multipronged action. However, each of these has associated side effects as well.

### 4.4.1 Anti-tumour Antibiotics

These chemotherapeutic agents, also known as anti-neoplastic antibiotics, are one of the commoners used drugs for cancer management. These interfere with DNA and RNA synthesis for its cytotoxic action and are usually cell-cycle non-specific. These are derived from microbial fermentation. These include anthracyclines, mitoxantrone, actinomycin D, and mitomycin C.

#### 4.4.1.1 Anthracyclines

The anthracyclines group of antitumor antibiotics includes doxorubicin and daunorubicin. These are used for management of solid tumours and haematological malignancies. Newer analogues (epirubicin, the analogue of doxorubicin; idarubicin, the analogue of daunorubicin) of these drugs have improved toxic profile and better antitumour efficacy.

**Pharmacology** Although these drugs are structurally similar with a similar mechanism of action

and resistance, the drugs have differing clinical activity and toxicity. These drugs have multiple modes of action:

1. Inhibit DNA and RNA synthesis in tumour cells by intercalating in its base pairs and thus stops tumour cell replication.
2. Blocks DNA transcription and replication by inhibiting topoisomerase enzyme that causes relaxation of supercoiled DNA.
3. Damage of DNA, proteins, and cell membranes of tumour cells by iron-mediated free oxygen radicals.
4. DNA damage response, epigenome, and transcriptome are deregulated by induction of histone eviction from chromatin.

**Pharmacokinetics and Metabolism** These drugs are redistributed to body tissues leading to a rapid fall in plasma concentration after its intravenous administration. It is principally metabolised by reduction and undergoes hepatic elimination. So, dose reduction of these agents is desirable in patients with liver dysfunction.

**Uses** These are one of the most common chemotherapeutic agents used in clinical practice and usually used as combination therapy with other agents. Doxorubicin and epirubicin are effective for cancer of the lung (small cell), breast, and soft tissue sarcomas. These are also effective in certain haematological cancers and paediatric solid tumours. These drugs may be administered intravenously as bolus or infusion and usually repeated every three weeks. The route of administration for idarubicin is oral. Daunorubicin and idarubicin are effective for acute lymphoblastic or myeloblastic leukaemia and multiple myeloma, non-Hodgkin's lymphomas, breast cancer, respectively.

Toxicity

Cardiotoxicity

Cumulative cardiotoxicity is specific to the anthracycline group of drugs and remains one of the important concerns for perioperative management. These drugs lead to toxic oxygen-free radicals (ROS) formation which in turn damages myocytes [3, 4]. The drug-induced oxidative stress causes cellular membrane lipid peroxidation which subsequently damages cells by vacuolisation. The damaged myocytes are replaced with fibrous tissue. Doxorubicin has been found to bind topoisomerase II and DNA to form a complex, which triggers cell death [5].

The overall reported incidence of anthracycline related cardiotoxicity is 9% [6–8].

Risk factors:

Anthracycline-induced cardiotoxicity is seen in certain clinical scenarios. These include:

- Age > 65 years or < 4 years old,
- Female gender,
- Preexisting cardiovascular disorders (e.g. left ventricular ejection fraction [LVEF] ≤50%),
- Hypertension, smoking, hyperlipidaemia, obesity, diabetes,
- High cumulative anthracycline exposure,
- Radiation therapy involving the chest, and
- Use of trastuzumab.

Clinical manifestations:

The anthracycline related cardiotoxicity includes cardiac failure, left ventricular dysfunction, reduced left ventricular ejection fraction (LVEF), etc. [6]. In elucidating symptoms, it should be kept in mind that anthracycline-induced cardiac injury may be present with maintained left ventricular ejection fraction [7]. So sole criteria of a normal LVEF should not be considered as the absence of cardiotoxicity during preoperative assessment. Other limitations of LVEF are that it is affected by transient conditions such as preload, afterload, and adrenergic state and is subject to variation. Other earlier and more sensitive markers may be helpful for detection of cardiotoxicity beyond LVEF include serum biomarker levels, myocardial strain using echocardiography, and detection of myocardial fibrosis using cardiac magnetic resonance.

In a large study of 2625 patients [8], cardiotoxicity was defined as either absolute drop of LVEF below 50% or reduction of >10% from the baseline. The onset time was 3.5 months from the end of chemotherapy and 98% cases were

detected within a year. The time course of anthracycline-induced cardiotoxicity is traditionally and arbitrarily defined as:

- Early or acute: Less than 1% incidence. Manifests largely as the acute reversible decline in contractility immediately after infusion.
- Early progressive or subacute: Features manifest within a year of exposure.
- Late progressive or chronic: Features manifest years after exposure.

The other manifestations include electrocardiographic abnormalities, arrhythmias (supraventricular or ventricular), atrioventricular block, and a pericarditis-myocarditis syndrome. Late features include cardiac failure-related symptoms like dyspnoea, fatigue, oedema, and orthopnoea. Depressed LVEF and/or dilated ventricles may be detected with or without heart failure.

Baseline Assessment, Monitoring, and Diagnosis

- A detailed clinical history, cardiac examination, an electrocardiogram are performed in all individuals before initiating anthracycline-based chemotherapy. A repeat clinical history and examination is done at least every three months by a clinician during the treatment course.
- Baseline cardiac imaging (usually by echocardiogram) to assess LVEF is performed before the initiation of anthracycline therapy. This baseline assessment is to identify preexisting cardiac abnormalities and thus to plan an alternative drug.
- 2D echocardiography is the recommended initial test, with 3D echocardiography preferred if available.
- The other options of assessing LVEF like radionuclide ventriculography (RVG, also known as multiple gated cardiac blood pool imaging [MUGA]) may also be considered, if available. Advantages include a high degree of reproducibility, although the test entails radiation exposure.
- A cardiac magnetic resonance scan with quantification of LVEF is suggested in cases of inadequate echocardiographic results.
- Cardiac troponins have shown some utility in the diagnosis of anthracycline-induced cardiomyopathy but are not routinely used.
- Brain natriuretic peptide has failed to show any benefit in the diagnosis of the same.

Management: A stepwise approach is desirable along with assessment for anthracycline-induced cardiotoxicity (Fig. 4.1).

Other toxicities of anthracycline chemotherapy include mucositis, myelosuppression, hair loss, etc.

#### 4.4.1.2 Bleomycin

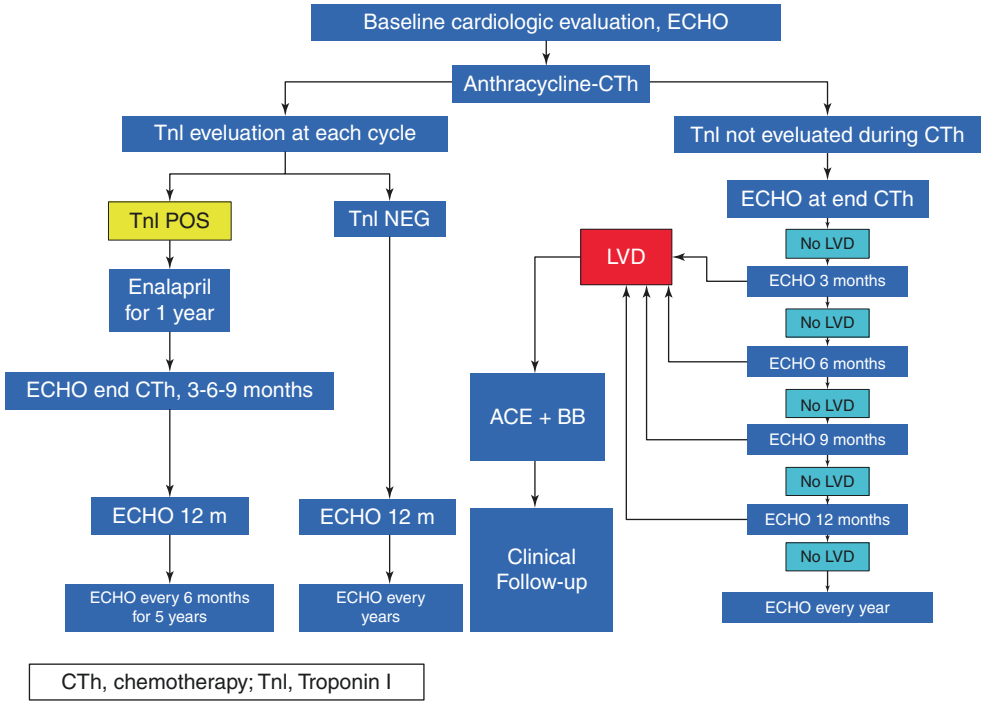
It is a non-ribosomal molecule used for cancer therapy. It has two binding regions: one for DNA and other for the iron molecule. So, this structure leads to chelation of metal ions (primarily iron) leading to pseudoenzyme formation that in turn produces oxygen-free radicals (superoxide, hydroxide free radicals) on its reaction to oxygen. These subsequently lead to cleavage of DNA strands leading to cellular death.

Bleomycin is primarily used in head and neck cancers, germ cell tumours, lymphoma, and squamous cell carcinomas of the skin, cervix, and vulva. It is also one of the sclerosing agents for the management of malignant pleural effusion.

Pharmacokinetics and Pharmacodynamics:

The oral bioavailability of bleomycin is poor. Peak plasma levels are obtained after 60 minutes of IM administration, but it reaches only one-third of an IV dose. After IV administration, plasma levels fall in a biphasic pattern as it is redistributed into tissues. It is metabolised in the liver and kidney by enzyme hydrolase and around 50–70% unchanged form is excreted via the kidney. So, drug toxicity can occur in patients with renal dysfunction.

Toxicity:




From: Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines †
Ann Oncol. 2012;23(suppl_7):vii155-vii166. doi:10.1093/annonc/mds293


**Fig. 4.1** Algorithm for the management of cardiotoxicity in patients treated with anthracyclines. Reproduced from Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2012 Oct 1;23(suppl_7):vii155–vii166 with permission from Oxford University Press

The bleomycin-induced pulmonary toxicity is an important concern for perioperative management of the patient.

Pathogenesis: The exact mechanism of pulmonary toxicity by bleomycin is not well elucidated. One of the proposed mechanisms includes oxidative pulmonary injury [9]. This mechanism is considered as use of anti-oxidants and chelating agent-induced iron depletion has been found to reduce pulmonary toxicity of bleomycin [10, 11]. The predilection of the lung may be due to the absence of bleomycin hydrolase which degrades bleomycin in the lung [12].

Rates of any grades of pulmonary toxicity range from 5 to 16% and rates of fatal pulmonary toxicity are between 0 and 3% [13]. The occurrence of bleomycin-induced pulmonary toxicity is higher in adults receiving ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) for Hodgkin lymphoma and ranges from 10 to 53%, and rates of fatal pulmonary toxicity are 4 to 5% [14]. Long-term functional respiratory impairment has been observed in 15–18% of the population receiving bleomycin [15].

Risk factors:

- Age: more common in old age.
- Dose-toxicity increasing with an increase in cumulative dose of bleomycin administration. The occurrence of high-grade bleomycin lung toxicity in a patient receiving cumulative bleomycin dose of <270 IU vs >360 IU is 0–2% vs 6–18%, respectively.

- Concomitant therapy affecting lung-drugs like cisplatin, gemcitabine, and radiation therapy when administered along with bleomycin exaggerates lung toxicity.
- Administration of high fraction of inspired oxygen in critical care setup or perioperative management has been reported to exacerbate lung dysfunction in patients who have received bleomycin.
- Cigarette smoking

Screening: The baseline lung function tests including pulmonary function tests (PFTs) and diffusing capacity for carbon monoxide (DLCO) should be done inpatient planned for bleomycin-based chemotherapy regime. Patients with poor PFTs and DLCO may be more likely to develop life-threatening pulmonary toxicity and bleomycin be discontinued if DLCO falls more than 30–35% of pre-treatment values.

Clinical presentation:

- Early or acute: May range from asymptomatic reduction in PFT or DLCO values to acute onset dyspnoea, cough, chest pain, and crackles on auscultation. Chest radiographs may show opacities. These usually develop within days to weeks of bleomycin exposure and before 6 months most patients. Acute chest pain syndrome is seen at the time of bleomycin infusion in 1% of the patients.
- Chronic progressive lung fibrosis may be diagnosed several years after exposure to bleomycin. Postoperative respiratory impairment may be the first evidence of such toxicity in some patients.
- The rapid progression of clinical symptoms is seen in patients who manifest bleomycin-induced hypersensitivity pneumonitis and diffuse alveolar damage.
- Fibrotic bleomycin toxicity presents with the indolent onset of dyspnoea on exertion which is manifested after several months of bleomycin administration.

Evaluation: Apart from the clinical evaluation on the background of cancer and bleomycin administration, certain other assessment tools are required for evaluation.

- Imaging: The pulmonary fibrosis is imaged as lung volume loss and bibasilar subpleural reticular opacification in the early stages. Fine nodular opacities and costophrenic angle blunting are also seen. Subsequently, these findings may evolve to progressive lung consolidation and honeycomb appearance. The high-resolution computed tomography (HRCT) chest reveals ground-glass opacities in dependent locations, extensive reticular markings at the periphery. Organising pneumonia may present as subpleural nodules which may mimic metastases.
- PFTs typically demonstrate a restrictive pattern with decreases in forced vital capacity (FVC), total lung capacity (TLC), and functional residual capacity (FRC). The DLCO is usually decreased.
- Broncho-alveolar lavage, per se does not provide a clue for pulmonary toxicity but rules out infection or malignancy as the differential diagnosis for symptoms.
- Lung biopsy is rarely needed for diagnosis. Lung biopsies reveal lung injury and fibrosis primarily with the subpleural distribution.

Treatment:

The definite treatment for bleomycin-induced lung injury is not known. The cessation of bleomycin therapy for all patients with signs and symptoms or asymptomatic fall in DLCO should be considered. For symptomatic patients, treatment with glucocorticoids may offer some benefits. Usually, patients who manifest hypersensitivity pneumonitis, organising pneumonia, diffuse alveolar damage, interstitial pneumonia respond to the administration of steroids [16, 17].

Other bleomycin related toxicities:

- Skin reactions: it is manifested in most cases with erythema, hyperpigmentation, striae, and vesiculation. Other manifestations include skin thickening, hyperkeratosis, and ulceration.
- Patients may manifest fever chills primarily as hypersensitivity response. It is seen in almost one-fourth of patients receiving bleomycin.

- Rare manifestation includes myocardial infarction, stroke, and Reynaud's phenomenon.
- Vascular events including myocardial infarction, stroke, the phenomenon are rarely reported.
- Patients may feature suggestive of mild myelosuppression.

#### 4.4.1.3 Mitomycin C

This is an anti-neoplastic antibiotic isolated from streptomyces caespitosus and used for various solid tumours. This agent is valuable as radio-sensitiser in patients receiving combined chemotherapy and radiation therapy. Its mechanism of action is via inhibition of synthesis and function of DNA by its action of alkylation to cross-link DNAs. It also targets DNA dependent RNA polymerase and thus inhibits transcription leading to inhibition of DNA synthesis. It has a hepatic metabolism using cytochrome P450. It metabolites have active and inactive forms.

Uses: This chemotherapeutic agent is used for upper gastrointestinal cancers like oesophagal, stomach, breast cancer, as bladder instillation for superficial bladder cancer, cervical cancer, non-small cell cancer, and head and neck cancer (in combination with radiation therapy).

Toxicity: The mitomycin manifests various adverse effects and is primarily dose-related. These include myelosuppression (most important and usually delayed onset), nausea, vomiting, anorexia, fatigue, pulmonary toxicity (interstitial pneumonia, pulmonary oedema), and haemolytic uraemic syndrome (microangiopathic haemolytic anaemia, thrombocytopenia, and renal failure).

### 4.4.2 Alkylating Agents

These are one of the oldest groups of anti-neoplastic agents. They bind covalently to guanine within the DNA via the alkyl groups and lead to apoptosis by causing arrest in the G1-S transition.

Major Groups of Alkylating Agents

1. Oxazaphosphorines: Cyclophosphamide, ifosfamide

These drugs are converted to their active form in the liver by cytochrome P450 system. The cytotoxic metabolites are phosphoramide mustard and acrolein. The antitumor mechanism is DNA synthesis inhibition by forming cross-linkages between DNA. These agents are non-specific to the cell cycle. It has hepatic metabolism and exclusive renal excretion.

Uses: These chemotherapeutic agents are used extensively in the treatment of various solid tumours and haematological malignancies. These are used for breast cancer, ovarian cancer, neuroblastoma, Wilms' tumour, sarcomas (bone and soft tissue), rhabdomyosarcoma, chronic lymphocytic leukaemia, and non-Hodgkin's lymphoma.

Toxicity: These agents' toxicity to various body functions:

- Myelosuppression is severe and dose-limiting. The nadir leukopenia is observed between 7 and 14 days and starts recovering by day 21. High dose of these agents leads to decrease platelets as well.
- Urinary bladder toxicity is seen in 5–10% of patients, occurs usually within 24 hours of drugs administration but may be delayed to some weeks in some patients. The manifestations are related to haemorrhagic cystitis, dysuria, and increased urinary frequency. The optimal hydration and use of mesna are uro-protective and may be sued in patients requiring high dose therapy.
- Cardiotoxicity is observed in patients receiving high dose therapy [18–20]. Patients who have received anthracyclines as well may present with subclinical myocardial toxicity [20]. The cardiac manifestations include left ventricular dysfunction, myocarditis, pericarditis, pericardial effusions, and QT prolongation [18, 19].
- Nausea vomiting, alopecia, hypersensitivity reactions.

2. Nitrogen mustards: Melphalan, chlorambucil.

These drugs are classic alkylating agents that inhibit DNA synthesis and function by forming inter- and intra-strand cross-links with DNA. The action of these agents remains cell cycle non-specific and acts at all cell cycle stages. Melphalan is used for cancers like breast cancer, ovarian cancer, multiple myeloma, polycythemia vera, etc. Chlorambucil is used for leukaemias, especially chronic lymphocytic leukaemia (CLL), non-Hodgkin's lymphoma, Hodgkin's lymphoma, Waldenstrom macroglobulinemia.

Toxicities include myelosuppression, nausea vomiting, hypersensitivity, alopecia, skin lesions. Chlorambucil may cause pulmonary fibrosis and seizures.

### 4.4.3 Anti-metabolites

These chemotherapeutic agents are weakly acidic molecules and include various agents like methotrexate, fluorouracil, cytarabine, mercaptopurine, etc.

#### 4.4.3.1 Methotrexate

It is an anti-folate analogue, cell cycle-specific, and acts at the S-phase of the cell cycle. The folates levels are reduced by inhibition of the dihydrofolate reductase (DHFR). This action causes a reduction in the synthesis of thymidylate and purine synthesis and subsequent inhibition of the synthesis and function of DNA.

Methotrexate is well absorbed orally but is usually administered IV. It is extensively distributed into body tissues and third space in case of fluid collections. Hepatic metabolism occurs for 10% of the drug and the rest of the drugs is excreted unchanged in the urine.

Uses: Methotrexate is used in various cancers including breast, head and neck, osteogenic sarcoma, urinary bladder, etc. It is also useful in the management of acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, primary CNS lymphoma, meningeal leukaemia, carcinomatous meningitis, and gestational trophoblastic cancer.

Toxicity: The adverse effect profile of the methotrexate is dose-dependent. It causes myelosuppression, mucositis, pneumonitis, etc. The drug and its metabolite can precipitate in the renal tubules leading to acute renal failure and azotemia. Liver toxicity may manifest as the elevation of liver enzymes and bilirubin.

#### 4.4.3.2 5-Fluorouracil

It is a pro-drug which is activated into several metabolites. The drug has various mechanisms and the major mechanism appears to be the inhibition of thymidylate synthase resulting in depletion of thymidine triphosphate (TTP) essential in the in vivo synthesis of DNA. It also inhibits RNA synthesis and processing. It is widely used in a variety of different malignancies like that of the breast, stomach, pancreas, oesophagus, head and neck, and ovaries.

Toxicity:

1. Common toxicities include nausea, vomiting, mucositis, headache, alopecia. Diarrhoea may be severe and may be dose-limiting.
2. Cardiotoxicity is fairly common and is usually limited to mild angina like symptoms associated with coronary artery spasm, but in about 1% develop life-threatening cardiotoxicity in the form of arrhythmias, ventricular tachycardia, and cardiac arrest, secondary to transmural ischemia may occur.
3. Neurotoxicity in the form of demyelinating degenerative changes within the CNS may be seen. Acute cerebral syndrome following injection of the drug that may persist for variable periods after cessation has also been described. Symptoms include ataxia, nystagmus, gait abnormalities.

### 4.4.4 Cisplatin and Analogues

Cisplatin is one of the most common chemotherapeutic agents with wide spectrum anti-neoplastic activity. The mechanism of action of cisplatin is via its covalent binding to DNA, leading to cross-linkage and thus affecting DNA functioning. Cytotoxicity is cell cycle independent. Significant

synergy is observed with concurrent administration of anti-metabolites. After IV administration, plasma concentrations decay rapidly due to redistribution. It has renal excretion with 10–40% excreted within 24 h and up to 50% excretion within 5 days.

Various cisplatin analogues have been introduced and used in cancer management. Carboplatin is one of the promising agents and has been used for many of the chemotherapeutic regimes except that of germ cell tumours where cisplatin is still preferred. Carboplatin is especially suitable for high-dose regimens in haematological malignancies owing to its low degree of non-haematological toxicity.

Uses: Cisplatin is used along with other chemotherapeutic agents for the management of ovarian cancers, malignant pleural mesothelioma, gastric cancer, colon cancer, lung cancers (small cell, non-small cell), head neck cancers, germ cell tumours, and pancreatic cancer cell lines.

Toxicity: These chemotherapeutic agents have various systemic toxicity. Renal toxicity is seen in 35–40% of patient receiving these chemotherapeutic agents and dose limited. The nephrotoxicity usually manifests after 10–20 days of drugs administration as electrolyte abnormalities (hypokalemia, hypomagnesaemia, hypocalcaemia), acute renal failure and may progress to chronic renal insufficiency. These effects are usually reversible. The adverse effect on the central nervous system is usually dose and duration dependent. It manifests as peripheral sensory neuropathy with primary clinical presentation as a classic glove and stocking pattern of paresthesias and numbness. Some patients also manifest motor neuropathy, focal encephalopathy, and even seizures. Ototoxicity is more common in children and manifests as tinnitus and high-frequency hearing loss. Ocular effects may manifest as optic neuritis, papilledema, and cerebral blindness. Vascular adverse events like myocardial infarction, cerebrovascular accidents, thrombotic microangiopathy, and vasculitis may be seen. Reynaud's phenomenon has also been reported. Myelosuppression is seen in 25–30% of patients. Nausea vomiting, headache, fatigue are all common. Renal, neurological, vascular toxicities are all relatively less with carboplatin as compared to cisplatin.

### 4.4.5 Anti-microtubule Agents

These are a class of anti-neoplastic agents which act by inhibiting microtubule formation, which remains one of the core structural units for cells and its activities. These drugs bind on specific sites on tubulin and inhibit their polymerisation.

#### 4.4.5.1 Vinca Alkaloids: Vincristine, Vinblastine

These are not absorbed orally and only administered IV. Vinca alkaloids are metabolised by cytochrome P450 in the liver and excreted in bile. Only a small amount is excreted in the urine.

Uses: These chemotherapeutic agents are primarily used for haematological malignancies including ALL, multiple myelomas, and lymphomas. Other indications include neuroblastoma, Wilms' tumour, rhabdomyosarcoma, Ewing's sarcoma, and thyroid cancer.

Toxicity: Neurotoxicity is one of the dose-limiting toxicity. It manifests at various levels including peripheral neuropathy, cranial nerve palsies, autonomic dysfunction, and various CNS related manifestations. CNS toxicity may even lead to seizures and coma. The toxicity may affect bowel function as well as leading to pain abdomen, constipation, and ileus. So, patients receiving vinca alkaloids are administered laxatives prophylactically. Myelosuppression is generally mild. Alopecia, skin rash, and hypersensitivity reactions may be seen. Vinblastine also has several cardio-respiratory effects like hypertension, vascular events like stroke or myocardial infarction, acute pulmonary oedema, bronchospasm, dyspnoea, and interstitial infiltrates.

#### 4.4.5.2 Taxanes: Paclitaxel, Docetaxel

The development of taxanes in the 1990s was the most encouraging development in oncology at the time. Paclitaxel offered significant prolongation of survival for patients with ovarian cancer.

Docetaxel has shown to improve survival in patients with metastatic cancer. These are poorly absorbed orally. After intravenous administration, these agents are redistributed in various body spaces and have extensive hepatic metabolism by the cytochrome p450 system. The major excretion is via the faecal route (70–80%) and some amount is cleared in urine (<10%).

Uses: The taxanes are primarily used in malignancies of breast, ovary, lung (non-small cell and small cell), oesophagus, urinary bladder, and prostate.

Toxicity:

1. Taxanes cause dose-limiting myelosuppression. The impact is maximum at 8th–10th day with maximum fall in leukocyte counts and starts recovering by day 15–21.
2. Hypersensitivity reactions occur in up to 20–40% of patients. The taxane induced hypersensitivity is manifested by cutaneous symptoms (rash, flushing, erythema), respiratory (bronchospasm, dyspnoea), and hypotension.
3. Sensory neuropathy in the form of numbness and paraesthesia is common.
4. Cardiotoxicity in the form of arrhythmias ranging from transient asymptomatic bradycardia to all degrees of heart block as well as ventricular arrhythmias.
5. Mucositis, diarrhoea, and transient elevation in bilirubin and liver enzymes may be seen.

### 4.4.6 Topoisomerase II Inhibitors: Etoposide, Teniposide

Topoisomerase enzymes are nuclear proteins which regulate the topology of the DNA helix. Two subtypes, i.e. topoisomerase I and II have been recognised. Etoposide initially found to have anti-neoplastic activity in the 1960s is a topoisomerase II inhibitor and its action by stabilisation of the topoisomerase II-DNA complex. Teniposide is structurally like etoposide but is more potent. These drugs are widely used in adult as well as paediatric malignancies. These agents are effective for lung cancer (small cell), germ cell tumours, ALL, neuroblastoma, rhabdomyosarcoma as well as preoperative regimens for bone marrow transplantation.

Myelosuppression is dose-limiting in most instances. Other toxicities include nausea, vomiting, anorexia, alopecia, and hypersensitivity reactions.

## 4.5 Systems Wise Approach to Pre-anaesthetic Assessment and Management

The chemotherapeutic agents have a short- and long-term effect on various systemic physiology. So patients scheduled for surgical interventions require a thorough assessment to identify these systemic effects and attempt to optimise should be done.

### 4.5.1 Cardiovascular System

Cardiovascular effects of prior treatment chemotherapeutic drugs are a frequently encountered challenge in the perioperative period. Careful evaluation, risk stratification, planning, and management are essential for optimum outcomes. Several chemotherapeutic agents have cardiac effects that may complicate the perioperative course. These drugs and their effects are summarised in Table 4.1 [18, 21].

#### 4.5.1.1 Preoperative Assessment

Active screening and identification of patients who have received chemotherapeutic drugs for cardiovascular risk are desirable. These high-risk individuals (cumulative dose, female gender, electrolyte disturbances, other cardiotoxic agents, preexisting heart disease) need to be further assessed by elaborate history, clinical examination and required investigations need to be done. The assessment needs to consider the timing of drugs administration, its doses and impact on the cardiovascular system (before and after cardiovascular system assessment findings). Patient-reported effort tolerance and estimation of

**Table 4.1** Various chemotherapy drugs causing cardiotoxicity and their manifestations

| Drug category | Drug name | Manifestation of cardiotoxicity |
|---|---|---|
| Anthracycline | Doxorubicin, epirubicin, daunorubicin | Acute and chronic forms. Usually in the form of decline in LVEF, heart failure, arrhythmias |
| Alkylating agents | Cyclophosphamide, ifosfamide | Left ventricular dysfunction, pericarditis and pericardial effusions, heart failure, acute QT prolongation |
| Anti-microtubule agents | Taxanes: paclitaxel, docetaxel | Arrhythmias: sinus bradycardia, Mobitz type I and II and complete heart blocks, ventricular ectopics. Low incidence of heart failure |
| Anti-microtubule agents | Vincristine, vinblastine | Hypertension, acute vascular events like stroke or MI, acute pulmonary oedema |
| Monoclonal antibodies | Trastuzumab, bevacizumab | Dyspnoea, peripheral oedema, and left ventricular dysfunction. Increased risk when used with anthracyclines. Reversible in most instances<br>Arterial and venous thromboembolic events: stroke, angina, MI, deep vein thrombosis; hypertension |
| Tyrosine kinase inhibitors | Imatinib, sorafenib, sunitinib, lapatinib | Fluid retention, ankle oedema. Asymptomatic drop in LVEF, QT prolongation |
| Selective oestrogen–receptor modulator | Tamoxifen | QT prolongation, fluid retention. Thrombotic events like DVT, pulmonary embolism |

maximum metabolic equivalent achieved is a powerful tool in risk assessment.

Apart from the routine preoperative investigations, a 2D echocardiogram and 12 lead electrocardiogram (ECG) provide a multitude of information. Many patients have at least one or serial echocardiogram performed during treatment with cardiotoxic agents. A repeat scan can be requested in patients deemed at high risk. Specific information to be looked for includes details of cardiac contractility, left ventricular ejection fraction, pericardial fluid collection. Patients with borderline reported effort tolerance or those with reduced left ventricular function benefit from a formal cardiopulmonary exercise test (CPET) and assessment of maximal oxygen consumption ($VO_2$ max) and anaerobic threshold (AT). Exercise-induced ST-segment changes and arrhythmias also indicate a high risk for perioperative events. Most patients who receive neoadjuvant chemotherapy have significant reductions in their CPET derived values after the completion of chemotherapy [22, 23]. This may be because of a variety of reasons including cardiorespiratory complications of chemotherapy, muscle deconditioning, or anaemia. Numerous studies have demonstrated thresholds for $VO_2$max and AT for perioperative morbidity [24–27]. Generally, the risk of perioperative complications begins to rise with a $VO_2$ max < 15 mL/kg/min or AT <11 mL/kg/min. The assessment using the revised cardiac risk index (RCRI) combined with echocardiogram and CPET should be sufficient for risk assessment in most patients. Biomarkers for cardiac injury like levels of B-type natriuretic peptide (BNP) (a hormone produced by heart), and N-terminal-pro hormone BNP (NTproBNP), cardiac troponins can provide the clue for any associated cardiac insult due to chemotherapeutic agents [28, 29]. NTproBNP is a useful marker for identifying heart failure patients. The patients who have cardiac symptoms or remains at high risk should get a cardiologist's consultation for further assessment and optimisation, if possible. Certain drugs like angiotensin-converting enzyme inhibitors are beneficial for these patients. The cardiac interventions should be weighed against the delaying of cancer surgery as it may lead to cancer progression.

#### 4.5.1.2 Perioperative Management

Perioperative management requires planning based on individual assessment (Fig. 4.1). Patients who have been chemotherapy-induced cardiac toxicity have increased chances of perioperative cardiac events. These patients should be monitored accordingly to identify any such

events and timely management. The intraoperative monitoring depends on the underlying cardiac conditions and usually invasive arterial pressure and cardiac output monitoring are useful. The hypothermia is associated with increased cardiac events, so core temperature monitoring is useful. This should also be continued during the initial postoperative period and all measures to maintain normothermia should be followed.

The myocardial depressant effects of anaesthetic agents are amplified in patients treated with cardiotoxic chemotherapeutic agents. Treatment with chemotherapeutic agents like anthracyclines exacerbates the cardiac depressant effects of the anaesthetic agents even if the preoperative patient is not manifesting cardiac symptoms [30]. The prolongation of QTc with isoflurane is seen in patients who received isoflurane based anaesthesia. Significant cardiac depression and decompensation may occur with induction boluses of myocardial depressant drugs like propofol and with neuraxial anaesthesia [31]. There is some recent evidence that shows that neoadjuvant chemotherapy reduces subsequent requirements of volatile anaesthetics [32, 33].

Several drugs used in anaesthesia and the perioperative period may cause prolongation of QT interval and exacerbate a chemotherapy-related long QT syndrome (LQTS). These include antiarrhythmics like sotalol, quinidine, amiodarone, procainamide, flecainide, antibiotics like clarithromycin, quinolones, anti-depressants, antifungals like voriconazole, fluconazole, itraconazole, antiemetics (granisetron, dolasetron, ondansetron), and bronchodilators like salmeterol, terbutaline [34]. These drugs should be avoided. However, beta-blockers should be continued. Premedication with drugs like droperidol [35], atropine [36], ondansetron should be cautious and possibly avoided. Benzodiazepines appear to be safe [37]. Drugs like ketamine, etomidate, isoflurane, sevoflurane, and desflurane can all possibly cause QT prolongation [38]. Opioids like fentanyl, remifentanil, and alfentanil are considered safe [39, 40]. Non-depolarising muscle relaxants are preferred as succinylcholine can significantly prolong QT interval [41]. Local anaesthetics in their toxic dose cause prolongation of QT interval by inhibiting cardiac sodium channels. The techniques that cause sympatholysis like thoracic epidural anaesthesia may reduce QT interval.

A plan for postoperative care should be in place preoperatively. Elective admissions to PACU/ICU/HDU are associated with better outcomes as compared to emergency admissions [42]. Continuous cardiac monitoring should include continuous ECG with automated QT interval analysis. Invasive cardiac output monitoring has become essential in guiding fluid and vasopressor/inotrope therapy. Temperature monitoring and maintaining normothermia are vital in the postoperative period. Adequate and though pain management cannot be emphasised enough. Multimodal analgesia with NSAIDs, opioids, and regional techniques should be employed. Figure 4.2 provides an algorithm for the perioperative care of patients who have received potentially cardiotoxic chemotherapy.

### 4.5.2 Respiratory System

Respiratory signs and symptoms after chemotherapy treatment present both a diagnostic challenge as well as for management of anaesthesia. Several chemotherapy drugs have implications on the respiratory system (Table 4.2).

#### 4.5.2.1 Preoperative Evaluation

Pulmonary signs and symptoms in patients who have received chemotherapy are a diagnostic dilemma as well as a challenge for anaesthesia management. Pulmonary signs and symptoms in cancer patients may arise due to many mechanisms: infection, metastasis, mass effects of the tumour, pleural effusion, pulmonary embolism, and drug-induced toxicity.

The patient's presentation due to pulmonary complications of chemotherapy ranging from an asymptomatic decline in PFTs and DLCO to mild cough and dyspnoea to life-threatening lung fibrosis results in the severe restriction on PFT and respiratory failure. So, a high index of suspicion is warranted especially for asymptomatic patients as underlying pulmonary limitations may be manifested during the stressful perioperative phase. Several patterns of pulmonary com-

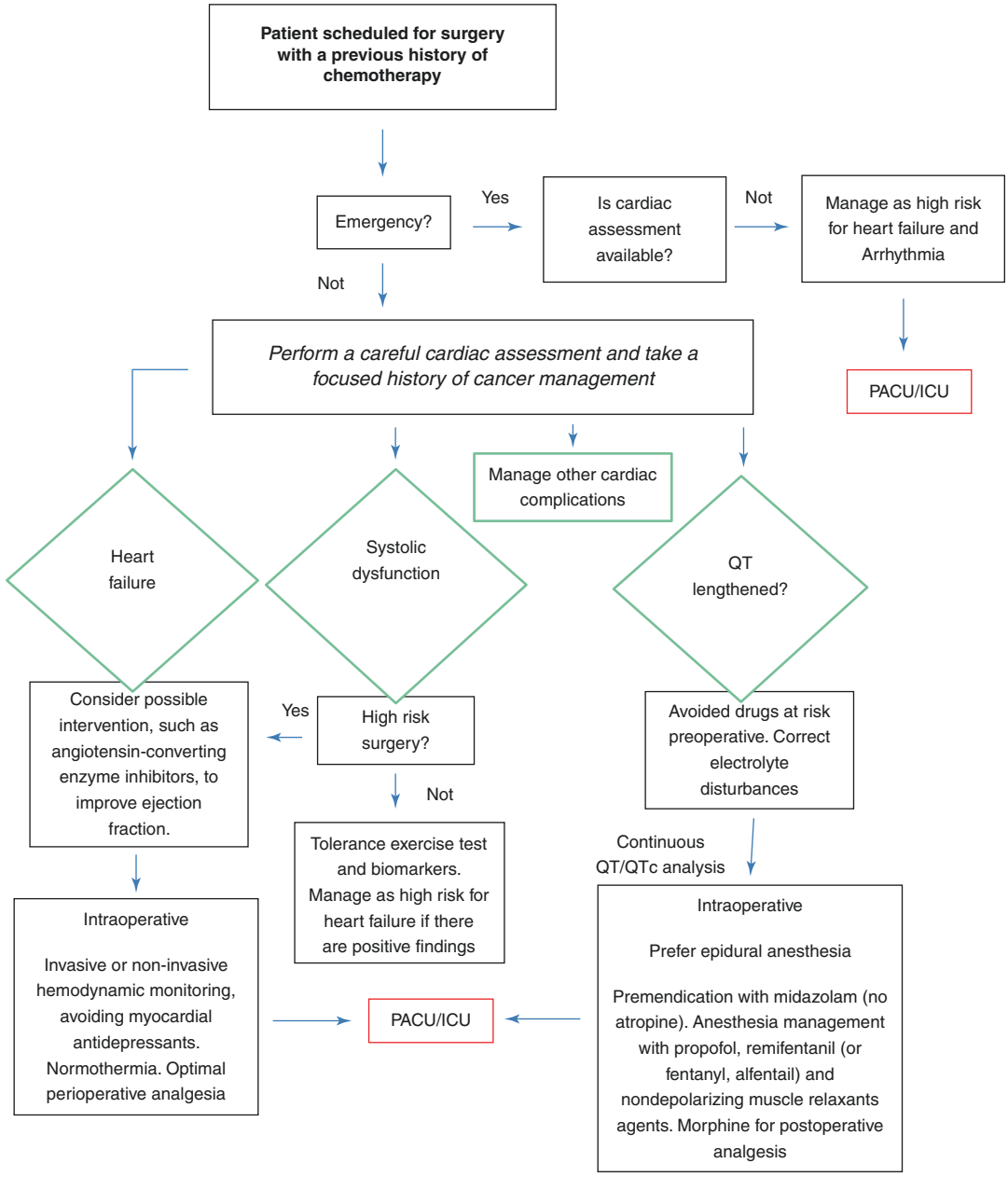



**Fig. 4.2** Algorithm for perioperative management of patients who have received chemotherapy. Reproduced with permission from Cascella M. Preoperative cardiac evaluation and anaesthetic considerations for cancer patients who underwent chemotherapy. Trends Anaesth Crit Care. 2017;14:9–18

plications are seen and may be common among the various chemotherapeutic agents. Patients may present with interstitial pneumonitis or hypersensitivity pneumonitis. At times, these conditions may progress to fibrosis. This complication is dose-dependent. The patient may also manifest as bronchitis obliterans with organising pneumonia. Pleural effusions, chest pain syndrome, pulmonary venoocclusive disease are the other manifestations.

A meticulous history should include details of oncologic therapy, drugs and their dosages, and the time elapsed since the last cycle of chemotherapy. A chronological relation between che-

**Table 4.2** Various chemotherapy drugs with pulmonary toxicities and their manifestations

| Drug category | Drug name | Manifestation of pulmonary complications |
|---|---|---|
| Anti-tumour antibiotics | Bleomycin | Acute—Asymptomatic deterioration of PFT and DLCO to features like cough, dyspnoea, chest pain, crackles. Chronic progressive interstitial fibrosis, hypersensitivity pneumonitis, diffuse alveolar damage |
| Anti-metabolites | Methotrexate | Hypersensitivity pneumonitis, organising pneumonia, acute interstitial pneumonia, lung fibrosis, pleural effusion, pleuritis |
| Taxanes | Paclitaxel, docetaxel | Acute/subacute diffuse interstitial pneumonitis, lung fibrosis<br>Docetaxel induced capillary leakage—peripheral oedema, pulmonary oedema, pleural effusions |
| Alkylating agents | Cyclophosphamide | Early onset (<6 months of therapy)—cough and dyspnoea, fever, fatigue. Ground-glass opacities on CT<br>Late onset (> 6 months of therapy)—progressive lung fibrosis with cough, inspiratory crackles, reticular, or nodular opacities |
| Anti-tumour antibiotics | Mitomycin C | Acute bronchospasm (4–6%)<br>Acute lung injury due to diffuse alveolar damage (6–8%)—high $FiO_2$ contributes to the risk<br>Interstitial pneumonitis (<5%)<br>Thrombotic microangiopathy and acute respiratory failure |

motherapy and pulmonary symptoms is often revealed by the patient and is a vital clue for possible pulmonary toxicity. The severity of the condition can be assessed by patient-reported changes in effort tolerance and grading of the dyspnoea experienced by the patient at rest or during exercise. Presence of fever and productive cough may indicate an infective aetiology. Cancer-related to mass effects and metastasis can be ruled out by reviewing the oncologist's notes and radiologic findings. As systemic glucocorticoid therapy has shown to be of some benefit in chemotherapy-related pneumonitis/toxicity, symptomatic patients may be referred to a pulmonologist for evaluation and initiation of therapy. The systemic examination should include signs of breathing difficulties like respiratory rate, use of accessory muscles, and nasal flaring. Chest auscultation is often unremarkable; crackles may be present in some instances. A quick surrogate pulmonary function test like breath-holding time > 25 sec may be used in the outpatient department or at the bedside to screen and identify patients at risk.

Patients receiving bleomycin often will have a baseline PFT and/or DLCO done before the initiation of treatment. Few patients also undergo serial PFTs and DLCO monitoring during treatment. A review of these is immensely helpful to ascertain or rule out the possibility of chemotherapy mediated lung toxicity. Repeat testing is indicated if there is significant worsening or new onset of symptoms. The role of PFT values like FEV1, FVC, and peak expiratory flow in predicting complications in lung resection surgeries is well recognised. The FEV1 and DLCO <30% have been predicted as the risk of increased perioperative complications for lung resections [43, 44]. However no such consensus exists for non-cardiothoracic surgeries. However, dynamic testing with CPET has shown to be predictive of outcomes after non-cardio-thoracic surgeries. Chest X-rays in such patients reveal basal reticular opacification and blunted costophrenic angles. At times these patients also present with fine nodular densities on imaging which may progress to consolidation and honeycombing. On an HRCT of the chest, it may be evident as ground-glass opacities in dependent locations, extensive reticular markings at the periphery. Organising pneumonia may present as subpleural nodules which may mimic metastases.

Perioperative management:

Although no direct evidence exists, supervised pulmonary prehabilitation is likely to benefit patients with pulmonary toxicity of chemotherapy especially in those undergoing thoracic or upper abdominal surgeries. This may include steam inhalation, respiratory muscle training, deep breathing exercises, incentive spirometry, smoking cessation. CPET guided prehabilitation programmes have shown to

improve postoperative recovery [45, 46] but it must be weighed against the risk of cancer progression.

Exacerbation and worsening of bleomycin lung toxicity due to perioperative oxygen supplementation or hyperoxia has been a significant cause of concern and debate. It all began in 1979 when Goldliner et al. reported 5 patients at a single institution who received bleomycin and were administered $FiO_2 > 39\%$ intraoperatively, developed ARDS and died [47]. Subsequently, a perioperative protocol was developed with perioperative oxygen restriction and judicious fluid administration. Thirteen patients who then underwent surgery did not have any pulmonary complications [48]. Subsequently, La Mantia et al. presented a different story and reported a series of 16 patients who received $FiO_2$ above 40% and had an uneventful perioperative course [49]. The patients who had received bleomycin and underwent resection surgery developed minor pulmonary complications only when $FiO_2 > 40\%$ [50, 51]. In these reports the occurrence of severe pulmonary compromise was seen in only very few patients and no meaningful concern of increase oxygen supplementation was reported. The threshold of $FiO_2$ beyond which the risk of exacerbation of bleomycin toxicity increases or the interval after bleomycin treatment when the patient is at high risk is still unknown.

The guiding principles of oxygen therapy in the perioperative care of patients who had received bleomycin need to be individualised. The most sensitive indicator of subclinical pulmonary toxicity of bleomycin is single breath DLCO. The decrease in DLCO by 10–15% is clinically significant. Patients without any major risk factors may be administered oxygen as per need. However, patients with the presence of risk factors should be administered lowest possible $FiO_2$ and $SpO_2$ of 88–92% is acceptable. The use of steroids may have some benefit and thus may be considered wherein oxygen supplementation is required.

Other measures to be followed in the patient who received bleomycin which has shown to reduce pulmonary complications after surgery [52] should also be employed to reduce the further lung damage. These include:

(a) Lung protective ventilation: The strategies need to be followed with tidal volumes of 6 mL/kg and airway pressures to <30 $cmH_2O$. The judicious use of PEEP has also been shown to reduce lung injury.
(b) Avoidance of hypervolemia: Overzealous fluid administration especially in thoracic procedures is a risk factor for ARDS. Optimal fluid administration may be guided by cardiac output and arterial waveform monitoring.
(c) Analgesia: The multimodal optimal analgesia maintains the lung function as such and should be ensured.
(d) Postoperative lung expansion: The strategies like pulmonary physiotherapy including deep breathing exercises, incentive spirometry, etc. need to be started preoperatively and continued in the postoperative period. In patients, who are either unable to perform these activities or have lung compromise, application of non-invasive respiratory support is useful.

### 4.5.3 Gastrointestinal System

Gastrointestinal toxicity is a common complication of chemotherapy with most anti-neoplastic agents. The common manifestations include nausea, vomiting, diarrhoea, and mucositis. These toxicities including mucositis not only cause patient discomfort but also compromise the nutritional status of the patient. Thus, owing to these complications, systemic chemotherapy combined with other factors like chronic inflammation, biochemical, and mass effects of cancer leads to the development of nutritional deficits in cancer patients. The spectrum may range from minor weight loss to severe cachexia. This is discussed in detail elsewhere in the text.

It is not surprising then that dehydration may be present in patients who have undergone chemotherapy. Fluid and electrolyte correction may be needed preoperatively. Rapid sequence induc-

tion may be considered in patients who are prone to vomiting. Oro-pharyngeal trauma during laryngoscopy in the presence of mucositis can cause severe bleeding and result in a catastrophic airway situation.

Abnormal liver function tests are common in patients who have undergone chemotherapy. Most of such instances will be inconsequential increases in liver enzymes or bilirubin. Occasionally a patient presenting for surgery may have markedly altered liver function directly attributable to the toxic effects of chemotherapy (methotrexate—liver fibrosis, cirrhosis; cyclophosphamide—diffuse hepatocellular damage). The various anaesthetic drugs and their dosages need to be modified as per the severity of hepatic dysfunction.

### 4.5.4 Renal System

The various chemotherapeutic agents like platinum-based agents cause renal toxicity (both acute and chronic). Carboplatin and oxaliplatin are less nephrotoxic compared to cisplatin with equal anti-neoplastic activity in most cases. The pathogenesis is multifactorial, including the increased renal concentration of the drug, renal vasoconstriction and inflammation [53]. This was before the use of intensive hydration regimens. Currently, the incidence is around 30% [54]. Both the incidence and severity of renal failure increase with subsequent courses and may become irreversible. Cisplatin is usually discontinued progressive renal impairment. Most patients typically develop non-oliguric acute kidney injury. Few will have a progressive renal failure, while others will show resolution over weeks. Hypomagnesemia may occur due to urine magnesium wasting in many patients with cisplatin nephrotoxicity. Concomitant hypocalcaemia or hypokalemia may also be present. Hypomagnesemia produces neuro-muscular signs like tremors, spasms, and seizures. On ECG QT prolongation may be noted which may progress to torsades de pointes and ventricular arrhythmias. Limiting the dose of cisplatin appears to be the foremost factor in preventing cisplatin-induced renal toxicity. Hydration regimens with intravenous saline, often with potassium or magnesium supplementation are also often employed. Amifostine is an organic thiophosphate that has renal protective action by donation of a thiol group. It is used as a prophylactic agent to prevent renal toxicity due to cisplatin. Other agents like sodium thiosulphate, N-acetylcysteine, theophylline, and glycine have all been used to prevent renal injury [55].

Other drugs which cause renal damage include methotrexate (intratubular precipitation related renal damage), mitomycin C (microangiopathic haemolytic anaemia, renal failure), ifosfamide (proximal tubular abnormality), and cyclophosphamide (haemorrhagic cystitis).

#### 4.5.4.1 Perioperative Implications

- Previously undetected subclinical renal injury may get unmasked in the perioperative period due to the effects of acute blood loss and hypoperfusion. Careful assessment of renal function and employment of renal protective strategies in the perioperative period mitigate the risk to a significant extent.
- Blood urea nitrogen, creatinine, and serum electrolytes should be done routinely. Assessment and correction of dehydration and electrolyte abnormalities preoperatively are vital.
- For patients with established acute or chronic renal injury, standard anaesthetic precautions must be taken. Dose modifications of anaesthetic drugs will be needed.
- Maintenance of normovolemia along with avoidance of nephrotoxic drugs in the perioperative period (e.g. NSAIDs, antibiotics) helps to mitigate the risk for AKI.

### 4.5.5 Nervous System

Chemotherapy can also have toxic effects on the human nervous system, complicating anaesthesia and perioperative management. The vincristine and cisplatin remain the most common chemotherapeutic agents that cause neurotoxicity.

The vinca alkaloid vincristine can cause severe and debilitating neuropathy. It is probably the only agent with neurotoxicity as the dose-limiting toxicity. The mechanism of neuropathy is the disruption of axonal microtubules and involves both sensory and motor fibres [56]. Initial symptoms are in the form of paresthesias in the fingertips and feet and muscle cramps. Pain and mild distal weakness may or may not be seen. Loss of deep tendon reflexes especially knee jerk and ankle jerk may be present at this stage. Symptoms generally develop after weeks of treatment, however, it may also be seen after the first dose or even develop after discontinuation of the drug. Symptoms may progress with or without additional exposure and may result in proximal parenthesis, gait and motor abnormalities, and seizures. Occasionally severe motor weakness with foot and wrist drop or profound sensory loss may also be seen. Mononeuropathies may develop and could involve cranial nerves. Usually, the oculomotor nerve gets involved but others such as the recurrent laryngeal, facial, auditory, or the optic nerve may also get involved.

Cisplatin has a neurotoxic effect as well along with nephrotoxic effect. The usual manifestation includes peripheral neurotoxicity (primarily large myelinated sensory affecting dorsal root ganglia), ototoxicity, and encephalopathy. Symmetrical sensory neuropathy with subacute development of numbness, paresthesias (abnormal sensations), and pain sometimes which ascends proximally and decreased. Decreased vibratory sensitivity in the toes and loss of ankle jerks may be the earliest signs.

Methotrexate can also cause acute, subacute, and chronic neurotoxicities. This may be manifested as aseptic meningitis, transverse myelopathy, and acute and subacute encephalopathy. Intrathecal methotrexate is often administered to treat leptomeningeal metastases and as prophylaxis in haematological malignancies. It is associated with aseptic meningitis, seizures, and focal neurological deficits.

Paclitaxel, and to a lesser extent docetaxel are associated with a predominantly sensory peripheral neuropathy. It presents as burning paresthesias in distal limbs with loss of tendon reflexes. Other features include perioral numbness, autonomic neuropathies, and seizures. Cytarabine administration in high doses may lead to the acute cerebellar syndrome that begins with somnolence and encephalopathy within days of administration. Ifosfamide and 5 fluorouracil can also cause cerebellar dysfunction, encephalopathies, and extrapyramidal abnormalities.

Perioperative considerations:

(a) Patients who have received neurotoxic chemotherapeutic agents need a detailed assessment including history and clinical examination. Many perioperative factors may lead to the worsening of neurological condition and hence baseline documentation is an absolute must. Signs and symptoms of autonomic neuropathy if present should be recognised. Various physiological tests directed at heart rate and blood pressure variations during standing up from sitting position, Valsalva manoeuvre, deep breathing, and sustained handgrip may be used to ascertain the diagnosis.
(b) Regional anaesthesia is a relative contraindication in the presence of neurological deficits. It may cause worsening of a subclinical unrecognised neuropathy or flaring of existing neuropathy. In case a regional block is desirable, the documentation of neurological status needs to be done and follow-up should be comprehensive.
(c) Several anaesthetic drugs have adverse effects related to the nervous system. Succinylcholine administration in patients with motor neuropathy and related muscle wasting may lead to rhabdomyolysis and life-threatening hyperkalemia. Judicious use of benzodiazepines and thiopentone is helpful in patients with seizures and drugs like tramadol and atracurium should be avoided as they may induce seizures in susceptible individuals.
(d) Perioperative hypotension and hypoxia can both lead to worsening of neurological status and should be carefully managed.

(e) Patients with autonomic neuropathy are prone to extreme haemodynamic response to laryngoscopy and intubation, surgical stress, and blood loss. These patients also often have autonomic gastroparesis and are at increased risk of aspiration. Adequate fasting times and prokinetic premedication along with rapid sequence intubation may be employed.

### 4.5.6 Haematopoetic System

Adverse effects on the bone marrow and peripheral blood cells are caused by most chemotherapy agents. Myelosuppression may affect any or all cell lines. Anaemia is a common occurrence in cancer patients. The reduced oxygen-carrying capacity of blood could cause several complications in the perioperative period. Blood transfusion itself is associated with numerous adverse effects. Of special concern in the oncologic population is transfusion-related immune-modulation which may contribute to cancer recurrence. Thus a balanced approach with restrictive transfusion thresholds, nutritional prehabilitation, and use of haematinics for prehabilitation, blood salvage techniques, and transfusion of leuko-depleted PRBCs should be adopted.

Leukopenia and neutropenia are fairly common in the initial weeks after chemotherapy. Although usually elective surgeries are usually not performed during this period, occasionally emergent or urgent procedures may be performed in a neutropenic patient. Severe and often refractory infections may occur leading to sepsis, multiorgan failure, and eventually death. Careful attention to aseptic precautions is necessary. Prophylactic antibiotics are usually administered in the perioperative period.

Thrombocytopenia is also frequently encountered in the pre-anaesthetic assessment. Guidelines often refer to thresholds of 50,000/$mm^3$ for general surgeries and 1,00,000/$mm^3$ for surgeries of closed cavities like ophthalmic and neurosurgeries. A count of 80,000/$mm^3$ is considered 'safe' for neuraxial anaesthesia but this is largely anecdotal.

## 4.6 Anaesthetic Effects of Radiation Therapy

### 4.6.1 Basic Principles of Radiation Therapy (RT)

The utility of radiotherapy to treat cancer was first described over a century ago. Since then the technology and its understanding and implications in oncology have grown leaps and bounds. Increasingly, RT has been used before or after surgery and other systemic therapies in a combined fashion for a wide range of malignancies to maximise tumour control and quality of life while minimising toxicity and preserving the organs.

RT primarily works by inflicting damage to the DNA of cancer cells by delivery of ionising radiation which results in broken atomic and molecular bonds. The therapeutic basis lies in the fact that normal cells have intact mechanisms to identify and repair DNA damage which many cancer cells do not, thus resulting in cell death.

Various techniques of radiotherapy are used clinically:

1. External beam radiation therapy (EBRT): It is the most common approach and includes delivery of radiation from a source outside the patient. Radiation may be produced by the decay of radioactive substances like cobalt or by the electronic acceleration of charged particles like electrons or protons. Linear accelerators have replaced cobalt and have become the most used modality in recent times. Anatomical determination of the radiation field along with the dose as the schedule of treatment is 'planned' before the actual treatment. Using high definition imaging studies like CT or MRI for planning, 3-dimensional conformed radiation beams are delivered to minimise tissue toxicity.
2. Brachytherapy provides radiation therapy using the catheter to deliver the dose to the desired area. This technique allows the delivery of dose to the dedicated tumour lesion only and surrounding normal tissues are

spared. It is mostly used in cancers of the prostate, cervix, vagina, and breast.

3. Stereotactic radiotherapy refers to the administration of the full dose of radiation in a very limited number of fractions using high-resolution imaging to delineate the tumour and its surroundings.

#### 4.6.1.1 Adverse Effects of Radiation [57, 58]

RT can lead to various treatment-related side effects which depend on the anatomic area, cumulative dose, dose per fraction, and tissue sensitivity. These adverse effects have been classically described as acute and late effects. The acute effects of RT are related to the cellular response to radiation exposure and it may be dose-limiting. Acute effects are predominantly caused due to loss of reproductive capacity of cells, thus interfering with the cellular turnover. Thus it primarily involves tissues with a rapid cell turnover like mucosa, skin, and bone marrow. Oral and pharyngeal mucosa is affected early. Erythema is often seen after 1 week of treatment. This may progress in following weeks through various stages of mucositis—from small patches to confluent or ulcerated areas. Salivary glands are also affected and the volume and composition of saliva are altered. Decreased volume and pH lead to altered mucosal flora and predispose to dental caries. Skin reactions like desquamation and altered colour may be seen. Gastrointestinal mucositis associated with diarrhoea is also commonly seen in the weeks following RT of abdominal or pelvic cancers.

Late effects of RT may be caused by tissue fibrosis, damaged microvasculature, obstructed lymphatics, or stem cell depletion. Fibrosis of the subcutaneous tissues of head and neck areas and masticatory muscles are of particular importance to the anaesthetist. The tissues may develop a woody texture with limited movement along with trismus. Xerostomia may develop and may be irreversible at a higher dosage. Irradiation of the spinal cord may result in transverse myelitis like syndrome, usually with sensory symptoms. The condition may progress and also show motor symptoms. Thyroid dysfunction may be seen due to direct effects or secondary effects on the hypothalamic-pituitary axis. Radiation-induced changes on various organ systems are summarised in Table 4.3.

**Table 4.3** Toxicity of radiation therapy on various organ systems

| Organ | Effects |
|---|---|
| Skin | Early effects: Erythema followed by_ desquamation and ulceration<br>*Late effects include*: Atrophy, contraction, radiation fibrosis, and telangiectasia |
| GIT | Acute mucositis often causes diarrhoea and gastritis; if occurs<br>Late effects: Mucosal ulceration, atrophy, fibrosis, necrosis |
| Nervous system | Risk if higher in doses more than 50 Gy<br>Early reaction (6 months): Demyelination in the CNS. Brain (somnolence); spinal cord (Lhermitte's syndrome)<br>Later reaction (1–2 years): Radiation-induced CNS necrosis, initially in white matter; telangiectasias, focal haemorrhage |
| Lung | Radiation pneumonitis: 2–6 moths<br>Lung fibrosis: Late (6 months to years) |
| Kidneys | Radiation nephropathy: Proteinuria, hypertension, usually develops late |
| CVS | Pericarditis (6 months–2 years); settles spontaneously<br>Cardiomyopathy: Decreased ventricular ejection; conduction blocks (10–20 years) |

#### 4.6.1.2 Airway Changes Due to Radiation [59, 60]

RT produces a gamut of changes involving the airway. Patients with head and neck cancers frequently present for surgery post radiation therapy. During the acute phase, radiation-induced oedema and mucositis may lead to a difficult airway situation even in patients with otherwise normal airways. Mucosal injuries and bleeding may be severe due to the presence of inflammation. Oedema of the oropharynx, vocal cords, and other peri-glottic structures make visualisation difficult. Oedema of the tongue may also lead to difficult laryngoscopy and also result in airway obstruction. The Mallampati classification may also be falsely obscured.

Longer-term changes of the airway and associated structures are responsible for most of the difficult airway situations encountered due to effects of radiation. Many different structures

may be involved including the mucosa, temporomandibular joint, muscles of mastication, tongue, dentition, the floor of the mouth, body structures, pharyngeal and laryngeal areas, and the trachea. Thus due to varying involvement of the different structures, each patients' airway is unique and has its own set of challenges. Difficult mask ventilation may result from ulcerations and fistulae in the face and buccal mucosa, loss of dentition, osteonecrosis of the mandible. Osteonecrosis of the mandible is a relatively rare complication caused due to disruption of intraosseous blood supply resulting in the non-vital bone. This leads to trophic changes in the bone and demise of osteocytes and destruction of the bone matrix. Secondary infection of the necrosed area may be severe and protracted. This ultimately results in a reduction of mandibular space, difficult mask ventilation, and laryngoscopy. Long-term fibrosis of various structures poses various kinds of threat. Fibrosis of the TMJ and facial muscles may lead to reduced mouth opening. Glossomegaly and fibrosis of floor of mouth result in limited tongue mobility and can cause difficult visualisation of the glottis. Fibrosis and oedema of the suprahyoid region lead to thickening and stiffness of neck tissue and limited mobility. The mobility of the larynx is also compromised rendering external manipulation to optimise the view almost impossible. Video laryngoscopes are an essential aid for limited mouth opening and reduced working space in the airway. The CMAC D blade is very useful in cases with an anterior and fixed larynx.

#### 4.6.1.3 Pulmonary Effects of Radiation [61, 62]

Radiation-induced lung injury (RILI) was first described over a century ago soon after the development of X-rays. Today a vast body of literature exists about the development of RILI, risk factors, pathological mechanisms, clinical presentation, diagnosis, and treatment.

RILI results from the combination of direct cytotoxic effects and radiation-induced fibrosis. Several biochemical pathways have been described including proinflammatory cytokines, interleukins, platelet-derived growth factor, and interferon-gamma.

Two separate entities, namely radiation-induced pneumonitis and radiation-induced fibrosis are recognised. The immediate phase begins within hours to days following radiation exposure characterised by hyperaemic and congested mucosa, leukocyte infiltration, increased capillary permeability, and oedema. Tracheobronchial secretions increase and degenerative changes are seen in the alveolar epithelium. This is followed by the accumulation of thick secretions due to ciliary dysfunction. After weeks of exposure, radiation pneumonitis ensues. It consists of sloughing of endothelial and epithelial cells. Narrowing of capillaries and thrombosis can also be present. A fibrin rich exudate leaks into the alveoli and results in hyaline membrane formation. Following this, there may be a resolution of pneumonitis or migration of fibroblasts and collagen deposition and thickening of the interstitium. Within months a final phase of fibrosis ensues and may progress for years. Anatomic narrowing of alveolar spaces results in reduced lung volumes, traction bronchiectasis, and chronic infections. Symptoms include cough, dyspnoea, fever, chest pain. Auscultation may be normal or crackles may be heard over the affected area. Chest X-ray may show perivascular haziness progressing to patchy densities. CT is considered superior to conventional X-rays. Scans may reveal ground-glass opacities followed by patchy areas of consolidation. Fibrotic phase shows linear opacities or dense consolidations. On PFTs a restrictive pattern is seen. DLCO and resting $SpO_2$ may be reduced.

#### 4.6.1.4 Cardiac Effects of Radiotherapy [63, 64]

Toxic cardiac effects of radiotherapy may occur in patients with radiation for thoracic malignancies, especially Hodgkin's lymphoma. The toxicity is related to radiation dose, its volume, dose per fraction, and combined use of cardiotoxic chemotherapy. The myocardium is affected leading to its fibrosis and manifesting as restrictive cardiomyopathy. Conduction abnormalities may

also occur due to fibrosis and manifests as various conduction abnormalities and arrhythmias. An echocardiogram may detect diastolic dysfunction even in asymptomatic survivors. A myocardial infarction may be seen in these patients. Heart failure usually develops after years of exposure, especially in the setting of anthracycline-based chemotherapy. Coronary artery disease is a long-term complication seen in many survivors who have undergone thoracic radiation, especially in left-sided breast cancer. Valvular heart disease is relatively common in survivors who have received mediastinal RT. It may involve aortic, mitral, or tricuspid valves. Administration of antibiotics for endocarditis prophylaxis is required in the perioperative period.

## 4.7 Summary

- The global burden of cancer surgery is huge and is rising. Lack of an adequate number of comprehensive cancer centres results in the majority of cases being treated in general hospitals often in smaller towns and cities. Surgery for cancer may be required in various stages of the disease and many patients receive chemotherapy and/or radiotherapy before presenting for surgery.
- Systemic chemotherapy has widespread effects on all major organ systems which may complicate the perioperative course and are vital for the anaesthesiologist to be well versed with the same.
- Anthracyclines cause cumulative cardiotoxicity by the production of oxygen-free radicals. Classically it is defined as a symptomatic or asymptomatic drop in LVEF, but other features may include ECG abnormalities, arrhythmias, varying degrees of heart blocks, and pericarditis-myocarditis syndrome. All patients who have received anthracycline-based chemotherapy are considered high risk for perioperative adverse cardiac events.
- Bleomycin-induced lung injury is likely caused by reactive oxygen species. Tissue iron stores are also implicated in the pathogenesis. Early manifestations in the form of a symptomatic or asymptomatic reduction in PFT or DLCO values may progress to chronic lung fibrosis. These patients are at risk of exacerbation of lung injury due to perioperative hyperoxia. In the absence of any consensus, it may be prudent to limit oxygen supplementation until necessary.
- Direct or indirect gastrointestinal effects of chemotherapy include mucositis, diarrhoea, malnutrition, cachexia, and dehydration. Transient derangement of liver function is also fairly common. Methotrexate can cause hepatic fibrosis and cirrhosis. Cyclophosphamide can also cause diffuse hepatocellular damage.
- Cisplatin and to a lesser extent carboplatin frequently cause adverse effects in the kidneys. Most commonly a non-oliguric acute kidney injury is seen which may progress to chronic renal failure along with electrolyte abnormalities. Subclinical renal dysfunction may get exacerbated in the perioperative period. Proper hydration and avoidance of nephrotoxic agents help mitigate the risk.
- Vinca alkaloids cause sensory and motor neuropathies. Cisplatin typically involves large myelinated sensory fibres resulting in numbness and paresthesias in the hands and feet. Methotrexate, taxanes, cytarabine, and ifosphamide are all known to cause CNS dysfunction. Thorough documentation of neurological status preoperatively is a must. Regional anaesthesia is a relative contraindication in the presence of neurological deficits. Autonomic neuropathy should also be looked for and adequate precautions must be in place.
- Haematological toxicity is caused by almost all chemotherapy drugs and may affect any or all cell lines. Generally, elective surgery is performed after 6 weeks of chemotherapy which allows for recovery of blood counts. Emergent procedures may have to be carried out which warrants extra caution. Guidelines for blood and blood product transfusion, blood salvage techniques should be employed.
- Radiation therapy affects normal tissues as it does the malignant ones. Acute effects are

caused due to loss of the ability of rapid turnover in tissues like skin, mucous membranes, and bone marrow. Late effects are caused due to tissue fibrosis, damaged microvasculature, and lymphatics. Resulting changes in the airway, respiratory, and cardiac systems pose a considerable challenge in the perioperative period.

## References


1. Sullivan R, Alatise OI, Anderson BO, Audisio R, Autier P, Aggarwal A, et al. Global cancer surgery: delivering safe, affordable, and timely cancer surgery. Lancet Oncol. 2015 Sep 1;16(11):1193–224.
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC cancer base no. 11. Lyon, France. International Agency for Research on Cancer, 2013. http://globocan.iarc.fr.
3. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. N Engl J Med. 1998 Sep 24;339(13):900–5.
4. Singal PK, Iliskovic N, Li T, Kumar D. Adriamycin cardiomyopathy: pathophysiology and prevention. FASEB J. 1997 Oct 1;11(12):931–6.
5. Lyu YL, Kerrigan JE, Lin C-P, Azarova AM, Tsai Y-C, Ban Y, et al. Topoisomerase IIβ-mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by Dexrazoxane. Cancer Res. 2007 Sep 15;67(18):8839.
6. Schwartz RG, McKenzie WB, Alexander J, Sager P, D'Souza A, Manatunga A, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy: seven-year experience using serial radionuclide angiocardiography. Am J Med. 1987 Jun 1;82(6):1109–18.
7. Ewer MS, Ali MK, Mackay B, Wallace S, Valdivieso M, Legha SS, et al. A comparison of cardiac biopsy grades and ejection fraction estimations in patients receiving Adriamycin. J Clin Oncol. 1984 Feb 1;2(2):112–7.
8. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015 Jun 2;131(22):1981–8.
9. Sleijfer S. Bleomycin-induced pneumonitis. Chest. 2001 Aug 1;120(2):617–24.
10. Chandler DB, Barton JC, Briggs DD, Butler TW, Kennedy JI, Grizzle WE, et al. Effect of Iron deficiency on bleomycin-induced lung fibrosis in the hamster. Am Rev Respir Dis. 1988 Jan 1;137(1):85–9.
11. Martin WJ II, Kachel DL. Bleomycin-induced pulmonary endothelial cell injury: evidence for the role of iron-catalyzed toxic oxygen-derived species. J Lab Clin Med. 1987 Aug 1;110(2):153–8.
12. Lazo JS, Merrill WW, Pham ET, Lynch TJ, McCallister JD, Ingbar DH. Bleomycin hydrolase activity in pulmonary cells. J Pharmacol Exp Ther. 1984 Dec 1;231(3):583.
13. Delanoy N, Pécuchet N, Fabre E, Combe P, Juvin K, Pujade-Lauraine E, et al. Bleomycin-induced pneumonitis in the treatment of ovarian sex cord–stromal tumors: a systematic review and meta-analysis. Int J Gynecol Cancer [Internet]. 2015;25(9). Available from: https://journals.lww.com/ijgc/Fulltext/2015/11000/Bleomycin_Induced_Pneumonitis_in_the_Treatment_of.8.aspx
14. Martin WG, Ristow KM, Habermann TM, Colgan JP, Witzig TE, Ansell SM. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's Lymphoma. J Clin Oncol. 2005 Oct 20;23(30):7614–20.
15. Avivi I, Hardak E, Shaham B, Igla M, Rowe JM, Dann EJ. Low incidence of long-term respiratory impairment in Hodgkin lymphoma survivors. Ann Hematol. 2012 Feb 1;91(2):215–21.
16. Maher J, Daly PA. Severe bleomycin lung toxicity: reversal with high dose corticosteroids. Thorax. 1993 Jan 1;48(1):92–4.
17. White DA, Stover DE. Severe bleomycin-induced pneumonitis. Chest. 1984 Nov 1;86(5):723–8.
18. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2012 Oct 1;23(suppl_7):vii155–66.
19. Kim PY, Ewer MS. Chemotherapy and QT prolongation: overview with clinical perspective. Curr Treat Options Cardiovasc Med. 2014 Apr 15;16(5):303.
20. Gottdiener JS, Appelbaum FR, Ferrans VJ, Deisseroth A, Ziegler J. Cardiotoxicity associated with high-dose cyclophosphamide therapy. Arch Intern Med. 1981 May 1;141(6):758–63.
21. Cascella M. Preoperative cardiac evaluation and anesthetic considerations for cancer patients who underwent chemotherapy. Trends Anaesth Crit Care. 2017 Jun;14:9–18.
22. Sinclair R, Navidi M, Griffin S, Sumpter K. The impact of neoadjuvant chemotherapy on cardiopulmonary physical fitness in gastro-oesophageal adenocarcinoma. Ann R Coll Surg Engl. 2016 May 3;98(6):396–400.
23. West MA, Loughney L, Ambler G, Dimitrov BD, Kelly JJ, Mythen MG, et al. The effect of neoadjuvant chemotherapy and chemoradiotherapy on exercise capacity and outcome following upper gastrointestinal cancer surgery: an observational cohort study. BMC Cancer. 2016 Sep 2;16(1):710.
24. West MA, Parry MG, Lythgoe D, Barben CP, Kemp GJ, Grocott MPW, et al. Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery. Br J Surg. 2014 Aug;101(9):1166–72.
25. West MA, Lythgoe D, Barben CP, Noble L, Kemp GJ, Jack S, et al. Cardiopulmonary exercise variables are

associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. Br J Anaesth. 2014 Apr 1;112(4):665–71.
26. Moyes L, McCaffer C, Carter R. Cardiopulmonary exercise testing as a predictor of complications in oesophagogastric cancer surgery. Ann R Coll Surg Engl. 2014 Jan 1;96(1):86.
27. Levett DZH, Grocott MPW. Cardiopulmonary exercise testing for risk prediction in major abdominal surgery. Anesthesiol Clin. 2015 Mar;33(1):1–16.
28. Lurati Buse GA, Koller MT, Burkhart C, Seeberger MD, Filipovic M. The predictive value of preoperative natriuretic peptide concentrations in adults undergoing surgery: a systematic review and meta-analysis. Anesth Analg [Internet]. 2011;112(5). Available from: https://journals.lww.com/anesthesia-analgesia/Fulltext/2011/05000/The_Predictive_Value_of_Preoperative_Natriuretic.7.aspx
29. Karthikeyan G, Moncur RA, Levine O, Heels-Ansdell D, Chan MTV, Alonso-Coello P, et al. Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery?: a systematic review and meta-analysis of observational studies. J Am Coll Cardiol. 2009 Oct 20;54(17):1599–606.
30. Huettemann E, Junker T, Chatzinikolaou KP, Petrat G, Sakka SG, Vogt L, et al. The influence of anthracycline therapy on cardiac function during anesthesia. Anesth Analg [Internet]. 2004;98(4). Available from: https://journals.lww.com/anesthesia--analgesia/Fulltext/2004/04000/The_Influence_of_Anthracycline_Therapy_on_Cardiac.12.aspx
31. Owczuk R, Wujtewicz MA, Sawicka W, Wujtewicz M, Swierblewski M. Is prolongation of the QTc interval during isoflurane anaesthesia more prominent in women pretreated with anthracyclines for breast cancer. Br J Anaesth. 2004 May 1;92(5):658–61.
32. Zhang L, Zuo M, Ma X, Dong Y. Effects of neoadjuvant chemotherapy on minimum alveolar concentration values of sevoflurane and desflurane in patients with hepatocellular carcinoma complicated with jaundice. Oncol Lett. 2018 May 2 [cited 2018 Jul 29]; Available from: http://www.spandidos-publications.com/10.3892/ol.2018.8621
33. Du W, Li C, Wang H, Zhao A, Shen J, Yong F, et al. Effect of neoadjuvant chemotherapy on sevoflurane MAC-BAR value of patients undergoing radical stomach carcinoma surgery. Int J Clin Exp Med. 2015;8(4):5649–57.
34. Fazio G. Drugs to be avoided in patients with long QT syndrome: Focus on the anaesthesiological management. World J Cardiol. 2013;5(4):87.
35. Staikou C, Chondrogiannis K, Mani A. Perioperative management of hereditary arrhythmogenic syndromes. Br J Anaesth. 2012 May 1;108(5):730–44.
36. Annila P, Yli-Hankala A, Lindgren L. Effect of atropine on the QT interval and T-wave amplitude in healthy volunteers. Br J Anaesth. 1993 Nov 1;71(5):736–7.
37. Michaloudis DG, Kanakoudis FS, Petrou AM, Konstantinidou AS, Pollard BJ. The effects of midazolam or propofol followed by suxamethonium on the QT interval in humans. Eur J Anaesthesiol. 1996;13(4)
38. Yildirim H, Adanir T, Atay A, Katircioglu K, Savaci S. The effects of sevoflurane, isoflurane and desflurane on QT interval of the ECG. Eur J Anaesthesiol. 2004;21(7)
39. Chang DJ, Kweon TD, Nam SB, Lee JS, Shin CS, Park CH, et al. Effects of fentanyl pretreatment on the QTc interval during propofol induction. Anaesthesia. 2008 Sep 5;63(10):1056–60.
40. Johnston AJ, Hall JM, Levy DM. Anaesthesia with remifentanil and rocuronium for caesarean section in a patient with long-QT syndrome and an automatic implantable cardioverter-defibrillator. Int J Obstet Anesth. 2000 Apr 1;9(2):133–6.
41. Scheinin B, Scheinin M, Vuorinen J. Lindgren l. Alfentanil obtunds the cardiovascular and sympathoadrenal responses to suxamethonium-facilitated laryngoscopy and intubation. Br J Anaesth. 1989 Apr 1;62(4):385–92.
42. Gillies MA, Harrison EM, Pearse RM, Garrioch S, Haddow C, Smyth L, et al. Intensive care utilization and outcomes after high-risk surgery in Scotland: a population-based cohort study. Br J Anaesth. 2017 Jan;118(1):123–31.
43. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier J-P, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J. 2009 Jul 1;34(1):17–41.
44. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. Chest J. 2013;143(5_suppl):e166S–90S.
45. Sebio Garcia R, Yáñez Brage MI, Giménez Moolhuyzen E, Granger CL, Denehy L. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2016 Sep 1;23(3):486–97.
46. Bobbio A, Chetta A, Ampollini L, Primomo G, Internullo E, Carbognani P, et al. Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. Eur J Cardiothorac Surg. 2008 Jan;33(1):95–8.
47. Goldiner P, Schweizer O. The hazards of anesthesia and surgery in Bleomycin-treated patients. Semin Iin Oncol. 1979;6:121–4.
48. Goldiner PL, Carlon GC, Cvitkovic E, Schweizer O, Howland WS. Factors influencing postoperative morbidity and mortality in patients treated with bleomycin. Br Med J. 1978 Jun 24;1(6128):1664.

49. LaMantia KR, Glick JH, Marshall BE. Supplemental oxygen does not cause respiratory failure in bleomycin-treated surgical patients. Anesthesiology. 1984 Jan 1;60(1):65–6.
50. Donat SM, Levy DA. Bleomycin associated pulmonary toxicity: is perioperative oxygen restriction necessary? J Urol. 1998 Oct 1;160(4):1347–52.
51. Aakre BM, Efem RI, Wilson GA, Kor DJ, Eisenach JH. Postoperative acute respiratory distress syndrome in patients with previous exposure to bleomycin. Mayo Clin Proc. 2014 Feb;89(2):181–9.
52. Marseu K, Slinger P. Perioperative lung protection. Korean J Anesthesiol. 2017 Jun;70(3):239–44.
53. Cvitkovic E, Spaulding J, Bethune V, Martin J, Whitmore WF. Improvement of cis-dichlorodiammineplatinum (NSC 119875): Therapeutic index in an animal model. Cancer. 1977 Apr;39(4):1357–61.
54. Madias NE, Harrington JT. Platinum nephrotoxicity. Am J Med. 1978 Aug 1;65(2):307–14.
55. Crona DJ, Faso A, Nishijima TF, McGraw KA, Galsky MD, Milowsky MI. A systematic review of strategies to prevent cisplatin-induced nephrotoxicity. Oncologist. 2017 May;22(5):609–19.
56. Legha SS. Vincristine neurotoxicity. Med Toxicol. 1986 Dec 1;1(6):421–7.
57. William M Mendenhall NB. A literature review of late complications of radiation therapy for head and neck cancers: incidence and dose response. J Nucl Med Radiat Ther [Internet]. 2013 [cited 2018 Jul 30]; Available from: https://www.omicsonline.org/a-literature-review-of-late-complications-of-radiation-therapy-for-head-and-neck-cancers-incidence-and-dose-response-2155-9619.S2-009.php?aid=9168
58. Barnett GC, West CML, Dunning AM, Elliott RM, Coles CE, Pharoah PDP, et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer. 2009 Feb;9(2):134–42.
59. Tolentino E d S, Centurion BS, Ferreira LHC, de Souza AP, Damante JH, Rubira-Bullen IRF. Oral adverse effects of head and neck radiotherapy: literature review and suggestion of a clinical oral care guideline for irradiated patients. J Appl Oral Sci. 2011;19(5):448–54.
60. Balakrishnan M, Kuriakose R, Koshy RC. Radiation induced changes in the airway—anaesthetic implications. South Afr J Anaesth Analg. 2004;10(2):19–21.
61. Ghafoori P, Marks LB, Vujaskovic Z, Kelsey CR. Radiation-induced lung injury. Assessment, management, and prevention. Oncol Williston Park N 2008 Jan;22(1):37–47; discussion 52-3.
62. Giridhar P, Mallick S, Rath GK, Julka PK. Radiation induced lung injury: prediction, assessment and management. Asian Pac J Cancer Prev. 2015 Apr 14;16(7):2613–7.
63. Menezes KM, Wang H, Hada M, Saganti PB. Radiation matters of the heart: a mini review. Front Cardiovasc Med [Internet]. 2018 Jul 9 [cited 2018 Jul 31];5. Available from: https://www.frontiersin.org/article/10.3389/fcvm.2018.00083/full
64. Aleman BMP, van den Belt-Dusebout AW, De Bruin ML, van't Veer MB, Baaijens MHA, de Boer JP, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood. 2007 Mar 1;109(5):1878.