Squamous Cell Carcinoma of the Oesophagus: The Indian Experience

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Abstract

Oesophageal cancer is a relatively common cancer among both men and women and is the fourth most common cause of cancer-related deaths in India. Squamous cell carcinoma is the most common histology (80 %) although there has been a recent relative increase in the incidence of adenocarcinoma. Aetiological factors for oesophageal squamous cell carcinoma (OSCC) in India are unique and include alternative forms of tobacco consumption, alcohol, tea drinking, nutritional and dietary factors and possibly human papillomavirus (HPV) infection. Most patients present with advanced stage of disease and in poor general health at the time of diagnosis. Diagnostic and staging workup of OSCC in India is similar to other countries though the use of PET–CT and endoscopic ultrasonography is not universal. The treatment of early stage disease (T1/T2 and N0) is primarily surgery alone, while for patients with more advanced, resectable disease (T3/T4a or N+), the treatment is usually neoadjuvant chemotherapy or chemoradiotherapy followed by surgery. Unresectable or metastatic disease is treated with palliative radiotherapy or oesophageal stenting. Surgical technique is widely variant with both transthoracic and transhiatal oesophagectomies being performed along with minimally invasive oesophagectomy depending on the specialization and expertise of the surgeon. Research on oesophageal cancer has focused on epidemiology, aetiological factors, primary treatment options, neoadjuvant and adjuvant therapy, surgical techniques, perioperative care and palliative treatment. The formation of the Indian Society for Diseases of the Esophagus and Stomach (ISES) is expected to promote collaborative research and standardization of treatment across the country.

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16.1 Introduction

Oesophageal cancer is a morbid disease and, globally, is a major cause of cancer-related deaths [1]. Worldwide, squamous cell carcinoma is the most common type of oesophageal cancer although there has been an exponential increase in the incidence of adenocarcinoma in the western world in the past three decades [2–5]. The overall disease spectrum has unique geographic distribution with squamous cancers being common in Asia (countries like China, Iran, India, Japan and Korea) and adenocarcinomas of the gastro-oesophageal junction and lower oesophagus in North America and Europe [3–5].

16.2 Epidemiology, Aetiology, Diagnosis and Staging of Squamous Oesophageal Cancer in India

16.2.1 Epidemiology of Oesophageal Cancer in India

In India, oesophageal cancer is the fourth most common cancer in males and the fifth most common cancer in females, with an estimated incidence of over 48,000 new cases in 2008 [2]. It is also the fourth most common cause of cancer-related deaths in India [2]. As in most parts of Asia, the majority of oesophageal cancers in India are squamous cell carcinoma [6, 7] although there has been a recent increase in the incidence of adenocarcinoma [8]. In a retrospective study [9] involving 1,000 oesophageal cancer patients over a 16-year period, patients were divided into four cohorts of 4 years each. Lower oesophageal cancers outnumbered the mid-oesophageal cancers in the fourth cohort though mid-oesophageal cancers represented the most common site of malignancy overall. However, there have been no systematic prospective studies on the changing epidemiology and histopathological profile of oesophageal cancer in India. Regional variations in the incidence of oesophageal squamous cancer have been observed in India with markedly higher rates seen in the Kashmir Valley [10] and northeastern India [11]. Overall, approximately 80 % of all oesophageal cancers in India are squamous cancers, with 20 % being adenocarcinomas.

16.2.2 Aetiology

The common risk factors for oesophageal squamous cell carcinoma (OSCC) in India include smoking, alcohol consumption, the combination of both, low socio-economic status, deficiency of micronutrients, dietary factors and intake of hot

beverages. Various case–control and other studies from certain areas of high incidence in India, such as the Kashmir Valley, demonstrate that there are unique risk factors in these areas for the development of oesophageal squamous carcinoma [12–17]. There have been several other studies from virtually all parts of the country evaluating various risk factors including tobacco, alcohol, tea drinking and other nutritional factors [11, 18–26].

16.2.2.1 Tobacco Consumption

Tobacco consumption in India is peculiar in the sense that smokeless tobacco use is far more prevalent than smoked tobacco. A number of smokeless tobacco products are popular and freely consumed across all age groups in India [27]. In a survey of over 300,000 adults, 30 % used tobacco in some form with over 20 % using chewed tobacco or pan masala. Chewed tobacco is considered to be one of the important risk factors for squamous oesophageal cancer [11, 18–21]. In a case–control study of 702 cases and over 1,600 controls, Dar and colleagues found that cigarette smoking was not a major risk factor for oesophageal cancer in the Kashmir Valley [17]. However, the consumption of smokeless tobacco (nass) and hookah smoking were associated with a significantly increased risk [17]. Nass chewing had an increased risk of oesophageal squamous cancer with an OR of 2.88. Ever-hookah smoking was associated with an increased risk of OSCC (OR 1.85; 95 % CI 1.41–2.44). They also found association between the intensity, duration and cumulative amount of hookah smoking [17].

A study conducted in South India identified both smoked tobacco and chewed tobacco to be associated with an increased risk of squamous oesophageal cancer with risk ratios of 2.8 and 2.5, respectively [21]. Another study found a risk of 3.16 times associated with the consumption of betel leaf with tobacco and 1.95 times with bidi smoking [18]. In a case–control study of 343 cases and 686 controls, Nandakumar and colleagues [19] found that chewing areca preparations was associated with an increased risk of developing cancer in the middle third of the oesophagus; in contrast, chewing tobacco was associated with lesions in the lower third of the oesophagus [19]. A study from the northeastern state of Assam (which has among the highest rates of oesophageal cancer in India) found betel nut chewing to be associated with higher risks of developing oesophageal cancer when compared to smoking and alcohol consumption [11]. The adjusted odds ratios for persons who chewed betel nut more than 20 times a day in comparison with non-chewers were 13.3 for males and 8.4 for females [11]. A case–control study conducted at the authors' institute included 442 cases of oesophageal cancer and 1,628 hospital controls [20]. Data was collected on chewing, smoking, alcohol habits and dietary habits. The results indicated a moderate 1.1 times excess risk for chewers of pan (betel leaf) with tobacco, 1.8-fold excess risk for bidi smokers and twofold for cigarette smokers [20].

16.2.2.2 Alcohol

Alcohol consumption is not as common in India as it is in other parts of the world both in frequency and quantity of consumption [28, 29]; however, it is one of the

known etiological factors for oesophageal cancer in India. In a case–control study conducted in South India with more than 500 oesophageal cancer patients and over 1,700 controls, alcohol consumption was shown to increase the risk by more than three times [23]. A significant dose–response relationship was observed for the duration of drinking and average daily amount of alcohol consumption with OSCC. Among all types of alcohol analysed, arrack, a locally brewed preparation, showed the highest risk—4.5 times that of the controls [23]. The intake of other types of alcohol (gin, rum, whisky and brandy) did not show a significant increase of risk, but this might be related to the amount of alcohol consumed rather than the type as these types of alcohol cost much more than arrack. In another study conducted in South India, the risk was found to be 3.5 times higher with alcohol consumption [21]. In the study conducted in the authors' institute [20], alcohol was found to be associated with an increased risk of 1.8 times, while a case–control study carried out in Kerala showed an increased risk of 2.33 for regular alcohol use [24]. Almost all studies that have evaluated the role of tobacco, smoking and alcohol consumption have found an elevated risk of oesophageal cancer with the use of alcohol in the range of 1.8–3.5.

16.2.2.3 Dietary Factors

It is widely recognized that a diet high in vegetables, fruits and other plant-based foods and low in animal fats can reduce the risk of cancer [30]. In a case–control study conducted at the All India Institute of Medical Sciences, low consumption of green leafy vegetables, low consumption of other vegetables, and consumption of alcohol were the three factors that are associated with increased risk for oesophageal cancer [25]. Other researchers also found an increased risk with less consumption of green and leafy vegetables and fruits and consuming more of spicy, fried and hot food and beverages [18, 26]. A case–control study done in Assam found a positive association between increased risk of oesophageal cancer and the consumption of spicy food, hot foods and beverages while green leafy vegetables and fruits were protective for oesophageal cancer [11]. The risk associated with the consumption of locally prepared food items, e.g. kalakhar, was found to be eight times.

The consumption of salt tea has been associated with increased risk of oesophageal cancer in Kashmir, where 90 % of the cases had history of salt tea consumption [12]. The mechanism of carcinogenic activity of salt tea has been attributed to the presence of nitroso compounds, which get activated due to its peculiar method of brewing and the presence of salt. Hyperthermic injury to the oesophageal mucosa due to consumption at high temperatures may also be responsible [13]. The presence of higher levels of nitrosamines was found in the sun-dried vegetables and chillies, which are commonly consumed in Kashmir [31]. A study conducted in the authors' institute showed a fourfold higher risk with tea drinking [20]. They also found that the consumption of fresh fish was associated with a 20 % reduction in the risk.

A study conducted in Jammu with 200 case–control pairs evaluated the role of dietary characteristics as risk factors for oesophageal cancer [14]. Among the

dietary and lifestyle risk factors, snuff was highest (OR = 3.86, 95 % CI = 2.46–6.08) followed by salt tea (OR = 2.53, 95 % CI = 1.49–4.29), smoking (OR = 1.97, 95 % CI = 1.18–3.30), sun-dried food (OR = 1.77, 95 % CI = 1.10–2.85) and red chilli (OR = 1.76, 95 % CI = 1.07–2.89) [14]. Pickle consumption was associated with an odds ratio of 2.5 in a study conducted in South India [21].

16.2.2.4 Low Socio-economic Status

Studies have associated oesophageal squamous cell carcinoma risk with low socio-economic status. A case–control study was conducted to assess the association of multiple indicators of socio-economic status and oesophageal squamous carcinoma risk in the Kashmir Valley [15]. A total number of 703 histologically confirmed OSCC cases were matched with 1,664 controls with respect to age, sex and district of residence. Composite wealth scores were constructed based on the ownership of several appliances using multiple correspondence analyses. Higher education, living in a constructed house, use of liquefied petroleum gas and electricity for cooking and higher wealth scores showed an inverse association with oesophageal cancer risk. Compared to farmers, individuals who had government jobs or worked in the business sector were at lower risk of oesophageal squamous cancer. They also found an inverse association between poor oral hygiene and increased risk of oesophageal cancer, suggesting that oral hygiene could be used as a surrogate marker for socio-economic status [15].

16.2.2.5 Genetic Factors

A study from Kashmir [32] which analysed TP53 mutations in oesophageal SCC in 55 patients revealed the presence of mutations in 36.4 % (20/55) tumours. Another study analysed the interaction of various habit-related factors and polymorphism of GSTM1/GSTT1 genes towards inducing promoter hypermethylation of multiple tumour suppressor genes [33]. In 112 cases with 130 matched controls, significantly higher methylation frequencies were observed in tobacco chewers than non-chewers for the genes under study ($p < 0.01$) [33].

Other studies have also found a high rate of protein overexpression and alterations in p53 gene expression in subjects with oesophageal squamous cancer and correlated a higher expression with increased intake of chillies [34]. These results have been corroborated by other workers who showed that somatic chromosomal mutations, especially in exon 6 of Tp53 gene, among oesophageal cancer patients of an ethnically homogenous population of Kashmir Valley are closely related to continued exposure to various common dietary risk factors, especially hot salty tea, meat, baked bread and “Hakh”, that are rich in nitrosamines and familial cancer history [35].

16.2.2.6 Role of Human Papillomavirus (HPV)

The role of human papillomavirus as a causative factor for oesophageal cancer is unclear. Various studies have demonstrated the presence of HPV in oesophageal cancer specimens in the range of 15–80 % [36]. Few studies in India have also demonstrated moderate to high HPV positivity rate, although the results are

conflicting and the etiological role of this virus remains unclear. One small study evaluated the prevalence of HPV infection in OSCC tumour and adjoining mucosa in 23 patients with paired samples [37]. They found an HPV positivity rate of 87 % in oesophageal cancer patients and higher rates were seen in smokers [37]. Another study identified HPV DNA in 46 % of non-keratinizing squamous cell carcinomas of the oesophagus and in none of the keratinizing squamous cell carcinomas or adenocarcinomas postulating an aetiological association with this subtype of OSCC [38].

16.2.3 Diagnosis

Most patients in India present at advanced stages of disease [39, 40]. The available investigations for the diagnosis and staging of oesophageal cancer in India include a double-contrast barium swallow, upper gastrointestinal endoscopy and biopsy, contrast-enhanced computed tomography (CECT) scan of the thorax and upper abdomen, fused positron emission tomography–CT (PET–CT) scan, endoscopic ultrasonography (EUS) and fibre-optic bronchoscopy. The usual workup followed in India in the diagnostic and staging process of a patient suspected to have oesophageal cancer includes endoscopic mapping of the disease, histopathological confirmation and staging using contrast-enhanced computed tomography (CECT) of the thorax and abdomen. Additional diagnostic methods such as endoscopic ultrasound and positron emission tomography with or without computed tomography (PET/PET–CT) are used only in select institutions where the infrastructure and expertise are available. Fibre-optic bronchoscopy is used to rule out the involvement of the tracheobronchial tree in patients with upper and middle third tumours planned for curative treatment.

16.2.3.1 Barium Swallow

Barium swallow is the initial diagnostic investigation in many patients in India presenting with dysphagia. Although it gives information regarding the site, length and extent of the disease, it is not useful in obtaining a tissue diagnosis and a normal barium swallow can be misleading. Therefore, in the authors' institution, barium swallow is rarely performed in the diagnostic evaluation of patients with suspected oesophageal cancer. However, it is conventionally performed at a primary health centre level prior to an endoscopic diagnostic procedure.

16.2.3.2 Endoscopy

Flexible upper gastrointestinal endoscopy visualizing the oesophagus from the cricopharyngeal to the gastro-oesophageal junction, the stomach and the duodenum is essential to map the extent of the disease, aids in planning the treatment (surgery/intraluminal brachytherapy) and is helpful in obtaining a tissue diagnosis by biopsy of the abnormal areas and tumour. In the authors' institute and in several other centres, this is also used to simultaneously introduce a nasogastric tube for enteral feeding in patients with grade 3 or more dysphagia.

A number of studies have been done in India on cytological and histological diagnosis of oesophageal cancer on endoscopy. One study evaluated the utility of brush cytology and its correlation with biopsy in 100 patients with upper gastrointestinal symptoms [41]. Cytohistopathological correlation was found in more than 80 % of the cases and the study concluded that brush cytology was an effective method for evaluation and screening of upper gastrointestinal lesions and could be utilized for rapid diagnosis with minimal discomfort to the patient [41]. Two other studies compared the sensitivity and specificity of cytology and biopsy in establishing the diagnosis of oesophageal cancer [42, 43]. Both studies concluded that cytology increases the diagnostic efficacy but also emphasized that cytology alone cannot be used instead of histology due to a high false-positive rate [42, 43]. A small study evaluated 48 patients with carcinoma of the oesophagus to assess the optimal number of biopsy specimens required to obtain the highest yield [44]. Eight specimens were obtained from each patient; the first two specimens provided a positive diagnosis in 95.8 % of cases, and the fifth and sixth specimens increased the positive yield to 100 %.

16.2.3.3 Endoscopic Ultrasonography

Accurate staging of oesophageal cancer is essential to plan the treatment. EUS helps to delineate the different layers of the oesophageal wall and it is a useful staging modality in combination with CT and/or PET. EUS-guided FNA is useful to get a tissue diagnosis from suspicious lymph nodes such as the celiac. Complete EUS, however, may not be possible in patients with obstructive growths. Endoscopic mucosal resection can be performed for superficial oesophageal cancers restricted to the mucosa without involvement of the lamina propria. Loco regional staging of the tumour invasion and lymph node involvement done by EUS has shown to be superior to that by CT. The utility of EUS is not well established in the evaluation of the residual oesophageal disease after neoadjuvant chemotherapy or chemoradiation, as it cannot reliably differentiate between fibrosis due to inflammation and residual/recurrent disease. However, the use of routine EUS in all patients diagnosed with oesophageal cancer is debatable as the ability to influence treatment decisions in all cases is unproven. Moreover, due to limited availability of equipment and infrastructure, it is not performed in many centres.

16.2.3.4 Contrast-Enhanced Computed Tomography (CECT) Scan of the Thorax and Upper Abdomen

A CECT scan of the thorax and upper abdomen is widely accepted to be the minimum staging investigation for oesophageal cancer. CECT scanning in the pre-treatment assessment of oesophageal cancer in the Indian setting was found to be highly accurate in the determination of the tumour "T" stage, invasion of surrounding structures and distant metastases but not effective in the determination of the nodal involvement [45]. The diagnosis of invasion of the tracheobronchial tree was 96 % accurate, whereas the invasion of the aorta and pericardium could be predicted in more than 85 % of the cases. Previous studies also indicated the utility of computed tomography in patients undergoing surgery for oesophageal cancer [46, 47].

Table 16.1 Clinical usefulness and accuracy of modalities used in staging of oesophageal cancer

Modality	Clinical utility	Overall accuracy (%)
Computed tomography (chest, abdomen)	Invasion of local structures (airways, aorta)	≥90
	Metastatic disease	≥90
Endoscopy	Local tumour (T) staging (operator dependent)	80–90
Endoscopic Ultrasonography (with or without fine-needle aspiration of lymph nodes)	Local nodal (N) staging (operator dependent)	70–90
Positron emission tomography	Metastatic disease, assessing response to neoadjuvant therapy	≥90

16.2.3.5 Positron Emission Tomography (PET/PET–CT)

The addition of CT to PET has resulted in better specificity and sensitivity than either of the modalities alone, as the combined approach gives functional and morphological details in a single investigation. The treatment algorithm for locally advanced oesophageal cancer includes neoadjuvant therapy, either chemotherapy alone or in combination with radiotherapy, followed by surgery. Accurate staging is important to avoid unnecessary morbidity due to treatment and futile thoracotomies in metastatic disease. A small study evaluated 28 patients with oesophageal carcinoma with contrast-enhanced computed tomography followed by PET/CT after 2 weeks [48]. Nine patients were upstaged by PET/CT compared to CECT, out of which seven (25 %) were correctly upstaged and two (7.14 %) were falsely upstaged. They concluded that PET/CT improved their ability to detect distant metastases in 25 % of patients who were missed by CECT [48]. Unusual sites of metastases, such as muscular metastases, have been detected without any morphological evidence of disease [49].

The clinical utility and accuracy of various imaging modalities [50] in the diagnosis of oesophageal cancer are summarized in Table 16.1.

16.2.4 Staging

TNM staging is one of the most important and reliable prognostic variables. Standardised and accurate staging of cancer is important for uniform reporting and comparison of results from various centres. It also determines whether the intent of treatment is curative or palliative. It is based on clinical examination and information obtained by imaging: CT scan/PET–CT and/or endoscopic ultrasonography (EUS). The seventh edition of the AJCC TNM classification came into effect in 2009 [51].

Some of the key modifications from the sixth edition are:

1. Inclusion of gastro-oesophageal junction tumours and tumours in the proximal 5 cm of the stomach extending into the oesophagus.

2. T4 is subclassified as T4a (resectable cancer invasion) and T4b (unresectable cancer invasion).
3. N staging is subclassified based on the number of positive regional lymph nodes (N1, 1–2 nodes; N2, 3–6 nodes; and N3, $\geq$7 nodes).
4. M classification is redefined based on the presence of distant metastasis, and the term non-regional lymph node is eliminated.
5. Histological grade and tumour location are incorporated.
6. Separate stage grouping for adenocarcinoma and squamous carcinoma.

The new staging system has shown remarkable homogeneity within stage groups and excellent separation of survival curves between stages. The authors also welcome the separation of resectable (T4a) from unresectable (T4b) tumours. However, while the seventh edition is clearly superior in terms of prognostication, it is not ideal for baseline clinical staging or staging of patients who have undergone preoperative therapy. This is because the emphasis on nodal count rather than anatomic location and the introduction of histological grading make pre-resectional staging extremely difficult and highly likely to be inaccurate. Moreover, most of the data on which the stage grouping was based was drawn from western countries with a predominance of adenocarcinomas. Whether the same prognostic separation of the stage holds true for squamous oesophageal cancers remains to be seen.

16.2.5 The Tata Memorial Centre Experience

The authors' institution, the Tata Memorial Centre, is the largest tertiary level cancer centre in the country and is a high-volume centre for the treatment of oesophageal cancer. Between 1,200 and 1,300 new patients with oesophageal cancer are seen every year, most of them presenting in advanced stage of disease or in an emaciated condition, precluding potentially curative treatment. Squamous oesophageal cancers predominate in a ratio of 80:20 and the most common location of tumours is in the lower third of the oesophagus. The typical diagnostic workup of patients with a good performance status includes a detailed flexible fibre-optic upper gastrointestinal endoscopy with mapping of the disease and biopsy, PET–CT scan with contrast, pulmonary function tests with diffusion coefficient of carbon monoxide (DLCO) and cardiac evaluation. Flexible fibre-optic bronchoscopy is performed in patients with upper and middle third lesions and those with an obvious change of voice; endoscopic ultrasonography is done selectively for patients with low-volume disease on CECT scan (to confirm early disease amenable for upfront surgery) or in borderline resectable disease after neoadjuvant therapy. This diagnostic workup is curtailed in patients who are emaciated and not fit for radical therapy and in patients with obviously metastatic disease. Patients who are high risk for surgery due to co-existing co-morbidities undergo a thorough cardiopulmonary evaluation and are discussed in a special "high-risk multidisciplinary team" meeting by surgeons, intensivists and critical

care specialists, anaesthesiologists and pulmonary physicians to optimize them prior to surgery. The preferred therapeutic approach is discussed in a subsequent section of the chapter.

16.3 Treatment of Squamous Oesophageal Cancer in India

16.3.1 Treatment

India is a vast and populous country with significant resource constraints. The wide variation in the availability of facilities and technical expertise across different regions has made standardization of treatment a difficult process. While the establishment of 27 regional cancer centres across the country has partially addressed the issue, the urban–rural divide and between-centre variability of care are still considerable. Efforts by the authors' institute and the Indian Council of Medical Research (ICMR) have culminated in the establishment of uniform oesophageal cancer treatment guidelines tailored to the country's varied levels of expertise and availability of infrastructure. One of the core recommendations of the guidelines is the establishment of multidisciplinary teams for the management of oesophageal cancer. While some major cancer centres in India have a multidisciplinary team including a surgical, medical and radiation oncologist in place, several others do not, and one of the biggest challenges has been to ensure the same standards of care and decision-making regardless of whether the patient initially presents to a surgeon, gastroenterologist and medical or radiation oncologist.

16.3.1.1 Patient Evaluation

The initial evaluation of the patient includes the assessment of physical (ECOG performance) status, oral hygiene, nutrition and cardiopulmonary status. This is particularly important in the Indian scenario, where patients generally present in an advanced stage and in poor general health. Generally, only patients who are ECOG performance score (PS) 0 or 1 are selected for radical treatment. Assessment of oral hygiene is necessary because of the high prevalence of tobacco chewing in India [27, 29] and the possibility of co-existing oropharyngeal malignancy. Since most patients present with significant dysphagia and some degree of nutritional impairment, assessment of nutritional status and early institution of rehabilitation is key. The enteral route is the preferred route of nutritional rehabilitation due to its inherent advantages of keeping the gut in use, as well as the ease of administration and relatively low complication rate compared to parenteral nutrition [52]. All patients considered for radical treatment undergo extensive evaluation of cardiopulmonary status including pulmonary function tests (PFT), 2D echocardiography and, in select cases, stress cardiac testing. Pulmonary rehabilitation is started at the outset for all patients planned for radical treatment with the active involvement of the chest physician and physiotherapists. Early institution of chest physiotherapy and tobacco and alcohol cessation are routinely advocated as soon as a diagnosis of oesophageal cancer is made.

16.3.1.2 Principles of Management

Broadly, decisions regarding the treatment are based on the anatomical location and stage of disease and the performance status of the patient. The authors' repeated emphasis on the performance status of the patient is primarily because poor general health precludes potentially curative treatment in considerable proportion of patients in India. Concurrent radical chemoradiation is the preferred therapeutic strategy for lesions in the upper third of the oesophagus, i.e., within 5 cm of the cricopharynx, while surgery is the preferred treatment for lesions in the middle and lower third oesophagus. Early stage lesions (T1/T2, N0) are usually treated by surgery alone for middle and lower third lesions. Endoscopic mucosal resection (EMR), though a less morbid procedure, is not widely practised in India primarily due to the fact that very few patients present at a stage amenable to the procedure and also due to the limited availability of expertise in select centres across the country. Patients with locally advanced disease (T3/T4, N+) undergo multimodality treatment, generally with neoadjuvant chemotherapy [53, 54] or neoadjuvant chemoradiotherapy followed by surgery. Patients with metastatic disease are usually treated with palliative radiotherapy or oesophageal stenting or a combination of the two and rarely with palliative chemotherapy.

16.3.2 Surgery

Surgery is the preferred modality of treatment for middle and lower third oesophageal cancer [55–58]. Most patients in India with early stage disease (T1/T2, N0) are considered for upfront surgery while patients with locally advanced disease undergo surgery after neoadjuvant therapy. Rarely, patients with residual disease after radical chemoradiotherapy are taken up for oesophagectomy albeit at the cost of significantly higher post-operative morbidity. In spite of the established role of surgery in the radical treatment of oesophageal cancer, there is very little consensus on what constitutes a standard oesophagectomy in terms of approach, extent and template for lymph node dissection. This may, in part, be because there is no organ-specific surgical training program in India. Oesophageal resections in India are performed by surgeons from varied surgical specialties including general surgery [55, 56], gastrointestinal surgery [57], thoracic surgery [58] and surgical oncology [59].

16.3.2.1 Approach

Transthoracic oesophagectomy predominantly by a modified McKeown three-stage procedure is considered to be the standard approach by most thoracic surgeons and surgical oncologists while most general and gastrointestinal surgeons prefer a transhiatal approach particularly for lower third tumours [55–59]. In a large series of 367 transhiatal oesophagectomies performed over a period of 18 years at the All India Institute of Medical Sciences, the 5-year overall survival was 38 % with a post-operative mortality rate of 12 %. Since there is no strong evidence favouring one approach over the other, both approaches are widely practised in India with a

bias towards transthoracic approach in high-volume oncology centres. In these centres, transhiatal resection is performed in limited numbers as a compromise surgery in patients with poor pulmonary function or extensive pulmonary fibrosis precluding transthoracic resection.

16.3.2.2 Lymphadenectomy

Lymphadenectomy for oesophageal cancer is a controversial topic in India, as in many other parts of the world [60]. Surgical oncologists who predominantly perform transthoracic oesophagectomies place more emphasis on extensive lymph nodal clearance. Infracarinal nodal dissection or a standard two-field dissection is considered to be the standard template for dissection by most surgeons performing a transthoracic oesophagectomy. In India, very few centres with high volumes of oesophageal surgery practice three-field lymphadenectomy routinely. The increase in lymph node yield with more radical lymphadenectomy needs to be balanced against an increased post-operative morbidity, primarily with recurrent laryngeal paresis and pulmonary complications. In contrast, the lymph node yield achieved by a transhiatal resection is low and is usually limited to the perioesophageal lymph nodes. However, as mentioned in the previous section, transhiatal resections are usually performed only as a compromise surgery in high-volume centres.

16.3.2.3 Minimally Invasive Surgery

Surgeons in India were early to adopt minimally invasive oesophagectomy. A few high-volume centres have published data showing better results with a minimally invasive approach with respect to pulmonary morbidity and operative blood loss [57, 59, 61–63]. A prospective study comparing minimally invasive oesophagectomy with open oesophagectomy [63] demonstrated comparable results in terms of lymph node yield (9.5 vs 7.3), duration of surgery (312 vs 262 min), average blood loss (276 vs 313 mL) and morbidity (26.5 vs 28.6 %). A larger series [57] of 463 thoracoscopic oesophagectomies demonstrated a lower morbidity rate (16 %) and post-operative mortality rate (0.9 %). However, no long-term (survival) outcome data is available from any of these studies. Different surgical groups in India use different patient positions for thoracoscopic oesophagectomy with lateral, prone and, more recently, semi-prone positions being utilized based on surgeon preference. The prone or semi-prone position offers the advantage of not requiring lung isolation for thoracoscopy, whereas the lateral position offers better exposure to the superior mediastinum for radical lymph node dissection. The authors' preference is to perform MIS oesophagectomy through the lateral approach. Robotic surgery for oesophageal cancer has just started in India and is confined to few centres currently. A series of 32 robotic oesophagectomies [64] showed comparable results to thoracoscopic oesophagectomy. However, no distinct advantage over thoracoscopic oesophagectomy has been demonstrated.

16.3.2.4 Reconstruction

The stomach is the preferred conduit for reconstruction, and in cases where the stomach is not available, the colon, either the right or left side, is the preferred alternative. The posterior mediastinum is the most commonly used route of reconstruction, the retrosternal route being used only when the patient is being considered for post-operative radiotherapy to the mediastinum or when the surgeon adopts an abdomen-first approach to a transthoracic oesophagectomy. A small randomized study of 49 patients comparing posterior mediastinal versus retrosternal conduit placement [65] found both routes to have comparable outcomes. The anastomosis is usually performed in the neck either by a stapled or handsewn technique [66]. Both techniques are widely practised in India depending upon surgeon preference and cost constraints. Some clinical trials on anastomotic technique are described in a subsequent section of the chapter.

16.3.3 Multimodality Management

India was late to embrace multimodality management in oesophageal cancer. This may have been primarily because of the delayed establishment of multidisciplinary teams and also the fear that multiple modalities of treatment may not be well tolerated by the generally frailer Indian patients. In view of the strength of evidence supporting neoadjuvant therapy currently, patients with locally advanced potentially operable oesophageal cancer are treated with either neoadjuvant chemotherapy [53, 54] or neoadjuvant chemoradiotherapy. The common chemotherapy regimens include doublets consisting of cisplatin with 5-fluorouracil or cisplatin with paclitaxel, while few centres use triplets of cisplatin, 5-fluorouracil and either paclitaxel or docetaxel, which have superior response rates at the cost of higher morbidity. The commonly followed schedule is to administer three cycles at three-weekly intervals followed by reassessment with CT scan imaging and surgery between 4 and 6 weeks after the last cycle of chemotherapy. The results with neoadjuvant chemotherapy have been encouraging in terms of tolerability and completion of planned treatment; however, no long-term outcome data is available. Neoadjuvant chemoradiotherapy is also rapidly gaining popularity in India. The most commonly used protocol is the CROSS protocol, i.e., radiation 41.4 Gy in 23 fractions of 1.8 Gy over 5 weeks with concurrent weekly chemotherapy, paclitaxel 50 mg/m^2 and carboplatin at AUC 2. Most centres are stringent in patient selection for this regimen, and the early results have been very encouraging.

Post-operative radiotherapy or chemoradiotherapy is not practised as a routine after oesophagectomy. The use of adjuvant radiotherapy is restricted to patients with positive resection margins and, occasionally, patients with significant residual metastatic lymphadenopathy after neoadjuvant chemotherapy.

16.3.4 Chemoradiotherapy

Chemoradiotherapy is the primary modality of treatment of upper third oesophageal cancers and locally advanced middle and lower third cancers that are unresectable. It is also the treatment of choice in patients who are medically inoperable or unwilling to undergo surgery. The most widely practised and well-tolerated regimen includes radiotherapy to 66 Gy in 33# in 6.5 weeks with concurrent weekly cisplatin 35 mg/m^2, 5–6 cycles [67]. In institutes with facilities for intraluminal brachytherapy the radiation regimen may be changed to teletherapy 50 Gy in 25# in 5 weeks followed by 2# of high-dose rate intraluminal brachytherapy of 12 Gy after 2 weeks, the chemotherapy regimen remaining the same. Several concurrent chemotherapy regimens are practised including three-weekly cisplatin and 5-fluorouracil and three-weekly paclitaxel and cisplatin along with standard doses of radiation.

16.3.5 Palliative Therapy

The emphasis of management in patients presenting with metastatic oesophageal cancer is on early palliation of dysphagia. Patients with metastatic disease but grade 3 or less dysphagia are treated with palliative radiotherapy with or without stenting [68]. Patients with absolute dysphagia who need immediate palliation are treated with oesophageal stents, most commonly self-expanding metal stents [69]. A few centres offer intraluminal radiotherapy for metastatic and locally advanced oesophageal cancer and have been found to offer faster and sustained palliation of dysphagia [70]. Rarely patients with bulky disease obstructing the tracheobronchial tree as well as the oesophagus are treated with double stents i.e., tracheal and oesophageal stents.

16.3.6 The Tata Memorial Centre Experience

At the authors' institute, patients with early (T1 or T2 with N0) disease are treated with primary surgery, while those with more advanced (T3 or T4a or N+) disease are treated with neoadjuvant chemotherapy (NACT) or chemoradiotherapy (NACTRT) followed by surgical resection. While the default option is NACT for most patients, eligible patients are currently getting randomized in a phase II trial comparing the two strategies. The diagnostic workup and treatment guidelines are summarized in Fig. 16.1. Over 1,700 surgeries have been performed for oesophageal cancer over the last 10 years. The preferred choice of surgery is a transthoracic three-stage oesophagectomy while transhiatal oesophagectomy is occasionally performed as a compromise procedure in patients with borderline fitness or extensive pulmonary fibrosis. Elective three-field lymphadenectomy is done in all patients with supracarinal disease and those with radiologically or metabolically metastatic supracarinal lymphadenopathy. Patients without these

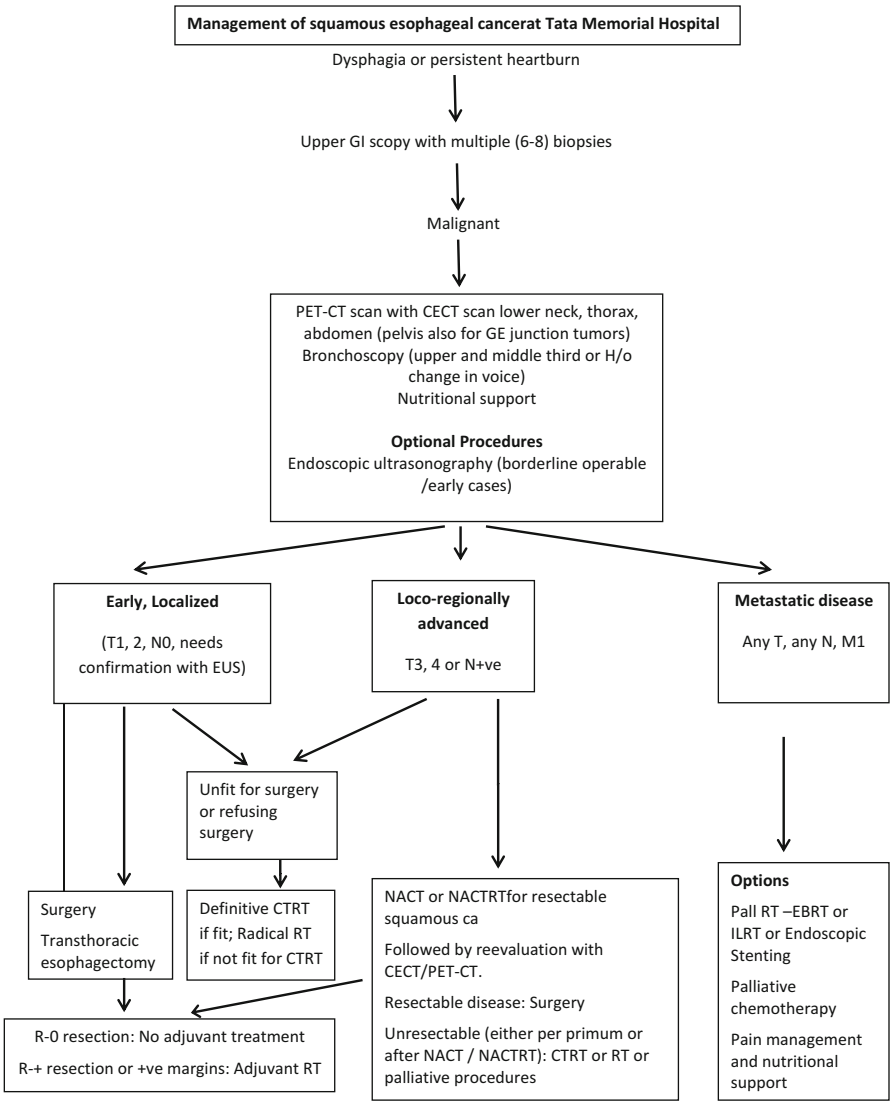

Fig. 16.1 OSCC treatment algorithm at the Tata Memorial Hospital

features are considered for randomization to a trial comparing standard two-field with elective radical three-field lymphadenectomy. Minimally invasive oesophagectomy (thoracoscopy and/or laparoscopy) is performed in approximately half of the patients undergoing transthoracic oesophagectomy. The preferred conduit is the stomach and the posterior mediastinum, the most common route of reconstruction. Oesophagogastric anastomosis is performed in the neck by a

triangulated stapled anastomosis. A nasojejunal tube is placed intraoperatively for post-operative enteral feeding.

Preoperative preparation includes chest physiotherapy, incentive spirometry and nutritional rehabilitation along with smoking cessation. Anti deep vein thrombosis (DVT) prophylaxis is started 12 h prior to surgery and continued post-operatively. Prophylactic antibiotics are given preoperatively and repeated once after 3 h intraoperatively and are not continued routinely in the post-operative period. Most patients are extubated immediately post-operatively on table and shifted to a recovery ward rather than the intensive care unit. Physiotherapy and active mobilization are started soon after shifting to the recovery ward. Enteral (nasojejunal) feeding is started the morning after surgery and stepped up gradually to full enteral feeds by the evening of the second post-operative day. The nasogastric tube is clamped on the second post-operative day and removed by the same evening if the chest radiograph shows no gastric tube dilatation. Routine laryngoscopy examination is done to check the vocal cord status on the fifth post-operative day and oral liquids started on the sixth post-operative day. Contrast swallows are not done prior to starting orals and patients are on full solid feeds by the 8th post-operative day. Uncomplicated patients are discharged by the tenth post-operative day. The post-operative major morbidity and mortality are 19.9 and 5.9 %, respectively. Common post-operative complications include pulmonary complications (27.1 %), anastomotic leaks (8.8 %), vocal cord paresis (31.4 %, of which 6.3 % have permanent palsy) and thoracic duct injuries (1.3 %). The 5-year survival of patients undergoing total oesophagectomy was 42 % with a median survival of 36 months (95 % confidence interval, 25.5–46.5 months).

16.4 Research in Oesophageal Cancer in India

Research on oesophageal cancer in India has a long history. The main areas of focus in oesophageal cancer research have been the possible aetiological factors and associations with squamous oesophageal cancer, the choice of primary treatment for the disease, modifications in surgical technique, the role of neoadjuvant and adjuvant treatment and palliative treatment options.

16.4.1 Epidemiology Research

Epidemiological research from the Kashmir Valley, which is a high incidence area for squamous oesophageal cancer, established that low socio-economic status was an independent risk factor [15]. A large case–control study, matched for age, sex and geographic area, showed a strong inverse association between higher education and wealth status and OSCC risk. The same study also established the probable aetiological role of “hookah” smoking and “nass chewing” on oesophageal squamous cell cancer with odds ratios of 1.85 and 2.88, respectively [17]. In a small study evaluating the prevalence of human papillomavirus (HPV) strains in OSCC,

researchers found that a high proportion (87 %) of patients with OSCC harboured high-risk HPV strains [37]. While association between HPV strains and OSCC is already established and the study supported the hypothesis of persistent oncogenic viruses in cancer development, a larger study would be required to firmly establish causation. In a study of epigenetic, genetic and environmental interactions in OSCC, significantly higher methylation frequencies were noted in tobacco chewers compared to non-tobacco users for all the four genes (p16, DAPK, BRCA1 and GSTP1) studied [33]. Betel quid chewing, alcohol consumption and a null GSTT1 genotype had maximum risk for OSCC without promoter hypermethylation whereas tobacco chewing, smoking and null GSTT1 variants were found to be associated with OSCC with promoter hypermethylation on logistic regression analysis [33].

16.4.2 Primary Treatment

One of the two randomized trials [71, 72] comparing surgery with radical radiotherapy for localized oesophageal cancer was conducted in the authors' institute. Although this trial was primarily designed to evaluate quality of life in patients treated with surgery or radiotherapy, it established that surgery was far superior to radiotherapy even for overall survival [72]. The study randomized 99 patients to either surgery alone ($n = 47$) or radiotherapy alone ($n = 52$). Outcomes with respect to disease-specific symptoms, which was the primary outcome, were consistently superior in the surgery arm; specifically, the quality of swallowing, which is an important endpoint of treatment of oesophageal cancer, was superior in the surgery arm compared to the radiotherapy arm. The secondary endpoint of survival was vastly superior in the surgery arm compared to the radiotherapy arm ($p = 0.002$) [72]. To date, this is one of only two randomized trials [71, 72] performed so far to address this important question.

16.4.3 Neoadjuvant Therapy

A small randomized trial compared quality of life (QOL) outcomes after transhiatal oesophagectomy with or without neoadjuvant chemotherapy [54]. Utilizing the validated EORTC QLQ C-30 and OES-18 questionnaires, the authors showed that quality of life (QOL) improved after surgery in all patients in functional, global health and symptom scales; in addition, the results showed an improved QOL in patients treated with neoadjuvant chemotherapy and surgery compared to those with surgery alone [54]. Currently, there is an ongoing phase II randomized trial comparing neoadjuvant chemotherapy with neoadjuvant chemoradiotherapy (both followed by radical surgery) in the authors' institution.

16.4.4 Surgical Trials

A number of trials have been conducted on surgical techniques and variations therein. These include the use of pedicled omentum to reinforce oesophagogastric anastomosis [73], modifications of the anastomotic technique [74] and the route of reconstruction [65]. In addition, observational studies on minimally invasive oesophagectomy [57, 59, 61–63] and robotic oesophagectomy [64] have also been performed.

A small randomized trial [65] was performed on 49 patients to compare outcomes between the anterior mediastinal (retrosternal) ($n = 24$) with the posterior mediastinal ($n = 25$) routes of reconstruction. The duration (235 vs 225 min) and blood loss (531 vs 538 mL) of surgery were similar in the two groups. Similarly, there were no significant differences between the retrosternal and posterior mediastinal routes, respectively, in immediate post-operative pulmonary (45.8 vs 48 %) or cardiac (25 vs 20 %) complication rates, anastomotic leaks (16.7 vs 16 %), hospital stay (15 vs 17 days) and mortality (12.5 vs 4 %) [65]. Long-term outcomes including stricture rate, dysphagia, aspiration, reflux and weight loss were also similar in the two groups [65]. In a small study involving patients who underwent oesophagectomy with a cervical anastomosis, patients were randomized into either no pyloric drainage or pyloroplasty with gastric emptying as the primary endpoint [75]. The study demonstrated significant delay in gastric emptying in both groups though it was less pronounced in the pyloroplasty group. The sequelae of delayed gastric emptying were seen in both groups and the authors concluded that the intrathoracic stomach causes delayed gastric emptying and pyloroplasty failed to prevent its occurrence [75].

16.4.4.1 Anastomotic Technique

A randomized trial [73] was performed to evaluate whether the addition of a pedicled omental wrap on the oesophagogastric anastomosis would decrease the incidence of anastomotic leaks. Patients undergoing radical oesophagectomy (63 % Ivor Lewis and 37 % transhiatal oesophagectomy) were randomized to conventional anastomosis (manual end-to-side oesophagogastric anastomosis) with ($n = 97$) or without an omental wrap ($n = 97$). The anastomotic leak rate was significantly lower (3.1 vs 14.4 %, $p = 0.005$) in patients who had the omental wrap [73]. This difference was seen in both the Ivor Lewis and the transhiatal oesophagectomy groups. Another randomized trial was conducted to evaluate whether a wide cross-sectional area at the anastomotic site would lead to lower rates of anastomotic leaks and strictures [74]. One hundred patients were randomized to the control arm (end-to-side oesophagogastric anastomosis on the anterior gastric wall without removal of the crescent) or the experimental arm (end-to-side anastomosis after removal of a crescent from the anterior gastric wall). Anastomotic leak rates (4.3 vs 20.8 %, $p = 0.03$) and strictures (8.5 vs 29.2 %, $p = 0.02$) were significantly lower with the modified (wider anastomotic) technique [74]. Another randomized trial was done comparing a side-to-side stapled anastomosis to a handsewn technique with anastomotic leaks and strictures as the

primary and secondary endpoints, respectively [66]. Out of 174 patients randomized, anastomotic leak rates were similar in the two groups (14/87 vs 16/87, $p = 0.33$); however, post-operative strictures were significantly lower (17/82 vs 7/81, $p = 0.045$) in the stapled anastomosis [66].

16.4.4.2 Perioperative Management

Two relatively large randomized trials of perioperative management were conducted in the authors' institute. The first, a randomized trial, evaluated whether it was safe to shorten the duration of nasogastric drainage after oesophagectomy [76]. One hundred and fifty patients undergoing modified McKeown three-stage or transhiatal oesophagectomy with gastric tube reconstruction were randomly allocated to either conventional (6–10 days) or shortened (2 days) nasogastric drainage. The primary composite endpoint was anastomotic leaks and/or pulmonary complications and was found to be similar (18.7 vs 21.3 %) in the two groups; patient discomfort scores were significantly lower in the early removal arm [76]. The trial established that it was feasible and safe to remove the nasogastric drainage tube two days after oesophagectomy and a neck anastomosis without any adverse effects [76]. The authors performed another randomized trial to evaluate the impact of restricted intraoperative and post-operative fluid administration on major post-operative pulmonary complications [77]. The study initially planned to recruit 320 patients was prematurely terminated after 183 patients were accrued on the advice of an independent data monitoring committee. Eligible patients were randomized to either conventional (liberal) fluid administration or restricted fluids intra- and post-operatively. At the planned interim analysis after 183 patients were accrued, the major post-operative complication rates were identical and the DSMC felt that continuing the trial would be futile as the likelihood of demonstrating an important difference between the two groups was very low [77]. Another randomized trial from the authors' institution evaluating the role of perioperative erythromycin (a motilin agonist) in reducing the immediate post-operative and medium-term occurrence of delayed gastric emptying is completed and awaiting data analysis [78].

16.4.5 Palliative Treatment

A randomized trial was conducted to evaluate whether the combined treatment of oesophageal stenting and radiotherapy was superior to stenting alone in advanced inoperable oesophageal cancer [68]. The study, which randomized 84 patients concluded that the combination of self-expandable metal stenting followed by 30 Gray radiation (10 fractions, over 2 weeks) offered longer dysphagia relief (7 vs 3 months, $p = 0.002$) and prolonged survival (median 180 vs 120 days, $p = 0.009$) compared to stenting alone [68].

16.4.6 Ongoing Research

There are several ongoing trials on various aspects of oesophageal cancer screening and treatment. The authors' institute, along with a rural hospital, is currently conducting a large community-based screening trial in Ratnagiri, one of the rural districts of western India where 110,000 individuals are being randomized in a cluster randomized design to either health education alone or health education with screening for upper aerodigestive tract (oral, hypopharyngeal and oesophageal) cancers. Trained health workers go to individual villages and screen high-risk individuals (tobacco and alcohol users) by visual examination of the oral cavity and a double-contrast barium swallow for early detection of oral and hypopharyngeal/oesophageal cancers, respectively. Results are expected in about 8 years. Another large randomized trial is underway in the authors' institution evaluating the role of radical lymphadenectomy in operable oesophageal cancer [79]. Patients with operable oesophageal cancer are randomized intraoperatively (after confirming operability and absence of gross supracarinal lymphadenopathy) to either standard two-field or radical three-field lymphadenectomy—430 out of a target 700 patients have been accrued so far.

16.5 Future Directions

Treatment for oesophageal cancer in India has so far been carried out in institutions with a wide range of experience in managing this disease without an organizational framework. Challenges to improve overall patient outcomes in oesophageal cancer include the wide disparity in quality of cancer care provision, availability of qualified, trained experts in all parts of the country and the relative lack of infrastructure. Healthcare provision in India is multi-tiered, with only basic medical facilities at a primary health centre level, while tertiary level treatment centres have state-of-the-art infrastructure and highly qualified medical and paramedical staff, especially in apex government and private institutions. Future efforts will include widespread dissemination of evidence-based treatment guidelines for the management of oesophageal cancer, training adequate manpower, centralization of treatment, wider adoption of multidisciplinary treatment teams and multimodality treatment protocols, creation of a collaborative network and standardized data capture.

The lack of a cooperative working group to meet the above challenges was felt to be a lacuna in the system. The Indian Society for Diseases of the Esophagus and Stomach (ISES) was recently formed to address this gap. The mandate for the ISES includes the formulation and adoption of uniform guidelines for the management of oesophageal diseases, more systematic data collection and collaborative multicentric research studies. It is expected that this society will also provide a forum for discussion among surgeons and oncologists treating oesophageal cancers and help identifying specific problems and questions to be answered in the Asian context. The authors also agree on the need for collaborative research in squamous

oesophageal cancers among countries like Japan, China, Iran and India where they are far more common than adenocarcinomas. Possible questions to answer include the dilemma of neoadjuvant chemotherapy or chemoradiotherapy, personalized therapy to guide the choice of neoadjuvant treatment, the ideal surgical approach and the extent of lymphadenectomy and quality of life issues.

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