

INDIAN COUNCIL OF MEDICAL RESEARCH



CONSENSUS DOCUMENT FOR MANAGEMENT OF ESOPHAGEAL CANCER

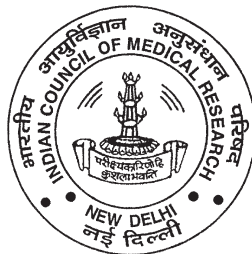
*Prepared as an outcome of ICMR Subcommittee on
Esophageal Cancer*



Indian Council of Medical Research
2017

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Indian Council of Medical Research,
Ansari Nagar, New Delhi – 110029
2017

Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline. One can use an alternate mode of therapy based on discussions with the patient and institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but will act only as a guidance for clinicians in complex decision –making.

Dr. Soumya Swaminathan
Secretary,
Department of Health Research
and Director General, ICMR

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Foreword

I am glad to write this foreword for Consensus Document for Management of Esophageal Cancer. The ICMR had constituted sub-committees to prepare consensus document for management of various cancer sites. This document is the result of the hard work of various experts across the country working in the area of oncology.

This consensus document on management of esophageal cancers summarizes the modalities of treatment including the site-specific anti-cancer therapies, supportive and palliative care and molecular markers and research questions. It also interweaves clinical, biochemical and epidemiological studies.

The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines worked tirelessly in formulating site-specific guidelines. Each member of the subcommittee's contribution towards drafting of these guidelines deserves appreciation and acknowledgement for their dedicated research, experience and effort for successful completion. We hope that this document would provide guidance to practicing doctors and researchers for the management of patients suffering from esophageal cancers and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on subject based on available evidence. Mention of drugs and clinical tests for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this first edition of Consensus Document on Management of Esophageal Cancer would serve the desired purpose.



(Dr. Soumya Swaminathan)
Secretary, Department of Health Research
and Director-General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as chairperson of ICMR Task Force project on guidelines for management of cancer.



The Task Force on management of cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, esophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukaemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome and Pediatric Lymphoma. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till December 2016 was reviewed while formulating consensus document and accordingly recommendations are made.

Now, that I have spent over a quarter of a century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall; worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCR's (2012-2014) and time trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.



(Dr. G.K. Rath)
Chairperson
ICMR Task Force Project

Preface

Esophageal cancer is a major problem in India, the incidence has a geographic variation, being more common in some parts of south India and pockets in the north. It seems to be related to specific habits especially the variation in diets in these regions. The patients usually present in late stages as the symptoms are non-specific, hence patients are treated for other causes over prolonged periods of time. Dysphagia, which is a manifestation of constrictive lesions bring them relatively early for medical help. The management of these cancers has improved significantly largely due to the multidisciplinary treatment options that have dramatically improved over the last decade.



Given the different levels of care provided all over India, the busy clinician is often left confused with regard to definitive treatment algorithms in specific clinical situations. Hence the Indian Council for Medical Research (ICMR) set up a task force to come up with a consensus statement for management of Esophageal Cancers in India. The task of this renowned expert group from all corners of India was to analyze the available literature and develop practical and sound guidelines that can serve to both update the practicing clinician and guide them in their day to day practice in the current Indian scenario.

We apply the western data to treat our patients which may not be applicable not only because of increased toxicity as quite a few of our patients are malnourished, but there are no cost-effectiveness analyses relating to a developing country. The onus is on us to create the Indian data, hence the research questions generated by the group will help us to take this further.

I take this opportunity to thank each and every member of the group who took time out from their busy schedules and remained committed to their assigned tasks in a time bound manner. I would like to especially thank Dr Rath for inspiring us in this effort and Dr Tanvir Kaur for her continuous effort to make us stick to timelines.

These guidelines would be updated from time to time and I would look forward to your constructive feedback that would help us all in ultimately treat our patients better than ever before.

A handwritten signature in blue ink, appearing to read 'Govind Babu', with a horizontal line underneath.

Dr Govind Babu
Chairman, Sub-committee on Esophageal Cancers

Preface

Cancer is a leading cause of death worldwide. Globally cancer of various types effect millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gallbladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.



The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.



(Dr. R.S. Dhaliwal)
Head, NCD Division

Acknowledgement

The Consensus Document on Management of Cancer is a concerted outcome of effort made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, stomach, gallbladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.



This document represents a joint effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document. The chairperson of subcommittee is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. Soumya Swaminathan, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking her special interest and understanding the need of formulating the guidelines which are expected to benefit the cancer patients.

I would like to acknowledge here the initiative undertaken with the able guidance of Dr. Bela Shah. I would like to thank Dr. R.S. Dhaliwal for his support and coordination in finalizing this document. I would like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged..

A handwritten signature in blue ink that reads "Tanvir Kaur".

(Dr. Tanvir Kaur)
Program Officer & Coordinator

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1. Introduction

Esophageal cancer is the eighth most common cancer in the world. There has been a significant increase in the incidence of esophageal cancer world over, particularly adenocarcinoma. Significant regional variation exists in incidence and pathology of esophageal cancer. Countries with a higher human development index (HDI) have a lower incidence of esophageal cancer¹, but higher proportion of adenocarcinoma². Countries with a low HDI like India have a high incidence of esophageal cancer with higher proportion of squamous cancers³. India has an age standardized incidence rate (ASR) of 6.5 per 100,000 population for males and 4.2 per 100,000 population for females. This translates into approximately 47,000 new cases each year and 42,000 deaths⁴. A very high incidence of esophageal cancers has been reported in North-East region of India. This is a part of an esophageal “cancer belt,” which extends from northeast China to the Middle East, where incidence rates of SCC of the esophagus have been reported as high as 100 cases per 100000 annually⁵).

The standard treatment of operable oesophageal cancer in the absence of medical contraindications is surgery. Radiation, chemo-radiation for definitive treatment and combination of radiation and chemotherapy with surgery are other treatment options. However, the overall survival continues to remain far from satisfactory. The reported five year survival ranges from 5% to 30%⁶.

Several international consensus guidelines are available for the management of esophageal cancers, but none them addresses Asian/Indian population in particular. Therefore, formulating reliable guidelines based on western data is questionable given the fact that esophageal tumors are biologically different in developed countries. There is obviously an urgent need to formulate consensus statement for the management of carcinoma of esophagus based on Indian data and experience which would not only incorporate the evidence available but would also be feasible to be practiced in the hospitals of India. The following part of this chapter provides some of the existing National and International guidelines for esophageal cancer and reviews the applicability of the given guidelines for patients with esophageal carcinoma, especially in Indian context. The proposed national consensus document for esophageal cancer is presented. Some of the key areas of research relevant to our country have also been mentioned.

2

EXISTING GUIDELINES

The sources of the current guidelines available for management of esophageal cancer are:

1. National Comprehensive Cancer Network (NCCN)⁷
2. Indian Comprehensive Cancer Network (ICCN)⁸
3. National Health Services (NHS)⁹
4. European Society of Medical Oncology (ESMO)¹⁰
5. TMH textbook on evidence based medicine¹¹
6. The Society of Thoracic Surgeons (STS)¹²
7. American cancer society (ACS)¹³

The NCCN guidelines are most widely followed and quoted. While these provide the general principles for the management of esophageal tumors, they do not address specific issues pertaining to cancer of esophagus which is more prevalent in our part of the world.

Interpretation and practice of the existing guidelines needs to be done with caution considering the following facts:

1. Many of published guidelines including that from TMH and ICCN are based on evidence from western experience.
2. There is a dearth of randomized, prospective studies from Indian subcontinent on chemoradiation (CT+RT), induction chemotherapy and palliative chemotherapy in esophageal cancers.
3. Esophageal cancers in India are different compared to the western countries. Majority of the cancers in India are of squamous histology as compared to the adeno histology in the western/developed nations. These cancers are also more likely to present in higher stage (stage III and stage IV) with higher risk of failure at local site. The nature of spread, biological behavior and the treatment is also different.

In the absence of international and national data specifically on esophageal cancer (large, randomized, prospective case series and trials), literatures of esophageal cancers in general has been reviewed.

Analysis of the available Indian literature revealed information on the following aspects.

- a) Epidemiological studies on esophageal carcinoma.
- b) Studies evaluating the role of clinical and molecular markers in the prognostication of esophageal cancers.
- c) Treatment experiences.

The following highlights only the studies which report on treatment outcomes.

Esophageal cancer is the 15th most common cancer in developed countries and 4th in the developing world¹⁴. The incidence of esophageal adenocarcinoma (AC) has shown a dramatic increase in several populations over the past 25 years¹⁵. The earliest documented epidemiology report is from P. B. Desai¹⁶ in 1969 which documents an distressingly high incidence of esophageal cancer in India, of 14.4 men per 100,000 is more than double that of Finland, which has the next highest frequency (Eleven women and 5.4 men per 100,000). An analysis of patient material reveals that 51% of cases are too advanced for any treatment at their initial presentation.

Jussawalla and Jain in 1976¹⁷ reported esophageal cancers during a 3-year period, 1970-1972 in Greater Bombay. The Bombay Cancer Registry recorded 1,081 cases of cancer of oesophagus 8696 males and 385 females. The crude and age-adjusted (to the world population average) incidence rates during the period were: in males 6.9 and 15.4 per 100,000 and among females 5.3 and 11.4 per 100,000. Another report by J. V. Cherian¹⁸, evaluated endoscopy records of 994 patients with carcinoma of the esophagus, either squamous cell (SCC) or AC, diagnosed between 1989 and 2004. Squamous cell carcinoma was the most common malignancy, seen in 912 (92%) patients. 82 patients (8%) had adenocarcinoma. 65 of these 82 patients (79%) had an esogastric junction malignancy and 17 (21%) a tumor in the distal third of the esophagus. No time trends were discernible with regard to the clinical presentation, frequency, mean age or gender. However, an increase in the number of patients below the age of 40 was noted ($p=0.008$). In squamous cell carcinoma of the esophagus, there was an overall increase in the mean age of occurrence ($p=0.05$), but no significant changes in the gender ratio. The lower esophageal cancers outnumbered the midesophageal cancers in the 4th cohort and the former represent the most common site of malignancy. An international geographical belt where carcinoma of the esophagus is endemic and is termed "Asain Esophageal Cancer Belt". The incidence rate of this disease as reported by Khan NA et al was 22.6 per 1,00,000 population in men and 11.5 per 1,00,000 population in women¹⁹.

Early stage cancer:

Given the low risk of LN involvement in mucosal disease, there is a general agreement of the reliability and of the efficiency of the endoscopic management of early stage esophageal cancer confined to the mucosa (T1a). More recently, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), radiofrequency ablation (RFA), cryotherapy, and free-hand mucosal resection have been increasingly applied²⁰. Because current data on what constitutes the best treatment are limited, it seems not possible at the present time to favor a technique compared to another²¹. However, there is global agreement that all visible lesions have to be removed by EMR for definitive histopathological staging and to ensure adequacy of resection margins.

A clinical series reported by Manner et al. demonstrated that EMR could be used to treat “low-risk” submucosal sm1 tumors with low-grade tumor differentiation²². With a mean follow-up of five years, there were no tumor-related deaths. However, two series reported high rate of nodes positive in sm1 tumor: 16.5% for Leers and 21% for Sepsesi²³. For tumor invading beyond sm1, existing literature demonstrates that the incidence of LN involvement in patients with T1b cancer ranges between 21% and 50%²⁴. For T2 lesion, a review of the outcomes of this subcategory demonstrated that the current approaches to clinical staging resulted in accurate pathologic stage in only 13% of cases. Of the patients inaccurately staged, 63% were overstaged and 37% were understaged. Subsequent recommendations for treatment of cT2N0M0 patients involved proceeding directly to surgery as this would currently be considered a definitive treatment in patients who are accurately staged or overstaged. Patients who are discovered to be understaged can be considered for adjuvant therapy²⁵.

Neoadjuvant therapy in early stage cancer: Esophagectomy remains the standard treatment of early stage cancer. There are very few data on the benefits of a neoadjuvant treatment for very localized esophageal cancer. The Fédération Francophone de la Cancérologie Digestive (FFCD) 9901 assessed whether preoperative CRT improves outcomes for patients with localized (stages I or II) esophageal cancer²⁶. From 2000 to 2009, 195 patients were randomized in 30 French centers: 98 were assigned to surgery alone and 97 to neoadjuvant CRT group. Postoperative morbidity rates were 49.5% in surgery group vs. 43.9% in CRT group (P=0.17). The 30 day-mortality rates were 1.1% in surgery group vs. 7.3% in CRT group (P=0.054) respectively. After a median follow-up of 5.7 years, the median survivals were 43.8 in surgery group vs. 31.8 months in CRT group [HR 0.92; 95% confidence interval (CI), 0.63-1.34; P=0.66]. The conclusion of this trial was that neoadjuvant CRT with cisplatin and fluorouracil does not improve overall survival but enhances postoperative mortality rate for patients with stage I or II esophageal cancer compared with surgery alone.

Locally advanced esophageal cancer:

Neoadjuvant chemotherapy or CRT: Gebski et al. have reported a meta-analysis that evaluated pooled data from clinical trials of neoadjuvant chemotherapy and CRT including both adenocarcinoma and SCC²⁷. This analysis combined the results of 10 randomized trials of neoadjuvant CRT vs. surgery alone and 8 randomized trials of neoadjuvant chemotherapy vs. surgery alone in patients with locally resectable esophageal carcinoma. The hazard ratio (HR) for all-cause mortality for neoadjuvant chemotherapy was 0.90 (95% CI, 0.81-1.00; P=0.05), indicating a 2-year absolute survival benefit of 7%. For patients with SCC, neoadjuvant chemotherapy did not have a survival benefit [HR for mortality 0.88 (0.75-1.03); P=0.12]. For the adenocarcinoma group, the survival benefit was significant [HR for mortality 0.78 (0.64-0.95); P=0.014]. The HR for all-cause mortality with neoadjuvant CRT vs. surgery alone was 0.81 (95% CI, 0.70-0.93; P=0.002), corresponding to a 13% absolute difference in survival at two years. Analysis of the neoadjuvant CRT studies that had histology data available found a significant benefit over surgery

for both histological tumour types: 0.84 (0.71-0.99; P=0.04) for SCC and 0.75 (0.59-0.95; P=0.02) for adenocarcinoma.

In 2011, Sjoquist et al. have published the latest updated meta-analysis²⁸. The inter-group analysis clearly demonstrated strong arguments for CRT compared to CT in patients with SCC or adenocarcinoma. The updated analysis contained 4,188 patients whereas the previous publication included 2,933 patients. They included all 17 trials from the previous meta-analysis and seven further studies. This updated meta-analysis contains about 3,500 events compared with about 2,230 in the previous meta-analysis (estimated 57% increase). The HR for all-cause mortality for neoadjuvant chemotherapy was 0.87 (0.79-0.96; P=0.005); the HR for SCC only was 0.92 (0.81-1.04; P=0.18) and for adenocarcinoma only was 0.83 (0.71-0.95; P=0.01). The HR for all-cause mortality for neoadjuvant CRT was 0.78 (95% CI, 0.70-0.88; P<0.0001); the HR for SCC only was 0.80 (0.68-0.93; P=0.004) and for adenocarcinoma only was 0.75 (0.59-0.95; P=0.02). The HR for the overall indirect comparison of all-cause mortality for neoadjuvant CRT versus neoadjuvant chemotherapy was 0.88 (0.76-1.01; P=0.07).

The Sjoquist's meta-analysis did not include the latest published phase III trial. The "CROSS trial" compared the outcome of concurrent CRT (carboplatine,plaxitaxel and 41 Gy) followed by surgery and surgery alone²⁹. A pathological complete response was achieved in 47 of 161 patients (29%) who underwent resection after CRT. Postoperative complications were similar in the two treatment groups, and in-hospital mortality was 4% in both. Median overall survival was 49.4 months in the CRT surgery group versus 24 months in the surgery group. Overall survival was significantly better in the CRT group [HR 0.657 (0.495-0.871; P=0.003)].

From the GebSKI's meta-analysis, there was no survival benefit of sequential CRT for patients with SCC [HR for mortality 0.9 (0.72-1.03); P=0.18] [27]. The results of sequential CRT were similar to that for patients with SCC assigned neoadjuvant chemotherapy. Concomitant CRT in patients with SCC had a significant benefit [HR for mortality 0.76 (0.59-0.98); P=0.04]. On this basis, the use of concomitant neoadjuvant CRT is strongly recommended compared to sequential CRT.

The Japan Clinical Oncology Group has conducted randomized, two controlled trials to assess potential benefits of adding adjuvant therapy to surgery in patients with SCC: the JCOG 9204 and the JCOG 9907³⁰⁻³¹. The JCOG 9204 study assessed the benefit of postoperative adjuvant CT with cisplatin plus 5-FU compared with surgery alone in patients with resectable stage I or II esophageal cancer³⁰. Overall survival did not differ significantly between the groups (5-year survival rate 52% vs. 61%; P=0.13). Disease-free survival was improved significantly in the patients who received postoperative CT and especially in N+ patients. In the JCOG 9907 study, neoadjuvant CT with cisplatin and 5-FU was compared with postoperative CT with cisplatin and 5-FU in patients with clinical stage II or III esophageal cancer³¹. Neoadjuvant CT was found to be superior to postoperative CT in overall survival. The 5-year survival rate was 55% in neoadjuvant group vs. 43% in adjuvant group (P=0.04). On the basis of these results, neoadjuvant chemotherapy followed by radical surgery compared to adjuvant strategy is recommended in case of locally advanced SCC.

The concept of a definitive CRT was introduced with the results of the Radiation Therapy Oncology Group (RTOG) 8,501 study³². This trial compared the effect of RT alone (64 Gy) to a scheme of a concurrent CRT (cisplatin, 5-FU, and radiotherapy 50 Gy). The study included both SCC or adenocarcinoma of the esophagus. This study demonstrated the strong sensitivity of SCC to a concomitant CRT. Concomitant CRT resulted in better overall survival and decrease in local failure than RT alone. These results lead a Japanese phase II to assess the effectiveness of definitive CRT (cisplatin, 5-FU, and classic portal radiation 60 Gy)³³. A complete response (CR) was obtained in 68% with a 3-year survival rate of 46%.

These results were not superior to those obtained with conventional surgical resection with or without chemotherapy. Two large randomized trials were conducted to compare definitive CRT with neoadjuvant CRT in esophageal SCC³⁴⁻³⁵. In a study performed by the German Esophageal Cancer Study Group, the 2-year overall survival results were similar in the surgery (39.9%) and nonsurgery (35.4%) treatment groups³⁴. A disadvantage of neoadjuvant therapy group was early postoperative mortality, while the definitive CRT in the nonsurgery group was associated with more local relapses. These results were confirmed in another large randomized study performed by FFCD 9102 study where surgery was proposed in responders to CRT. Once again, surgery improved local control, but did not improve survival, because neoadjuvant therapy was associated with increased early mortality³⁵. An FFCD trial comparing systematic surgery vs. salvage esophagectomy in responders after a neoadjuvant CRT is ongoing in France and it will provide an answer to this important issue.

Recurrent and metastatic disease:

Bedenne et al reports that locoregional control is often quite poor with definitive CRT, and 40% to 60% of the patients have persistent or relapsed tumor at the primary site within one year³⁵. Previous studies have demonstrated the feasibility of the salvage esophagectomy³⁶⁻⁴⁵. A recent pooled-analysis of more than eight studies comprising 954 patients revealed that salvage esophagectomy resulted in significant higher mortality and morbidity rate. Salvage resection was associated with a significantly increased incidence of post-operative mortality, anastomotic leak, pulmonary complications and an increased length of hospital stay⁴⁶. Much of this concern originated from a historical impression that surgical resection outside of 4-8 weeks following radiotherapy or CRT was more technically challenging and associated with increased postoperative morbidity and mortality⁴⁷. This opinion has recently been challenged⁴⁸ and there are now several publications demonstrating that selected utilization of salvage surgery in patients who have failed definitive CRT for SCC can be done with acceptable levels of both mortality and morbidity^{37,40,45}. Special attention has to be paid of the volume dose of radiation. Salvage surgery is a highly invasive and morbid operation after a volume dose of radiation exceeding 55 Gy⁴⁵. It should be noted, however, that a randomized clinical trial that assessed long-term outcomes indicated that definitive radiation chemotherapy had the potential for producing progressive deterioration in pulmonary function when compared to surgery alone⁴⁸.

Author/ Institute/ Group	Study subjects	Results	Comments
P. B. Desai ¹⁶	Period of 26 years (1941-66) covers 7,973 cases of cancer of the esophagus	14.4 men per 100,000 population and 51% of cases are too advanced for any treatment at their initial presentation	First publication from India on esophageal cancer
Jussawalla and Jain in 1976 ¹⁷	1,081 cases of cancer of oesophagus 8696 males and 385 females	6.9 and 15.4 per 100,000 and among females 5.3 and 11.4 per 100,000	Incidence in India was approx. double that of Finland
J. V.Cherian ¹⁸	994 patients of esophageal	92% of the patients were squamous cell carcinoma, 8% had adenocarcinoma, 79% had an esogastric junction malignancy and 21% a tumor in the distal third of the esophagus	Majority of the patients were in the esogastric junction.
Khan NA et al ¹⁹	680 patients of esophageal cancer	22.6 per 1,00,000 population in men and 11.5 per 1,00,000 population	High burden of esophageal cancer in India is from Kashmir and northern regions of India
Manner et al. ²²	EMR for treating low risk disease	EMR could be used to treat "low-risk" submucosal sm1 tumors with low-grade tumor differentiation. With a mean follow-up of five years, there were no tumor-related deaths.	EMR could be used to treat "low-risk" submucosal sm1 tumors with low-grade tumor differentiation
Fédération Francophone de la Cancérologie Digestive (FFCD) 9901 ²⁶	2000 to 2009, 195 patients were randomized in 30 French centers: 98 were assigned to surgery alone and 97 to neoadjuvant CRT group.	Postoperative morbidity rates were 49.5% in surgery group vs. 43.9% in CRT group (P=0.17). The 30 day-mortality rates were 1.1% in surgery group vs. 7.3% in CRT group (P=0.054) respectively. After a median follow-up of 5.7 years, the median survivals were 43.8 in surgery group vs. 31.8 months in CRT group	neoadjuvant CRT with cisplatin and fluorouracil does not improve overall survival but enhances postoperative mortality rate for patients with stage I or II esophageal cancer compared with surgery alone.

Gebski et al. ²⁷	Meta-analysis of 10 randomized trials of neoadjuvant CRT vs. surgery alone and 8 randomized trials of neoadjuvant chemotherapy vs. surgery alone in patients with locally resectable esophageal carcinoma.	The hazard ratio (HR) for all-cause mortality for neoadjuvant chemotherapy was 0.90 (95% CI, 0.81-1.00; P=0.05), indicating a 2-year absolute survival benefit of 7%.	Analysis of the neoadjuvant CRT studies that had histology data available found a significant benefit over surgery for both histological tumour types
Sjoquist et al. ²⁸	meta-analysis of 24 studies including 17 trials	The HR for all-cause mortality for neoadjuvant chemotherapy was 0.87 (0.79-0.96; P=0.005); the HR for SCC only was 0.92 (0.81-1.04; P=0.18) and for adenocarcinoma only was 0.83 (0.71-0.95; P=0.01).	The HR for the overall indirect comparison of all-cause mortality for neoadjuvant CRT versus neoadjuvant chemotherapy was 0.88 (0.76-1.01; P=0.07).
CROSS trial ²⁹	161 patient evaluation compared the outcome of concurrent CRT (carboplatine,plaxitaxel and 41 Gy) followed by surgery and surgery alone	A pathological complete response was achieved in 47 of 161 patients (29%) who underwent resection after CRT	Overall survival was significantly better in the CRT group
JCOG 9204 ³⁰	study assessed the benefit of postoperative adjuvant CT with cisplatin plus 5-FU compared with surgery alone in patients with resectable stage I or II esophageal cancer	Overall survival did not differ significantly between the groups (5-year survival rate 52% vs. 61%; P=0.13)	Disease-free survival was improved significantly in the patients who received postoperative CT and especially in N+ patients
JCOG 9907 ³¹	neoadjuvant CT with cisplatin and 5-FU was compared with postoperative CT with cisplatin and 5-FU in patients with clinical stage II or III esophageal cancer	The 5-year survival rate was 55% in neoadjuvant group vs. 43% in adjuvant group (P=0.04).	neoadjuvant chemotherapy followed by radical surgery compared to adjuvant strategy is recommended in case of locally advanced SCC
RTOG 8,501 study ³²	compared the effect of RT alone (64 Gy) to a scheme of a concurrent CRT (cisplatin, 5-FU, and radiotherapy 50 Gy)	Concomitant CRT resulted in better overall survival and decrease in local failure than RT alone	Concomitant CRT resulted in better overall survival and decrease in local failure than RT alone
Kato K et al ³³	to assess the effectiveness of definitive CRT (cisplatin, 5-FU, and classic portal radiation 60 Gy)	A complete response (CR) was obtained in 68% with a 3-year survival rate of 46%.	These results were not superior to those obtained with conventional surgical resection with or without chemotherapy.
Stahl M et al ³⁴	to compare definitive CRT with neoadjuvant CRT in esophageal SC	2-year overall survival results were similar in the surgery (39.9%) and nonsurgery (35.4%) treatment groups	A disadvantage of neoadjuvant therapy group was early postoperative mortality, while the definitive CRT in the nonsurgery group was associated with more local relapses
FFCD 9102 study ³⁵	surgery was proposed in responders to CRT	Surgery improved local control, but did not improve survival, because neoadjuvant therapy was associated with increased early mortality	Surgery improved local control, but did not improve survival

Diagnostic Investigations:

1. **Esophagoscopy:** Fiberoptic esophagoscopy is essential for histopathological confirmation of cancer

- a) Biopsy preferable – Minimum 6 samples
- b) Cytology if biopsy not feasible (Brush cytology/FNAC in strictorous lesions)
- c) Endoscopic ultrasonography guided FNAC, If biopsy and brush cytology not feasible

2. **Barium Swallow (optional):** Gives information regarding site, extent, morphology of tumour and extraesophageal spread. However it is of limited utility in the modern era.

If facility for flexible esophagoscopy with biopsy is available, barium swallow study may be avoided.

In metastatic patients pathological diagnosis from metastases with evidence of obvious lesion in the esophagus on imaging can be accepted as proof of disease.

Dilatation of strictorous lesions is generally not advisable

Pathology reporting to be done by

- a) Oncopathologist / Pathologist trained in Oncopathology
 - b) Telepathology
- **Staging investigation / Definitive treatment to be started only after histopathological and locational diagnosis**

Multidisciplinary team

The staging investigations and treatment plan ideally should be finalized *after the patient has been assessed by a multidisciplinary team*. This is to optimize investigations and formulate a multimodal treatment plan for the patient

The optimal multidisciplinary team should have inputs from

- a) Surgical Oncologist
- b) Medical Oncologist
- c) Radiation Oncologist
- d) Oncopathologist
- e) Medical Gastroenterologist
- f) Radiologist / Bio imaging specialist
- g) Pulmonary physician/Intensivist

Staging Investigations⁴⁸

- Endoscopic Ultrasonography (EUS) desirable
- PET CECT Desirable
- CECT Thorax essential
- Fibre optic bronchoscopy (in selected cases)
- Diagnostic thoracoscopy and laparoscopy

Endoscopic Ultrasonography (EUS)

- EUS is used for refining locoregional staging and hence should be employed after exclusion of distant metastasis. EUS should be performed by experienced endosonographers performing at least at least 100 staging examinations annually^{49, 50}. (Level 2, Grade B)
- Assessment of stenosed tumors should be done using the slim blind tapered probe positioned over a guidewire⁵¹. The use of High frequency EUS catheter probes (20-30 Mhz) increases the accuracy for T1 and T2 tumors⁵³. (Level 2, Grade B)
- Residual inflammation, edema and fibrosis after chemotherapy and radiation makes EUS performance lower for both T and N staging for re-staging after neo-adjuvant therapy as compared to primary stage evaluation. The T stage accuracy ranges from 27-82% and N stage accuracy ranges from 38 to 73%⁵⁴ Level 2, Grade B).
- Accuracy of EUS for more than 50% regression in the tumor's maximum transverse cross sectional area after 18 days post therapy has been used as a marker of response to chemotherapy and chemoradiation and correlates with pathological regression^{55, 56}(Level 2, Grade C)

Integrated Positron Emission Tomography-Contrast Enhanced Computerized Tomography (PET-CECT)

Staging

(PET-CECT) is the preferred investigation in all patients planned for radical treatment. It provides incremental staging information and can lead to management change in a significant number of patients. PET can avoid potentially futile thoractomies by detecting metastatic disease not diagnosed on conventional staging procedures^{57,58}. It should be a part of the diagnostic algorithm in esophageal cancer staging. (Level of evidence: II, Relevance of test – Appropriate, Hierarchy of diagnostic accuracy- Level 4).

Assessment of response to treatment and prognostication

Patients who respond to induction therapy have a significantly improved survival, compared with patients who do not respond to the therapy. Therapy response can be assessed with 18F-FDG PET late, that is, after completion of therapy, and early during the course of therapy⁵⁹.

Single-center studies investigating response assessment in patients with esophageal cancer have provided promising results. Early metabolic response evaluation is fairly accurate, and shows the feasibility of a PET-guided treatment algorithm⁶⁰. (Level of evidence: II, Relevance of test – Appropriate, Hierarchy of diagnostic accuracy- Level 4).

Contrast Enhanced Computerized Tomography (CECT) Thorax

Is the preferred modality when PET CECT not available/ In patients planned for palliative treatment because of advanced disease/poor physical status. CECT Thorax is an adequate staging tool in the

absence of PET CECT. It has equivalent accuracy in comparison with PET CECT vis a vis T and N staging. It is also capable of detecting liver, lung, bone metastases and non regional metastatic lymph nodes in the scanned area. However its ability to pick up distant metastases is limited.

Fibre optic bronchoscopy: should be performed for all bulky lesions at and above the level of carina to rule out infiltration of tracheo bronchial tree.

Thoracoscopy and laparoscopy for staging has been investigated and have reported increased rate of detecting advanced disease, positive lymph nodes and metastatic disease than non-invasive staging modalities⁶¹. (Level IIb, Grade B).

Functional evaluation:

- 2D ECHO
- PFT + DLCO

A detailed functional evaluation is mandatory for all patients planned for radical treatment (Surgery/ Chemoradiotherapy) and those who have compromised cardiac or pulmonary function. Forced expiratory volume in 1 second (FEV1) and Diffusion Capacity of the lung for Carbon Monoxide (DLCO) have been shown to be independent predictors of pulmonary complications after esophagectomy⁶².

Ideally both PFT and DLCO should be performed for all radically treated patients

Patient optimization

1. Oral hygiene
2. Nutritional assessment for all patients.
3. Enteral feeding as route of choice for patients at risk of malnutrition.
4. Pulmonary rehabilitation for all patients planned for radical treatment/those with compromised lung function. Adequate pulmonary rehabilitation has been shown to significantly decrease the rate of postoperative pulmonary complications after esophagectomy⁶³.

6

STAGING

Disease definition

1. Esophageal squamous carcinoma
2. Esophageal adenocarcinoma
3. Esophagogastric junction tumours Type I, II and some III

Staging

The TNM staging system is the cornerstone of management of esophageal cancers. It forms the basis for all management decisions and prognostication. Staging of cancer is also important for uniform reporting and comparison of results from various centres. It is based on clinical examination, imaging and in the current revised edition the histopathology report of the surgical specimen.

The 7th edition of the AJCC TNM classification (Table 1) came into effect from 2009 and introduced several changes over the previous version.

Some of the key modifications⁴⁸ are:

1. Inclusion of gastroesophageal junction tumours and tumours in the proximal 5 cm of the stomach extending into the esophagus
2. T4 is subclassified as T4A (resectable cancer invasion) and T4B (unresectable cancer invasion).
3. N is subclassified based on the number of positive regional lymph nodes (N1: 1 to 2 nodes; N2: 3 to 6 nodes; and N3: 7 nodes).
4. M classification is redefined based on the presence of distant metastasis, and the term non-regional lymph node is eliminated.
5. Histologic grade and tumor 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. However the present system may not be ideal for baseline clinical staging or staging of patients who have undergone preoperative therapy. This is because of the emphasis on nodal count rather than anatomic location and the introduction of histological grading. However in terms of prognostication the 7th edition is superior to the 6th edition⁴⁸.

Table 1. Esophageal Squamous Cell Cancer

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as the aorta, vertebral body, and trachea
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Histologic grade (G)	
GX	Grade cannot be assessed—stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated—stage grouping as G3 squamous

Anatomic stage/prognostic groups

Stage	T	N	M	Grade	Tumor location
0	Tis (HGD)	N0	M0	1, X	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
IIA	T2-3	N0	M0	1, X	Upper, middle
	T2-3	N0	M0	2-3	Lower, X
IIB	T2-3	N0	M0	2-3	Upper, middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

Table 2. Esophagogastric Junction Adenocarcinoma

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as the aorta, vertebral body, and trachea

Regional lymph nodes (N)

NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes

Distant metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic grade (G)

GX	Grade cannot be assessed—stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated—stage grouping as G3 squamous

Anatomic stage/prognostic groups

Stage	T	N	M	Grade
0	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1-2, X
IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

Principles of management

- Factors deciding treatment
- Location of the disease
- Stage of the disease
- Performance status of the patient

Treatment recommendations

- In lesions within 5 cm of the cricopharynx, concurrent, radical chemoradiation is the preferred therapeutic strategy to surgery ⁶⁴ (level 3, Grade B)
- Surgery is the most effective treatment for resectable esophageal cancer in the middle and lower third and esophagogastric junction ⁶⁵ (Level Ib, Grade A)
- Early stage lesions can be treated with a single modality - Endoscopic mucosal resection ⁶⁶ (T1m N0)/ Surgery (T1/T2,N0) / Surgery (T1/T2,N0) ⁶⁷. (Level 3, Grade B)
- Locally advanced disease (T3/T4a/ Node positive) should receive multimodality treatment. Neoadjuvant chemotherapy/ Neoadjuvant chemoradiotherapy followed by surgery have superior outcomes to surgery alone. There is insufficient evidence to strongly suggest one of the neoadjuvant treatment strategies. (Level I, Grade A).

Patients with metastatic disease should receive treatment which best palliates their symptoms – Palliative radiotherapy/ Esophageal stenting/ palliative chemotherapy. (Level 2, Grade B)

Pre requisites for surgery

- Performance status ECOG 0, 1
- Adequate cardiopulmonary reserve
- Potentially resectable lesion on available investigations

Indications for Surgery

- a. Early stage disease T1/T2, N0
- b. Locally advanced disease T3/T4a, N+ following neoadjuvant treatment
- c. Residual disease following chemoradiation if disease is resectable and patient is in good performance status

- d. Local recurrence following radical chemoradiation if there is no evidence of distant disease and patient is in good performance status

Principles of surgery

General

- Achieve a longitudinal margin of at least 5cm proximally⁶⁸ and distally⁶⁹ from the primary tumour
- Achieve a free circumferential radial margin – No tumour at the cut margin⁷⁰
- Two field lymphadenectomy should be performed. More extensive lymphadenectomy (Three field/ En bloc) may be considered where multiple lymph node fields are involved. However, there is no evidence currently supporting their routine use.
- Minimum lymph node yield of 15 should be achieved⁷¹ to be considered as adequate staging.
- The approach for esophagectomy should be chosen based on
 - e. Location of tumour
 - f. Ability to achieve negative margins and adequate lymphadenectomy
 - g. Least morbidity while not compromising on oncological resection.
 - h. Expertise and experience of the operating surgeon

Surgical Approach

- Lesions involving the middle third of the esophagus are best treated by trans thoracic total esophagectomy with cervical esophagogastric anastomoses. This approach provides the best access for both resection of the primary and lymphadenectomy⁷².
- Lesions involving the lower third of the esophagus and esophagogastric junction can be resected through different approaches. Transthoracic, Transhiatal, Left thoraco abdominal and Ivor Lewis are acceptable approaches⁷³.
- A randomized trial comparing transhiatal esophagectomy to transthoracic esophagectomy and lymphadenectomy for adenocarcinoma of the oesophagus did not find difference in median overall and disease free survival between the two procedures⁷⁴. However, there was a trend towards superior long term (5-year) survival, not reaching statistical significance, in favour of transthoracic esophagectomy (Level Ib, Grade B).
- Similarly a randomized trial comparing trans abdominal transhiatal resection with left thoracoabdominal approach for esophagogastric junction tumours with extension < 3 cm into the esophagus failed to show a survival advantage with a left thoracoabdominal approach⁷⁵. (Level Ib, Grade B).
- The published meta analysis of over fifty trials (both prospective and retrospective) comparing transhiatal to transthoracic esophagectomy did not find any difference in the overall survival but the randomized and prospective comparative studies within the meta-analysis showed a significant difference favouring transthoracic resection⁷⁶. (Level IIc, Grade C).
- In a systematic review consisting of 10 case-control studies comparing open to MIE (minimally invasive surgery), blood loss for MIE (compared to open esophagectomy) was uniformly lower in all studies, whereas hospital and ICU length of stay, total complication rate, and pulmonary complications were significantly lower with MIE in most studies⁷⁷. (Level 2, Grade B)

- The first multicentric randomized trial comparing open versus minimally invasive esophagectomy demonstrated a reduction of almost 30% in pulmonary complications in the minimally invasive group⁷⁸. (Level Ib, Grade B)

However, in view of the lack of strong evidence favouring a particular approach, the preferred surgical approach will continue to be biased by surgeons' choice and experience.

Extent of lymphadenectomy

Lymph node metastasis is one of the most important prognostic factors for carcinoma of the oesophagus.

- Three field lymph node dissection (lower cervical, mediastinal and abdominal) is reported to improve survival without significantly increased procedure related morbidity and similar mortality⁷⁹⁻⁸¹. (Level IIa, Grade B).
- However, most reported studies are small or have compared results with historical controls. A large nationwide survey from Japan showed benefit with three field lymphadenectomy (Level IIa, Grade B)⁸².
- The only randomized trial of over 60 patients reported 18% improved survival with three field lymph node dissection, which however did not reach statistical significance because of the small number of patients⁸³ (Level Ib, Grade B).
- Extensive lymph node dissection provides 'accurate nodal staging' resulting in stage migration and apparent 'improvement in survival'⁸⁴.
- In absence of conclusive Level I evidence, the advantage of three field lymph node dissection over the conventional limited lymph node dissection remains speculative. In fact, an adequately powered randomized trial could answer the question regarding the importance of lymph node dissection in management of carcinoma oesophagus.

Surgical reconstruction

- Stomach is the preferred conduit for reconstruction⁸⁵, if stomach is unavailable, colon or jejunum may be considered.
- If stomach is used as conduit, a pyloric drainage procedure should be considered⁸⁶ (Level I, Grade A). This has been shown to decrease pulmonary complications, especially aspiration.
- Route of reconstruction – Posterior mediastinum or retrosternal are associated with similar perioperative outcomes and conduit function⁸⁷. (Level 1, Grade A)
- Stapled and handsewn anastomoses have similar leak rates but (end to end anastomosis) staplers have a higher rate of anastomotic strictures⁸⁸. (Level 1, Grade A).

Definitive radiation and chemo-radiation therapy

Concurrent *chemoradiation is superior to radiation alone* (Level IA, Grade A). Two published (RTOG and ECOG) randomized trials have reported better overall survival with concomitant chemo-radiation than radiation therapy alone⁸⁹. However, increasing the dose of radiation therapy (50.4 versus 64.8) in concomitant chemo radiotherapy setting did not result in increased survival (Inter Group trial)⁹⁰.

- Meta analysis of 13 trials combining radiation with chemotherapy published in the Cochrane library has reported an absolute reduction in the mortality and local recurrence rate of 7% and 12%

respectively in favour of combination therapy, at the cost of increased life threatening toxicities (Level Ia, Grade A)⁹¹.

- Two trials comparing surgery to radiation alone have reported better survival with surgery (Level Ib, Grade A)⁹².

Based on the available evidence, if a patient is to be treated with definitive non-surgical treatment, it should be concomitant chemoradiotherapy, provided performance status is optimal. However, the issues of radiation volumes (margins to the gross tumor, elective nodal irradiation), total doses and optimal concurrent chemotherapy schedule still remain a matter of debate, with most practice being dictated by individual philosophy. If chemoradiation is used, 5FU with Cisplatin has the maximum evidence but due to logistic reasons, taxane with platinum is commonly used⁹³⁻⁹⁴. (Level II b, Grade B)

Radiotherapy technique: Conventional or 3DCRT are acceptable standards for radiation therapy. IMRT with IGRT may be especially useful for GE junction tumors

Neo-adjuvant Therapy

Pre-operative radiotherapy

A meta analysis as well as the five published randomized trials comparing preoperative radiation therapy to surgery alone have not shown benefit of pre operative radiation over surgery alone⁹⁵. (Level Ia, Grade A)

Pre-operative concomitant chemo-radiation

There are three major trials and several smaller trials comparing preoperative concomitant chemoradiation to surgery alone. Of these, one trial has shown statistically improved survival with chemoradiation⁹⁶.

- Meta analysis of pre operative chemoradiation and surgery to surgery alone (nine trials) has reported improved 3-year survival and reduced loco-regional recurrence⁹⁷⁻¹⁰⁰. (Level Ia, Grade A). However, combination treatment is associated with trend towards increased treatment related morbidity and mortality.
- A recent randomized controlled trial (CROSS) comparing surgery alone to neoadjuvant chemoradiotherapy followed by surgery showed improved R0 resection, pathological response and significantly improved survival (49.4 versus 24 months) in the neoadjuvant group, while the post-operative complications and mortality were similar in both groups²⁹. (Level 1, Grade A)

Pre-operative chemotherapy

There are two major and several smaller published trials of pre-operative chemotherapy in the management of carcinoma of the oesophagus. The two large trials reported results, which are discordant.

- The Intergroup trial of 440 patients reported by Kelsen et al observed no improvement in survival with pre operative combination of cisplatin and fluorouracil among patients with adenocarcinoma or squamous cell carcinoma of the oesophagus¹⁰¹.
- The MRC trial of 802 patients published more recently reported improved survival with two cycles of cisplatin and fluorouracil without additional serious events¹⁰².
- The meta analysis of all trials concludes that preoperative chemotherapy plus surgery appears to offer a survival advantage at 3, 4, and 5 years, which is significantly superior to surgery alone for resectable thoracic esophageal cancer of any histologic type. The number needed to treat for one extra survivor at five years is eleven patients¹⁰³.

An updated meta-analysis in 2011 looked at neoadjuvant therapy given to over four thousand patients with esophageal carcinoma, and found strong evidence for survival benefit with neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy over surgery alone¹⁰⁴. (Level 1, Grade A). A clear advantage of neoadjuvant chemoradiotherapy over chemotherapy has not been established.

In patients with operable gastric or lower esophageal adenocarcinomas, a perioperative regimen of ECF (Epirubicin, 5FU, Cisplatin) decreased tumor size and stage and improved progression-free and overall survival as compared to patients who underwent surgery alone^{105,106}. (Level 1, Grade A).

Chemotherapy regimens commonly evaluated in clinical trials are 5FU /Cisplatin and ECF (Epirubicin, 5FU and Cisplatin)¹⁰⁶. (Level Ia, Grade A). But due to logistics of administration, taxane and platinum based chemotherapy is commonly used¹⁰⁷. (Level IIb, Grade B)

Post-operative radiotherapy

Three trials have compared surgery and postoperative radiation to surgery alone.

- The Chinese trial of 495 patients observed improved 5-year survival in patients with positive lymph nodes and stage III disease receiving postoperative radiation. However, the difference in the overall survival between the two groups was statistically not different¹⁰⁸.
- The meta analysis of all three trials also does not show benefit of postoperative radiotherapy¹⁰⁹. Therefore, in the absence of Level I evidence postoperative radiotherapy is indicated only for patients with positive margin and residual disease.
- For lower third and GE junction adenocarcinomas with the multiple lymph nodes, positive margins, T3 tumors; adjuvant CTRT maybe considered with the increased incidence of treatment related toxicity¹¹⁰. (Level 1, Grade A).

Postoperative chemotherapy

Phase III trials of surgery and post operative chemotherapy have not reported survival benefit over surgery alone.

- A Phase III study by Japanese Clinical Oncology Group (JCOG) reported better disease free survival at 5-year with post operative chemotherapy; however there was no difference in the overall survival¹¹¹. (Level Ia, Grade A).
- In adenocarcinoma of the cardio oesophageal junction (and stomach) postoperative chemoradiotherapy is shown to improve the median overall survival¹¹¹. (Level Ib, Grade A).
- Similarly, another randomized trial (MAGIC) showed superior disease free and overall survival with perioperative (three cycles pre and three cycles post operative) chemotherapy over surgery alone for lower esophageal and GE junction cancers¹⁰⁶. (Level 1, Grade A)
- Thus in patients with adenocarcinoma of the cardia having good performance status, perioperative chemotherapy or postoperative chemo-radiation should be the standard of care^{111,106}. (Level 1, Grade A).

Principles of Radiation therapy

Radical radiotherapy

The inclusion criteria are:

- All lesions in upper / mid / lower esophagus
- Lesion < than 5 cm length (preferred for RT alone)
- Histologically proven esophageal carcinoma
- Karnofsky Performance Status (KPS) of > 60%
- Metastatic work - up negative (No palpable nodes, Bronchoscopy & USG abdomen normal)

External beam radiotherapy (EBRT) alone

Dose : 60 - 64Gy / 30 - 32 fractions, with reducing fields, conventional fractionation

Portal design :

Extended field: esophageal lesion including the lymph drainage areas, with 5 cm margin on either side upto 39.6Gy / 22 fractions/ 4.5 weeks Reduced fields/ boost: Lesion with 3 cm. margins, with oblique portals, upto 60 - 64Gy / 30 - 32 fractions

External beam radiotherapy and brachytherapy

When feasible, external Radiotherapy can be combined with Intraluminal radiotherapy (ILRT) as a boost.

Dose of EBRT : 50.4Gy / 28 fractions with reducing fields.

ILRT Boost : 6Gyx 2fractions high dose rate (HDR), one week apart or single fraction 20Gy low dose rate (LDR).

Concomitant chemo-radiation regimen

1. 50Gy in 25 fractions over 5 weeks, plus cisplatin 75-100 mg/m² intravenously on the first day of weeks 1, 5, 8, and 11, and fluorouracil, 750-1000mg/m² per day by continuous infusion on the first 4 days of weeks 1, 5, 8, and 11 - RTOG regimen⁸⁹.
2. Other concurrent chemo radiation regimen includes Paclitaxel 50 mg/m² and carboplatin at AUC 2 weekly for 5 to 6 weeks - CROSS regimen²⁹.

Principles of Chemotherapy

Neoadjuvant chemotherapy protocols

- Cisplatin 80 mg/m² by infusion over 4 h plus fluorouracil 1000 mg/m² daily by continuous infusion for 4 days every 3 weekly for 2 cycle - MRC protocol¹⁰⁶.
- Cisplatin, at a dose of 100 mg per square meter of body-surface area, given as a rapid intravenous infusion after pre hydration on day 1 followed by 5- fluorouracil administration at a dose of 1000 mg per square meter as a continuous infusion from day 1 through day 5 (120 hours) of each cycle. The cycle to be repeated beginning on days 29 and 58. Surgery performed two to four weeks after chemotherapy - Intergroup trial 011¹¹².
- When Platin and Taxane based neo-adjuvant chemotherapy is used we commonly use Cisplatin 75 mg/m² and Paclitaxel 175 mg/m² every 3 weekly for 3 cycles^{113,114} or docetaxel 75mg/m², 5FU750 mg/m² and Cisplatin 75 mg/m² every 3weekly for 3 cycles¹⁰⁷.

Palliative treatment

1. If the general condition is good,
2. Relief of dysphagia by placement of esophageal stent alone, preferably self expanding metallic stent as these are easy to deploy.
3. Radiation therapy with intubation if associated with significant dysphagia
4. Intraluminal radiation therapy alone.
5. Endoscopic laser destruction of tumour or electrocoagulation.

Palliative radiotherapy

The intent of treatment is to achieve quick and good palliation in the form of relief of dysphagia and pain.

The inclusion criteria are :

- Lesions in upper / mid / lower esophagus
 - Lesion < 10 cm long on barium swallow and esophagoscopy
 - Histologically proven esophageal carcinoma
 - Karnofsky performance status (KPS) of > 50%
 - Recurrent / metastatic disease.
- Dose (EBRT): 3000cGy /10 fractions /2 weeks
 - Portal : Esophageal lesion with 3 cm margin
 - Evaluation and response assessment is done after 2 weeks and further external Radiotherapy or Brachytherapy boost may be delivered. Reduced field / boost: 2000cGy/10# / 2 weeks, using oblique portals^{115,116}.
 - Palliative radiation can also be delivered in the form of ILRT alone or in combination with EBRT. Suggested dose per fraction: 8Gy, in 2fractions, one week apart.
 - There is no difference in local control or survival between high dose rate brachytherapy compared with external beam radiation.
 - Various schedules of brachytherapy have been compared and two fractions of 8Gy are found to be equivalent to three fractions of 6 Gy⁸⁴. (Level 1, Grade A).
 - Addition of EBRT to ILRT improves the dysphagia free survival⁸⁵. (Level1, Grade A)

Palliative chemotherapy

In advanced adenocarcinoma of esophagus palliative chemotherapy improves survival as compared to best supportive care¹¹⁷. (Level I a, Grade A).

Targeted therapy with Trastuzumab along with chemotherapy in Her-2 positive metastatic gastroesophageal cancer has improved survival¹¹⁸. (Level I b, Grade A)

Palliative combination chemotherapy has been used in advanced oesophageal cancers¹¹⁹. Multiple regimens have been used. Chemotherapy relieves dysphagia in majority of patients with dysphagia relief

ranging from 64% to 90% with duration of dysphagia relief ranging from 5.6 months to 9.3 months. There is no trial to show that chemotherapy prolongs survival ⁸⁸.(Level II b, Grade C)

If the general condition is poor with limited life expectancy

1. Nasogastric tube placement for feeding if possible.
2. Supportive care.

Treatment of esophageal fistula

1. Esophageal intubation with stent.
2. Oesophageal and tracheal/bronchial stent placement (double stenting) when possible if the fistula is large or if the tracheal lumen is compromised.

Treatment of Recurrent disease

1. Salvage surgery for localized resectable failures.
2. Palliative treatment or supportive care alone as described before.
3. Locoregional chemoradiotherapy for localized failures post surgery

1. Esophageal carcinoma among young individuals
2. Molecular and genetic diagnosis
3. Role of chemotherapy in the neo adjuvant setting
4. Role of new techniques for diagnosis and management like PET-CT and IMRT
5. Role of targeted therapies

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