

## Review

# Esophageal Cancer and Treatment Modalities

Takalkar Unmesh Vidyadhar, MS<sup>1\*</sup>; Umesh Kulkarni, MS<sup>2</sup><sup>1</sup>Chief Medical Director, Department of Gastroenterology, United CIIGMA Hospital, Aurangabad, Maharashtra, India<sup>2</sup>Consultant, Department of Gastroenterology, United CIIGMA Hospital, Aurangabad, Maharashtra, India

\*Correspondence to: Takalkar Unmesh Vidyadhar, MS; United CIIGMA Hospital, Plot No. 6, 7, Survey No. 10, Shahanoorwadi Dargah Road, Aurangabad-431005, Maharashtra, India; Tel. +91-240-6676666, +91-9822042425; E-mail: drunmesh.aurangabad@gmail.com

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## ABSTRACT

Esophageal cancer is eighth most common cancer worldwide with high biological aggressiveness and poor prognosis. Switching of predominant type from squamous cell carcinoma to adenocarcinoma in Western population, ethnic discrepancies and increased occurrences have identified it as major public health problem. Though monotherapy includes – surgery, radiotherapy and chemotherapy, optimal therapy for esophageal cancer is still debated. Treatment requires a multi-modal approach which includes chemotherapy, radiation therapy with or without surgical follow-up for most patients and chemoradiation for those with inoperable disease; endoscopic therapies, including radiofrequency ablation, endoscopic mucosal resection and endoscopic sub mucosal dissection for Barrett's esophagus/early carcinoma patients and minimally invasive surgical approaches are standards for esophagectomy. Advancement in diagnostic techniques and the multi-modal treatment approach has led to an improvement in the overall survival of esophageal cancer patients.

**Key words:** Esophageal Cancer, Treatment, Surgery, Radiation, Chemotherapy, Chemoradiation.

**Abbreviations:** EC: Esophageal Carcinoma; ESCC: Esophageal Squamous Cell Carcinoma; EAC: Esophageal Adenocarcinoma; BE: Barrett's Esophagus; CT: Computed Tomography; RFA: Radiofrequency Ablation; EMR: Endoscopic Mucosal Resection; ESD: Endoscopic Sub Mucosal Dissection; THE: Transthoracic Esophagectomy; MIE: Minimally Invasive Esophagectomy; RAMIE: Robotic-Assisted Minimally Invasive Esophagectomy; 5-FU: 5-Fluorouracil.

## INTRODUCTION

Esophageal carcinoma (EC) is the eighth most common cancer ranking sixth in mortality worldwide, with developing countries accounting for more than 80% cases as well as deaths.<sup>1</sup> Its aggressive nature and low survival rate makes it one of the deadliest cancer with a low 5-year relative survival rate of meagre 17%. This low survival rate is due to its late stage diagnosis, with more than 50% patients already metastasized and nearly 30% with locally advanced stages.<sup>2</sup> EC is a male dominant disease and is 2-3 times more common in men than women.<sup>1</sup> Recent advances in image-enhanced endoscopic techniques and therapeutics have paved way for its early detection and improved clinical management.<sup>3</sup>

## ESOPHAGEAL CARCINOMA

The two most common histological types of EC are Esophageal Squamous Cell Carcinoma (ESCC) and Esophageal Adenocarcinoma (EAC). Though ESSC is more common histological type worldwide,

EAC occurrences have increased dramatically in past 40 years making it more predominant of the two. Sarcomas and small cell carcinomas account for 1-2% of EC, lymphomas, carcinoids, melanomas being even rarer.<sup>3</sup> ESCC mainly affects middle/lower esophagus, major causes being alcohol and tobacco consumption. EAC affects the distal esophagus with high grade dysplasia and obesity being the risk factors apart from its link with gastro esophageal reflux disease which when untreated progresses to Barrett's esophagus (BE).<sup>4,5</sup> The incidence increases with age in both subtypes.

EC is highly aggressive and may spread by direct extension, lymph system or hematogenous metastasis; latter being more common in advanced stages.<sup>6</sup> Accurate pretreatment staging is crucial as it directly affects the treatment options as well as prognosis. TNM system developed by the American Joint Committee on Cancer is used for assessment as it concentrates on the critical aspect of distinguishing the depth of invasion of the primary tumor (Table 1) which in turn helps determine the stage-specific treatment protocols. (Table 2)<sup>7</sup>

**Table 1.** TNM System indicating depth of invasion in T staging.

Stage of Tumor	Description
Tis	Carcinoma in situ
T1	Tumors invade lamina propria or submucosa
T2	Tumors invade muscularis propria
T3	Tumors invade adventitia
T4	Tumors invade adjacent structures
N0	No regional lymph node metastases
N1	Regional lymph node metastases
M0	No distant metastasis
M1a, M1b	Distant metastasis

**Table 2.** TNM System indicating depth of invasion in T staging.

Stage	Tumor	Node	Metastasis	Therapeutic Options
0	Tis	N0	M0	Local ablative therapy
I	T1	N0	M0	Surgery
IIA	T2	N0	M0	Surgery
	T3	N0	M0	-
IIB	T1	N1	M0	Neo-adjuvant therapy with or without surgery
	T2	N1	M0	-
III	T3	N1	M0	Neo-adjuvant therapy with or without surgery
	T4	Any N	M0	-
IVA	Any T	Any N	M1a	Chemotherapy or radiation therapy with or without surgery
IVB	Any T	Any N	M1b	Palliative treatment

## DIAGNOSIS

EC patients usually present with dysphagia or odynophagia. Confirmation of diagnosis is carried out using imaging tools such as endoscopy, endoscopic ultrasonography, esophagography, computed tomography (CT) and positron emission tomography and is followed by clinical staging.<sup>8</sup> Laparoscopy and thoracoscopy are minimally invasive techniques used for staging where CT fails, while bronchoscopy is used to check for tracheobronchial involvement. Magnetic resonance imaging is rarely indicated to evaluate liver, spine and other lesions.

## TREATMENT

Treatment plan for EC depends on the location and size of lesion, presence/absence of metastases, histological type and patient goals though optimal induction therapy remains controversial. Endoscopic therapies, including radiofrequency ablation (RFA), endoscopic mucosal resection (EMR) and endoscopic sub mucosal dissection (ESD), are considered standard treatment modality for BE and early carcinoma.<sup>9,10</sup> Multimodal treatment, which includes induction therapy – radiation, chemotherapy and chemo-radiotherapy often followed by resection surgical/non-surgical as per disease progression, used in adjuvant or neo-adjuvant setting, remains the primary mode of treatment for most patients.

## SURGERY

For loco-regional disease, surgery is considered primary mode of treatment with mortality rate as low as 3%, 5-year survival rate of 10-40%, and distant metastasis as the most common mode of treatment failure.<sup>11</sup> A total esophagectomy, although controversial,

has become a suggested approach owing to anatomy of the esophageal lymphatics which favors longitudinal spread. Primary esophagectomy techniques are transhiatal esophagectomy (THE) and transthoracic esophagectomy, former of which is associated with reduced operating time, length of stay in hospital, postoperative respiratory complications, and decreased early mortality while the latter with fewer anastomosis leaks, anastomotic strictures, and vocal cord paralysis; with no significant difference between 5-year survival rate.<sup>12</sup> Minimally invasive esophagectomy (MIE) is preferred standard of care with low mortality rate (1.4%) along with robotic-assisted minimally invasive esophagectomy (RAMIE) which has an advantage of improved lymph node dissection.<sup>13</sup> In absence of metastasis, another treatment option is EMR/ESD which aids staging early carcinoma, offers better chance for cure in localized and locally advanced disease while maintaining a five year survival rate between 15-20%. It can be used in conjunction with RFA and cryotherapy ablation to eradicate BE.<sup>10,14</sup>

## RADIATION THERAPY

Radiation therapy when evaluated alone for local control of EC had only 6% 3-year survival rate.<sup>15</sup> Though it was the sole treatment modality used for inoperable ESCC, it had negligible effect on EAC, which is radio-insensitive. Traditionally, it is a standard treatment used for EC, either alone or in combination with surgery but is not recommended as a single therapy due to its association with short as well as long term morbidity and tendency to increase perioperative complications as well as mortality without improving survival.<sup>16</sup> External beam irradiation such as 30 Gy (27) or 49-56 Gy is commonly used and though not capable of converting unresectable cancers into resectable ones, it helps decrease loco-regional recurrence.<sup>17</sup>

## CHEMOTHERAPY

Chemotherapy as a single agent has been shown to have a positive response in up to 50% cases. It may improve baseline dysphagia, downstage a tumor increasing resection rates and improving local control, treat micro-metastatic disease not detected in imaging and has capacity to specify biologic behavior of the tumor based on patient response thus aiding the course of further therapy.<sup>18</sup> But, its relapse rates are high with low long-term survival, toxicity induced morbidity/mortality, disease progression and delay of definitive surgical treatment.<sup>19</sup> Platinum agents (Cisplatin, Carboplatin and Oxaliplatin) and 5-fluorouracil (5-FU) are the most common agents for primary management while Vindesine, Vinorelbine (Navelbine), Topoisomerase Inhibitors and Taxanes (Docetaxel and Paclitaxel- response rates of 20% to 34%) are newer effective single agent chemotherapeutics.<sup>20</sup> Recent literature suggests that a multi-modal approach has yielded better results over single chemotherapy. For example, a 3-drug regimen of DCF (Docetaxel and Cisplatin plus 5-FU) has exhibited a 62% response rate.<sup>21</sup>

## CHEMORADIOTHERAPY/CHEMORADIATION

The aim of concomitant chemotherapy and radiation therapy is to improve local control by radio-sensitizing while simultaneously treating micro-metastases. It has been observed that higher drug concentrations along with exposure yields better results but, is associated with significant toxicity and hence is considered only if the patient is in good health. Accordingly, a combination of 5-FU, Mitomycin and radical radiotherapy is often used for EC management.<sup>22</sup> Cisplatin and 5-FU are synergistic with radiation (30 Gy)<sup>23</sup>, and Gemcitabine, with its potent radio-sensitization capability is another candidate.<sup>24</sup>

## CONCLUSION

EC is an aggressive disease with ESCC being the globally common histological subtype although EAC cases have superseded ESCC in the Western world, especially in Caucasian males. Management of EC is based on histologic type and stage at which it is diagnosed as there is marked difference between the two subtypes not only in characteristics but also in treatment outcomes. The three primary treatment options of EC were surgery, chemotherapy, and radiation therapy which had poor overall survival and high relapse rates when used alone. Hence, there was no consensus upon optimal therapy. Literature suggests a more effective approach of multidisciplinary treatment involving usage of advanced surgical techniques such as MIE/RAMIE, endoscopic treatment, radiotherapy, chemotherapy and chemoradiation along with palliation to improve outcomes as well as prolong patient survival. But, despite advances in surgery, endoscopic therapy and newer therapeutic agents, management of EC remains a great challenge due to its aggressiveness and overall poor survival.

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