

## Original Research Article

# To study the short-term outcome of multimodality treatment on morbidity and quality of life in patients with carcinoma oesophagus

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## ABSTRACT

**Background:** Oesophageal cancer is sixth most common cause of cancer related deaths worldwide. Despite complete resections, overall survival remained low. To improve the existing treatment combination of chemotherapy and radiotherapy in both neoadjuvant and adjuvant settings was introduced. Impact of treatment on quality of life, morbidities and toxicities associated with multimodality treatment in patients of carcinoma oesophagus was studied prospectively and retrospectively.

**Methods:** A total of 40 patients histologically proven carcinoma of the oesophagus were enrolled in the study. Study included assessment of clinical features, risk factors, biopsy, multimodality treatment and associated morbidities and toxicities. Quality of Life (QOL) in patients of multimodality treatment assessed using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Core 18 before, immediate post treatment and 6 months after completion of the planned treatment.

**Results:** In 40 patients, male to female ratio was 1.10:1. Dysphagia was the leading complain. 3 patients were treated using neoadjuvant therapy (chemotherapy and radiotherapy followed by surgery) among them 2 patients expired, 1 patient is under regular follow up. 6 patients underwent upfront surgery followed by adjuvant therapy out of which 3 patients expired, 15 patients were treated with curative intent by definitive chemotherapy and radiotherapy out of which only 7 patients survived for >1 year. 16 patients were treated with palliative intent (radiotherapy, chemotherapy, oesophageal stenting and feeding procedures) in which only 1 patient survived for 1 year.

**Conclusions:** The present study demonstrates that patients over all QOL was reduced after treatment and in the follow up period which was due to the treatment related toxicities but in contrast symptom improvement was observed simultaneously.

**Keywords:** Neoadjuvant therapy, Oesophageal cancer, Quality of life

## INTRODUCTION

Oesophageal cancer is the eighth most common cancer and considered as a serious malignancy with regards to mortality.<sup>1</sup> Surgery remains the primary modality of treatment for localized and locally advanced oesophageal

cancer, despite complete resection; overall survival has remained low due to high rates of loco regional and distant failure.<sup>2</sup> Present study attempt to address the clinico-pathological profile and outcome of multimodality treatment. Morbidity, mortality and quality of life (QOL) related issues were studied by cancer

specific questionnaires in patient of carcinoma oesophagus.

## METHODS

The present study was an observational and descriptive study on morbidities and toxicities associated with multimodality treatment of carcinoma oesophagus and to assess the impact of treatment on QOL. Prior approval was taken from institutional ethical committee. The study was conducted in the Department of Surgery at a tertiary care teaching institute of North India.

Forty patients suffering from the histologically proven carcinoma of the oesophagus were enrolled in study and treatment were as per tumour board recommendations, toxicities and morbidities in the associated treatment were recorded and patients were assessed for QOL using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 18 (EORTC QLQ-C18) questionnaires before, immediate post treatment and after the six months completion of planned treatment.

The following inclusion and exclusion criteria were used while selecting patients:

### Inclusion criteria

- Patients attending the department of surgery and having diagnosis of carcinoma oesophagus would be registered prior to commencement of treatment.
- Patients suffering from the histologically proven carcinoma of the oesophagus.

### Exclusion criteria

- Patients who were lost to follow up.
- Patients with confirmed distant metastasis.

Multimodality treatment options included:

- Neoadjuvant therapy in the form of chemotherapy and radiotherapy followed by surgery.

- Upfront surgery followed by adjuvant therapy
- Radical chemotherapy and radiotherapy
- Palliative (palliative radiotherapy, palliative chemotherapy, oesophageal stenting, feeding procedure)

### Data management and statistical analysis

The data was collected, tabulated, evaluated and described using Microsoft excel software version 2010.

## RESULTS

Total number of patients included in the study were 40, patients age varied from 20 to 80 years, maximum number of patients that is 14 patients (35%) were between 50 to 60 years of age group and only 1 patient (2.50%) was between 20 to 30 years age group. M:F ratio in this study was 1.10:1. The most common risk factor was smoking (47.5%), second most common was alcohol (45%), and the third contributing risk factor was seen in tobacco chewers (35%). Dysphagia was found to be the leading complain that was present in all the patients (100%) most of patients had grade III dysphagia that was sixteen patients (40%) out of forty patients and least common complaint was of hoarseness of voice (2.5%) as shown in Table 1.

**Table 1: Distribution of presenting clinical features of patients with carcinoma oesophagus.**

Clinical feature	Percentage
Dysphagia	100%
Loss of weight	40%
Chest pain	15%
Regurgitation	10%
Hoarseness of voice	2.5%

All 40 patients underwent upper gastrointestinal endoscopy and biopsy, 92.50% patients were squamous cell carcinoma (SCC) and 7.50% were adenocarcinomas. Out of 40 patients, 7.5% showed lesions in the lower 1/3<sup>rd</sup> of oesophagus, 37.50% in middle 1/3<sup>rd</sup> of oesophagus and 55% of patients in the upper 1/3<sup>rd</sup> of oesophagus respectively.

**Table 2: Neoadjuvant treatment and survival.**

	Total	Stage	1 Month	2 Months	3 Months	6 Months	9 Months	>1 Year
Neoadjuvant + Surgery	3	IIIA				1		
		IIIB	1					1

**Table 3: Upfront surgery with adjuvant treatment and survival.**

	Total	Stage	1 Month	2 Months	3 Months	6 Months	9 Months	>1 Year
Upfront surgery	6	IIA				1		1
		IIB	2		1			1

**Table 4: Radical chemotherapy and radiotherapy treatment and survival.**

	Total	Stage	1 Month	2 Months	3 Months	6 Months	9 Months	> 1 Year
Radical chemotherapy and radiotherapy	15	IIB		1				3
		IIIA		1		1	2	2
		IIIB	1			1	1	2

**Table 5: Palliative treatment and survival.**

	Total	Stage	1 Month	2 Months	3 Months	6 Months	9 Months	1 Year
Palliative treatment	16	IIIA	2					
		IIIB	1	1	1	1		1
		IV	2	5		2		

Multimodality treatment options included were neoadjuvant therapy in the form of chemotherapy and radiotherapy followed by surgery which included 3 patients, 1 patient expired at 1 and 6 month respectively only one patient is still alive as shown in Table 2.

6 patients were included in upfront surgery followed by adjuvant therapy in which 4 patients expired and two patients survive more than one year (Table 3). In radical chemotherapy and radiotherapy treatment as shown in (Table 4), out of 15 only 7 patients survived for more than 1 year.

Palliative treatment included 16 patients in which only 1 patient survived up to 1 year (Table 5).

All the patients were followed and looked for grades of toxicities and morbidities caused by multimodality treatment. 36 patients had acute toxicities which gradually decrease at 3<sup>rd</sup> and 6<sup>th</sup> month. The maximum number of patients had weakness, vomiting and malnutrition. Some of the patients had these toxicities and morbidities in common. Morbidity observed which was related to surgery, post-surgery 3 patients expired due to pulmonary sepsis.<sup>1</sup> patient had minor anastomotic leak which was managed conservatively. All 7 patients had malnutrition and pain post-surgery which was gradually decreased at 3<sup>rd</sup> and 6<sup>th</sup> month respectively.

The longitudinal measurement of functional scale, QOL, EORTC QLQ-C30 physical function score at baseline, post treatment and six months follow up in patients who underwent multimodality treatment for carcinoma oesophagus. Post treatment 13 and 6 month follow up 26 patients expired respectively. Baseline physical functioning score was 78.80±19.45 which become poorer just post treatment that was 35.20±21.24 and persisted throughout the follow-up period that was 15.05±23.87 in remaining patients respectively.

EORTC QOL-QES 18 score (dysphagia, eating and pain) the longitudinal measurement of functional scale, QOL EORTC QLQ-QES 18 dysphagia, eating and pain score

at baseline, post treatment and 6 months follow up in patients who underwent multimodality treatment for carcinoma oesophagus was done. Post treatment 13 patients and 26 patients at six month follow up expired respectively. Dysphagia, eating and pain as significantly better following post treatment and persisted throughout the follow up period.

## DISCUSSION

Oesophageal cancer usually presents later in life as in our study maximum number of patients that is 14 were more than 50 years of age comparing with the Naufal Rashid Net al which were cohort studies observed that the incidence of oesophageal cancer increases with age the average of onset is between 65 to 70 years.<sup>3</sup> Male predominance was seen in this disease such that 21 cases (52.50 %) were male and 19 (47.50 %) were female. M:F was 1.10:1. Comparing with study, In Socialstyrelsen, National Board of Health and Welfare, Sweden and by Melhado RE et al observed that oesophageal cancer is three times more common in men than in women, most common risk factor for oesophageal cancer was smoking (47.5%).<sup>4,5</sup> In present study and the study done by Daly JM et al, Muwonge R et al and Talback M et al had same observation.<sup>6-8</sup>

Patients mostly present with complain of dysphagia such that it was found to be the leading complain in our study was present in all the patients (100%) and 16 patients (40%) out of 40 patients presents with grade III dysphagia. Talback M et al Fitzgerald K et al both of them observed that dysphagia was found to be the leading complain and other complains were loss of weight and hoarseness of voice.<sup>8,9</sup> Study done by Mchembe MD et al observed that grade IV dysphagia (43%) was most common at the time of presentation followed by least common grade II dysphagia (4.6%) that was dissimilar to present study.<sup>10</sup>

Histopathological examination in our study revealed that most patients 92.50% had SCC and minimum patients 7.50% had adenocarcinoma and same was observed by

Napier KJ et al, Brown LM et al, Erasmus JJ et al respectively.<sup>1,3,11</sup>

Multimodality treatment and survival of patients was seen for carcinoma oesophagus, neoadjuvant therapy which was followed by surgery, it was found that in present study perioperative morbidity and mortality is higher after neoadjuvant chemotherapy and radiotherapy and as observed by Kreditsu KK et al.<sup>12</sup> MRC studies showed benefit with neoadjuvant chemotherapy and Sjoquist KM et al in meta-analysis found that definite survival benefit with preoperative chemotherapy in locally advanced oesophageal cancers.<sup>13,14</sup> The meta-analysis conducted by Arnott et al reported a poor benefit rate with preoperative radiotherapy alone.<sup>15</sup> Burmeister BH et al found that most published randomized clinical trials comparing local modalities have not shown a survival benefit but rather one in terms of local control and improved resectability where surgery has been involved.<sup>16</sup>

Upfront surgery with adjuvant therapy and survival, in present present study 4 patients who received postoperative radiation therapy 2 patients expired following surgery due to pulmonary sepsis, it was observed that survival was not improved significantly with the addition of RT, comparing with the study done by Xion et al included 495 patients with SCC of the oesophagus who received postoperative radiation therapy (n=220) or surgery alone (n=275) and survival was not improved significantly with the addition of RT (only change observed was of from 32% to 41%).<sup>17</sup>

Radical chemotherapy and radical radiotherapy was done in 15 patients (37.50%) seven patients survived for more than 1 year thus comparing with the study done by Cooper JS et al in their study 134 patients of radiation therapy oncology group (RTOG) 85-01 trial were randomized to cisplatin combined with infusional fluorouracil and concurrent radiation or to radiation alone.<sup>18</sup> The 5 year overall survival was 27% vs. 0% with radiation alone and thus they concluded that combined therapy increases the survival of patients who have SCC or adenocarcinoma of the oesophagus, T- 1-3 N- 0-1 M- 0, compared with RT alone.

Palliative treatment was given to 16 patients out of 40 patients. These patients underwent palliative treatment. Patients had low performance status so concurrent chemoradiotherapy (CIRT) and radical surgery was not done and in our present study maximum number of patients that is 11 out of 16 died within 2 months in comparison to study done by Parkin DM et al which was a case-control study showed that the median survival time for patients with advanced oesophageal cancer was only 3-5 months.<sup>19</sup>

Siersema PD et al found that endoscopic placement of SEMS has become the most widely practiced treatment for palliative care, in part due to the comparatively simple

technique and rapid effect on dysphagia.<sup>20</sup> Jiang XJ et al suggested that after stents placement, 3D-CRT could be performed as long as patient's physical condition allowed, and whenever their dysphagia was relieved, the malnutrition of the patients was ameliorated.<sup>21</sup> In this study, compared with the patients treated with stenting only, at least 25% of the inoperable patients after 3D-CRT survived one year, and their 6 month survival rate was also higher. Though, Fietkau et al thought that simultaneous CRT should be considered as the standard treatment for inoperable carcinoma of the oesophagus with the median survival time between 13 and 18 months.<sup>22</sup> The reason why Fietkau's result was better than ours may be that there were more inoperable stage III /IV patients in present study as compared with the stage II/III patients in Fietkau's study.

Morbidity related to the chemotherapy, radiotherapy and surgery, 36 patients had acute toxicities which gradually decreases at 3<sup>rd</sup> and 6<sup>th</sup> month. The maximum number of patients had weakness, vomiting and malnutrition. Some of these patients had these toxicities/morbidities in common. Post-surgery 3 patients expired due to pulmonary sepsis. 1 patient had mild anastomotic leak which was managed conservatively. All 7 patients had malnutrition and pain post-surgery which was gradually decreased at 3<sup>rd</sup> and 6<sup>th</sup> month. Study done by Staal et al found that frequently reported toxicities with NACTRT are neutropenia, which may occur in up to 60% of patients, oesophagitis grade 3/4 in up to 43% and nausea and/or vomiting, with 6 to 35% requiring some form of nutritional support (enteral or parenteral) during CIRT.<sup>23</sup> Anbai a et al<sup>14</sup> shows the incidences of acute toxicities associated with CIRT. Grade III leukopenia was observed in 40 patients (35.1%). Grade III neutropenia occurred in fourteen patients (12.3%). Grade III anemia occurred in 15 patients (13.2%), other complications included Grade III-IV thrombocytopenia, grade III or higher severe oesophageal ulcer and fistula formation, and three patients died because of respiratory failure due to pneumonia followed by fistula formation. In addition, included grade III or higher severe lung disorders, pleural effusion, pericardial effusion, grade V cerebrovascular ischemia. Toxicities such as oesophageal fistula, radiation pneumonitis, pleural effusion, pericardial effusion, and cerebral infarction may have contributed to the deaths of seven patients (6.1%). Blazeby JM et al in their study have also seen pulmonary complications and anastomotic leak are the major morbidities and mortalities post-surgery in oesophageal carcinoma.<sup>24</sup>

EORTC QOL 30 (physical functioning), the longitudinal measurement of functional scale, QOL, physical function score at baseline, post treatment and 6 months follow up was observed in patients who underwent multimodality treatment for carcinoma oesophagus. Post treatment 13 and 6 month follow up 26 patients expired respectively. Baseline physical functioning score was 78.80±19.45 which become poorer just post treatment that was 35.20±21.24 and persisted throughout the follow up

period that was  $15.05 \pm 23.87$ . Whereas study done by Malmstrom M et al in 79 patients who completed the EORTC QOL questionnaires (QLQ-C30 and QLQ-OES18) before and 2,4,6,9, and 12 months after surgery.<sup>25</sup> Results for the function scales (QLQ-C30) exhibited an overall significant deviation in experienced function levels over time ( $p=0.006$ ). Blazeby JM et al had also observed in a study of 92 patients in all functional scale was poorer after treatment.<sup>24</sup>

EORTC QOL-QES 18 score (dysphagia, eating and pain) the longitudinal measurement of functional scale, QOL EORTC QLQ-QES 18 dysphagia, eating and pain score at baseline, post treatment and 6 months follow up in patients who underwent multimodality treatment for carcinoma oesophagus was done. Post treatment 13 patients and 26 patients at six month follow up expired respectively. Base line dysphagia was significantly better following post treatment and persisted throughout the follow-up period. Study done by Shen H et al the EORTC QLQ-OES 18 scores demonstrated that the postoperative dysphagia scores of the patients in both groups were significantly lower compared to their preoperative scores.<sup>26</sup>

Eating and pain was significantly better following post treatment and persisted throughout the follow-up period. Malmstrom M et al they also observed that quality of life EORTC QLQ-QES 18 post treatment in carcinoma patients there was improvement in symptoms that was pain and eating significantly.<sup>25</sup>

## CONCLUSION

The present study demonstrates that patients over all QOL was reduced after treatment and in the follow up period which was due to the treatment related toxicities but in contrast symptom improvement was observed simultaneously.

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