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Original Article

Prospective Analysis of Quality of Life in Patients with Inoperable Esophageal Carcinoma with Definitive Concurrent Chemoradiotherapy – A Single-center Study

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Abstract

Introduction: Cancer of the esophagus is a fatal disease and ranked the 6th most common cause of cancer-related death worldwide. Treatment for esophageal carcinoma is characterized as curative or palliative. Data from different studies show only 20% of patients present with cancer of the esophagus that is truly localized to the esophagus, indicating that at the time of diagnosis, approximately 80% of patients have either locally advanced or distant disease.

Aim: This study aims to study the clinical assessment of quality of life (QOL) before, during, and after treatment of concurrent chemoradiotherapy in inoperable esophageal cancers.

Materials and Methods: A single-arm prospective study of patients undergoing definitive chemoradiation treatment for locally advanced esophageal carcinoma was included in the study. All patients will have to undergo QOL assessment by the European Organisation for Research and Treatment of Cancer questionnaire before, during, and after treatment.

Results: A total of 40 patients were included in the study. Among the functional scales, emotional functioning, cognitive functioning, role functioning, physical functioning, and anxiety show a significant positive mean difference. This indicates a healthy level of functioning after treatment.

Conclusion: Definitive concurrent chemoradiation with cisplatin and 5-fluorouracil (FU) was well tolerated, promising a reasonable therapeutic option for patients with inoperable locally advanced esophageal squamous cell carcinoma.

Key words: Chemoradiotherapy, Esophageal cancer, Quality of life

INTRODUCTION

Cancer of the esophagus is a highly lethal malignancy which is the 6th most common cause of cancer deaths worldwide and is more common in men than women.[1] It is an endemic in many parts of the world, particularly in the developing nations, where it is the 4th most common cause of cancer-related deaths.[1] In 2015, an estimated 16,980 people will be diagnosed with esophageal cancer and 15,590 people will eventually die of their disease in the United States.[2] High prevalence areas include Asia, Southern and Eastern Africa, and Northern France.[3]

According to the data from the US Surveillance, Epidemiology, and End Results Program, the 5-year survival for all patients with esophageal cancer improved only modestly over the past 30 years, from 5% in the years 1975–1977 to 19% during the period of 2001–2007.[2] These sobering figures were indicative of the advanced stage of disease (local-regional or metastatic) at diagnosis in most patients.[3]

The management of local-regional esophageal cancer has undergone a major evolution over the past 25 years.

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The low cure rates after locoregional therapy alone prompted the inclusion of systemic chemotherapy (CRT) in multimodality treatment approaches, to control distant micrometastatic disease and enhance local radiation effects. The seminal Radiation Therapy Oncology Group (RTOG) 85-01 randomized controlled trial demonstrated a survival benefit for the addition of cisplatin-based CRT to radiation therapy in non-surgically treated patients.[4,5] Less than one-third of all patients were cured by multimodality therapy, and distant failure accounts for three-fourths of all recurrences.[6]

Despite many advances in both surgery and radiotherapy, the treatment of esophageal cancer remains a challenge for both surgeons and clinical oncologists. The biggest problems affecting patient outcomes are late presentation, as most symptomatic patients present with advanced disease and the lack of an effective screening program. Only a minority of patients is suitable for curative treatment, and 5-year survival for all patients remains poor at just 13% and surgical series report survival of 20%. This overview examines the role of definitive chemoradiotherapy (dCRT) in localized esophageal cancer.[5]

For patients with early localized and resectable disease, surgery, with or without neoadjuvant CRT, remains widely regarded as the gold standard treatment option, leaving dCRT as an alternative for those patients unsuitable for surgery due to medical comorbidities and extent of locoregional disease.[5-7] With the emergence of improved radiotherapy techniques with lower rates of morbidity, together with the development of more effective and targeted systemic therapy, the trend toward treating more patients with organ-preserving dCRT or as part of trimodality treatment is likely.

Aim

This study aims to study the clinical assessment of quality of life (QOL) before, during, and after treatment of concurrent chemoradiotherapy in inoperable esophageal cancers.

MATERIALS AND METHODS

A single-arm prospective study of patients undergoes definitive chemoradiation treatment for locally advanced esophageal carcinoma at the department of radiotherapy and oncology in a tertiary care hospital.

Inclusion Criteria

The following criteria were included in the study:

1. Histologically confirmed, potentially unresectable squamous cell carcinoma of the esophagus.
2. Tumors of clinical stage T4N0 or T4 N1-3.
3. Inoperable or locoregionally advanced disease.
4. Age group 30–70 years.
5. Both male and female.
6. WBC count >4000 cells/mL.
7. Platelet count of >100,000 platelets/mL.
8. Serum creatinine <1.5 mg/dL.
9. Creatinine clearance>80 mL/min.

Exclusion Criteria

The following criteria were excluded from the study:

1. Histology other than squamous cell carcinoma.
2. Operable carcinoma esophagus.
3. Presence of tracheoesophageal fistula.
4. Age >70 years.
5. WBC count <4000 cells/mL.
6. Platelet count <100,000 platelets/mL.
7. Creatinine clearance <80 mL/min.

Initial Assessment

Staging including contrast-enhanced computed tomography scan of thorax, abdomen, and upper gastrointestinal (GI) endoscopy and biopsy for histological confirmation will be done along with routine blood examinations. All patients will have to sign informed consent forms. All patients will have to undergo QOL assessment by the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire before, during, and after treatment.

Radiotherapy

All patients will be irradiated by external beam radiation with megavoltage beams on telecobalt machine with a total dose of 50.4 Gy given in 28 fractions of 1.8 Gy per fraction, five fractions per week, starting the 1st day of the first cycle of CRT. The gross tumor volume (GTV) is defined by the primary tumor and any enlarged regional lymph node and will be drawn on each relevant CT slice. The GTV will be determined using all available information (physical examination, endoscopy, and CT thorax/abdomen). The planning target volume will provide a proximal and distal margin of 5 cm. A 2 cm radial margin around the GTV will be provided to include the area of subclinical involvement around the GTV and to compensate for tumor motion and set-up variations.

CRT

5 fluorouracil (FU) (1000 mg/m^2) × 4 days and cisplatin (75 mg/m^2) will be given by intravenous infusion on weeks 1, 5, 8, and 11. All patients receiving cisplatin must be hydrated before, during, and post-drug administration. Usual approach is to give at least 1 l before and 1 l post-drug treatment of 0.9% sodium chloride. Mannitol diuresis may be used after hydration. They will also receive

premedication ½ h before the start of the cisplatin infusion. Standard antiemetic prophylaxis of 3 mg of granisetron and 16 mg of dexamethasone and 50 mg of ranitidine will be given as intravenous bolus as pre-medication. Antiemetic prophylaxis will be continued with granisetron orally 3 days after each cycle of CRT.

Evaluation of Patients during Treatment

The regimen will be administered on an outpatient basis. During irradiation, all patients were scored weekly during the course of CRT for early toxicity skin reaction, GI toxicity, and neutropenia using the RTOG/EORTC acute radiation morbidity scoring scheme. Clinical examination, complete blood picture, and liver and kidney function tests were done before each cycle.

Table 1: Comparison of EORTC QOL before and after treatment

Dimensions	Mean±standard deviation of score			Z-value	*P* value
	Before	During	After		
Eating	11.6±1.97	13.08±1.53	8.92±1.63	5.263**	<0.001
Reflux	3.28±1.65	3.95±1.96	3.16±1.35	1.645ns	0.100
Pain	5.73±2.23	8.49±2.35	3.84±0.89	4.416**	<0.001
Trouble swallowing saliva	1.88±0.69	2.62±0.78	1.26±0.45	4.234**	<0.001
Chalked when swallowing	1.7±0.88	1.9±0.94	1.18±0.39	3.275**	0.001
Dry mouth	1.3±0.46	1.74±0.59	1.26±0.45	1.000ns	0.317
Trouble with taste	1.65±0.66	2.64±0.78	1.29±0.46	3.153**	0.002
Trouble with coughing	1.55±0.71	2.31±1	1.39±0.5	2.646**	0.008
Trouble with talking	1.1±0.3	1.62±0.67	1.08±0.27	1.000ns	0.317
Dysphagia	9.25±1.43	7.36±1.4	12.53±16.5	3.329**	0.001

**: Significant at 0.01 level, *: Significant at 0.05 level, ns: Non-significant at 0.05 level. QOL: Quality of life, EORTC: European Organisation for Research and Treatment of Cancer

Follow-up

The patients will require to follow-up at 6 weeks from completion of therapy to assess response, toxicity, and disease status. Subsequent follow-up visits will be scheduled at 3 monthly. At follow-up, patients will undergo thorough clinical examination for detection of locoregional disease. Patients who drop out or do not complete planned course of treatment will be excluded.

RESULTS

The median age of the study population was 58.2 years that range from 45 to 70 years. Majority of the population were between 51 and 60 years. 8 of 38, 20% were female and 32 patients were male (80%). 26 patients (65%) were using both alcohol and smoking, 7 patients (17.5%) smoking only, and 4 patients (10%) were addicted to smoking, alcohol, and pan chewing.

Five patients (12.5%) had upper one-third of esophagus, as primary site of disease, 13 patients (32.5%) had lower one-third and majority of patients being affected at middle one-third as primary site (55%).

Seven patients had T_2 tumor, 25 patients had T_3 tumor, and eight patients being affected as T_4. 19 patients with N_1, 18 patients with N_2, and 3 patients had N_3 nodal involvement of the disease [Figure 1].

Stage wise, 40% of the patients were Stage 3A and only 10% were Stage 2B. Stage 3B and Stage 3C constitute 25% each of the total number of the patients [Figure 2].

Neutropenia was absent for 40% of the total population, Grade 1 for 12 (30%) patients, Grade 2 for 6 (15%), Grade 3 for 5 (12.5%), and Grade 4 for one patient [Figure 3].

Table 2: Comparison of QLQ before and after treatment

Dimensions	Mean±standard deviation of score			Z-value	*P* value
	Before	During	After		
Global health status	7±1.34	5.33±1.2	8.18±2.4	4.043**	<0.001
Physical functioning	9.85±1.56	11.51±1.54	9±2.11	4.134**	<0.001
Role functioning	5.45±1.13	6.23±1.11	5.26±1.22	2.041*	0.041
Emotional functioning	8.78±1.8	9.38±1.93	8.29±1.49	3.305**	0.001
Cognitive functioning	4.98±1.53	5.31±1.51	4.47±1.2	4.185**	<0.001
Social functioning	4.55±1.15	5.33±0.93	4.18±1.01	3.578**	<0.001
Fatigue	7.45±1.58	8.31±1.51	6.68±1.44	4.604**	<0.001
Nausea and vomiting	4.58±1.62	5.79±1.2	3.74±1.01	4.647**	<0.001
Pain	5.45±1.01	6.15±0.93	4.08±0.88	4.959**	<0.001
Dyspnea	1.85±0.74	2.38±0.85	1.76±0.71	2.000*	0.046
Insomnia	2.4±0.59	2.82±0.6	1.74±0.5	4.327**	<0.001
Appetite loss	2.48±0.6	2.79±0.8	1.58±0.55	5.014**	<0.001
Constipation	1.63±0.71	1.69±0.69	1.39±0.55	2.324*	0.02
Diarrhea	1.4±0.5	2.49±0.85	1.34±0.48	0.535ns	0.593
Financial difficulties	1.68±0.62	2.62±0.78	1.53±0.56	1.508ns	0.132

**: Significant at 0.01 level, *: Significant at 0.05 level, ns: Non-significant at 0.05 level. QOL: Quality of life

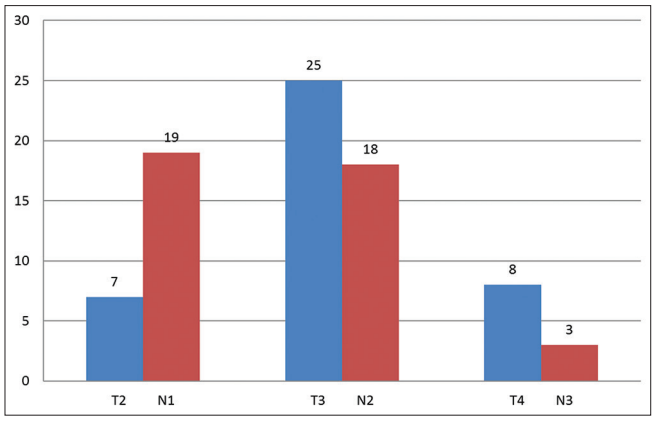

Figure 1: Computed tomography tumor, node, and metastasis

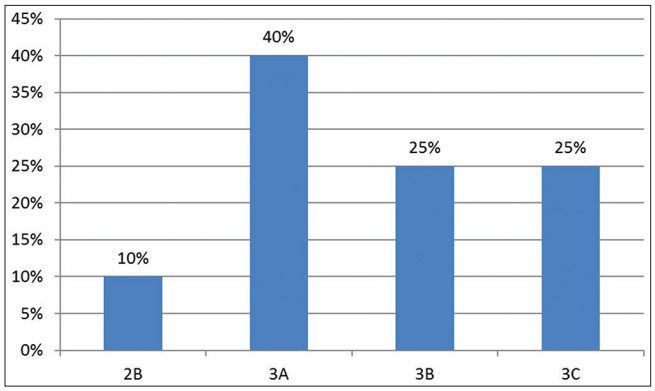

Figure 2: Computed tomography stage

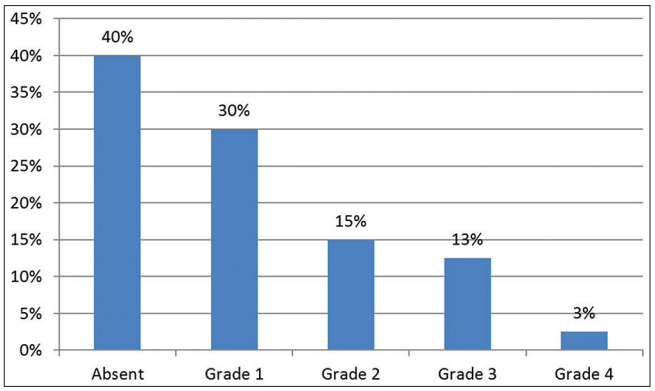

Figure 3: Neutropenia grade

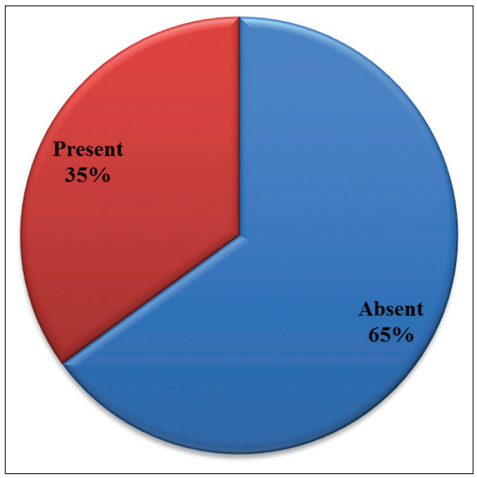

Figure 4: Disease progression

Disease progression was seen in 14 patients (35%) of the total population that include death during the time of treatment and during follow-up. Disease progression was absent in 26 patients until the last follow-up [Figure 4].

Among the functional scales, emotional functioning, cognitive functioning, role functioning, physical functioning, and anxiety show a significant positive mean difference. This indicates a healthy level of functioning after treatment.

Considering the symptom scale scores, except for financial difficulties and diarrhea, other symptoms show a significant mean difference.

All other symptoms decreased after radiation, of which pain, trouble swallowing saliva, chalked when swallowing, trouble with coughing, trouble with talking, and dysphagia show a significant reduction. Global health score also shows a significant improvement after definitive concurrent chemoradiation [Tables 1 and 2].

DISCUSSION

Esophageal cancer is usually associated with a poor prognosis due to a high local recurrence rate or distant metastasis.[8] Although surgery alone or chemoradiotherapy has been widely accepted as the standard treatment for esophageal cancer, the 5-year survival rate is only 20–30%.[9,10] The most efficient treatment remains uncertain as there are only a few clinical trials that have compared chemoradiotherapy and esophagectomy.[11,12] It is well known that radiotherapy can cause numerous complications including radiation esophagitis, radiation pneumonitis, and anorexia.[13,14] During radiotherapy, dysphagia of patients may become aggravated due to radiation edema of the esophagus, which induces a feeding disturbance. Patients who have undergone esophagectomy also suffer from continual problems associated with the function domains and specific symptoms. Particular studies have indicated that surgery also has an effect on the QOL.[15,16] QOL is one of the important factors for patients choosing to undergo therapy, particularly for older patients. Therefore, it is important to determine the variation in QOL for different treatments, and investigation of the factors that affect the QOL is necessary to provide a reference for clinicians to improve the QOL for patients. Since the 1990s, the potential contribution of the QOL for cancer therapy evaluation has gained increasing recognition. QOL assessment has been used to identify the optimal

therapy, estimate the efficiency of drugs and as one type of indicator for the prognosis of cancer.

QOL assessment using EORTC guidelines showed decrease in symptoms after completion of definitive chemoradiotherapy, even though there was an apparent increase in symptoms for the patients during the time of concurrent chemoradiation. Among the functional scales, emotional functioning, cognitive functioning, role functioning, physical functioning, and anxiety showed a significant positive mean difference. That indicates a healthy level of functioning after treatment and all other symptoms decreased after radiation, of which pain, trouble swallowing saliva, chalked when swallowing, trouble with coughing, trouble with talking, and dysphagia showed a significant reduction. Global health score also shows a significant improvement after definitive concurrent chemoradiation. All these findings were statistically significant, providing a clear advantage of concurrent chemoradiation in inoperable esophageal carcinomas.

CONCLUSION

Definitive concurrent chemoradiation with cisplatin and 5-FU was well tolerated, promising a reasonable therapeutic option for patients with inoperable locally advanced esophageal squamous cell carcinoma. QOL assessment using EORTC guidelines showed decrease in symptoms after completion of concurrent chemoradiotherapy, even though there was an apparent increase in symptoms for the patients during radiotherapy.

Further studies with larger sample size are required to confirm the effect of definitive concurrent chemoradiation on QOL in inoperable disease status of carcinoma esophagus. The need of adjuvant treatment in reducing the progression of locally advanced disease should be evaluated. Carefully designed randomized clinical trials with more number of patients would be the answer to these issues.

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