Original Article

Chemoradiation therapy for oesophageal carcinoma in Sudan

Ahmed MA Dirweesh, CMD, Mohamed ElMakki Ahmed MS, FRCSI

Department of Surgery, Faculty of Medicine, University of Khartoum

Abstract

Background

Chemoradiotherapy is an established form of treatment in oesophageal cancer as radical, palliative, adjuvant or neo-adjuvant therapy. The aim of this study is to evaluate the role of chemo-radiotherapy treatment, its morbidity and outcome in patients with oesophageal cancer referred to the Radio-Isotope Centre Khartoum.

Patients and Methods

During the period from July 2007 to July 2009, a total of 148 patients were studied prospectively; 78 patients with early disease and 70 patients with advanced or metastatic disease. The protocol of management included six cycles of 5-FU continuous infusion for 24-48 hours (1g/m2) and cisplatin {CDDP} (60 mg/m2) on day one, followed by an external beam radiation dose of 20-50 Gy in 20-25 fractions (5Fs/week). Clinical responses, survival data and treatment toxicities were graded according to the National Cancer Institute common toxicity criteria.

Corresponding author

Ahmed MA Dirweesh
E-mail: dirweesh79@hotmail.com
Results

There were 107 patients with squamous cell carcinoma and 41 were with adenocarcinoma. Radical chemoradiotherapy was given to 78 patients with early disease. Partial clinical response occurred in 45% (n=35) while 41% (n=32) showed no response. Renal impairment occurred in 81% of patients (n=63), diarrhea in 78% (n=61), myelosuppression in 52% (n=41) and 4 patients died (5%).

In those with advanced and metastatic disease (n=70), partial clinical response was reported in 33% of the patients (n=23) while 67% (n=47) patients showed no response. Adverse gastrointestinal reactions occurred in 54% of patients (n=38); pneumonitis in 28% (n=19), meningoencephalitis in 15% (n=13) and 39 patients died (56%).

Conclusion

In our settings, unsatisfactory clinical responses with high rate of adverse reactions were seen in patients with oesophageal cancer receiving chemoradiotherapy. A more critical approach is needed to this therapeutic modality.

Introduction

Oesophageal cancer is the ninth most common cancer in the World and the fifth most common cancer in developing countries. It is now one of the most common causes of cancer deaths among blacks. Presently, the ordinary non-surgical treatment of oesophageal cancer is parallel chemotherapy and radiotherapy (chemoradiation) with results comparable to best surgical series, however, direct comparison between chemoradiation and surgery alone in treatment of oesophageal cancer is a bit difficult due to lack of well-controlled randomized data. Globally, combination of preoperative (neoadjuvant) chemoradiation and surgery is now being tested in many clinical trials to improve the relatively gloomy survival outcome.

The relative frequency of oesophageal cancer in Sudan is 5.4% which accounts for >60% of gastrointestinal cancers in patients seen at the Radio-Isotope Centre Khartoum (RICK). Facilities for either surgical treatment or chemoradiotherapy (CRT) are simply available in Khartoum and in Medani for the latter modality. The aim of this study was to evaluate the role of chemoradiotherapy treatment, its morbidity and outcome in patients with oesophageal cancer referred to RICK.

Patients and Methods

In the period from July 2007 to July 2009, 148 patients with oesophageal cancer were randomly selected for enrollment in a prospective, hospital based, analytical study conducted in Radio-Isotope Centre Khartoum (RICK). Patients included were those with histologically confirmed oesophageal cancer (squamous or adenocarcinoma). Patients with tumors extending 4 cm or more into the stomach, previous CRT to the chest or abdomen, pre-existing arrhythmias or heart failure were excluded. Patients were divided into two groups: Group A - who received definitive therapy for early disease (n=78) and Group B were those given palliative treatment for advanced disease (n=70).

The definitive chemoradiation protocol given was as follows: six cycles of 5-FU as continuous infusion for 24-48 hours (1g/m2) and cisplatin (60 mg/m2) on day one. This was followed by an external beam radiation dose of 40-50 GY in 20-25 fractions (5 Fs/week).

The palliative protocol for patients with advanced and metastatic disease consisted of six cycles of 5-FU and cisplatin on day one. This was followed by radiation dose of G20/5F – G30/10F in the form of 5 fractions per week. An overall dose of chemotherapy was given to 63% of patients while all the cases received full radiation dose.

Analysis of the histopathological results, hospital stay, acquired clinical response, and
treatment-related morbidities and mortalities for each group was performed. Evaluation of clinical response was performed through upper gastrointestinal endoscopy, barium study and CT scan when indicated. A complete response (CR) was defined as 100% regression of all visible tumors at the primary site. A partial response (PR) was defined as a ≥50% reduction in the tumor and no response was defined as a ≤50% reduction in the tumor. Progressive disease (PD) was defined as a ≥25% enlargement of the tumor or the appearance of a new tumor which had not been observed before the CRT. Clinical tumor response was assessed at a median of 3 weeks after treatment completion. Patients were considered to have a complete clinical response (CCR) to CRT when no residual tumor was identified on endoscopy and when no metastatic disease occurrence was observed on CT-scan. Patients were followed for 2-12 months with an average of 7 months. All statistical analyses were performed by SPSS statistical software version 9.0. P values of <0.05 were considered significant.

Results
One hundred and forty-eight patients were included, 78 patients (52.7%) were in Group A (early disease) and 70 patients (47.3%) in Group B (advanced disease). The mean age was 62 ± 11.4 years with a male: female ratio 1.5:1.
One hundred and seven patients were squamous cell carcinoma (72%) while 41 were with adenocarcinoma (28%).
The tumor was in the middle third in 79 patients (53%), the lower third in 56 patients (38%) and the upper third in 13 patients (9%). The hospital admission time ranged from 1-4 days with a mean duration of 51 hours.
In Group A, complete clinical response occurred in 7 patients (9%), partial response in 35 patients (45%) and no improvement in 21 patients (27%). In addition, the dysphagia became worse in 11 patients (14%). All patients had post treatment nausea and vomiting. Furthermore, renal impairment was reported in 81% (n=63), diarrhea in 78% (n=61), myelosuppression in 52% (n=41) acute neurological manifestations in 41% (n=32), peripheral neuropathy in 37% (n=29) and alopecia in 13% of patients (n=10).
Radiation related morbidities were divided into either acute or late. Under the acute morbidities, esophagitis occurred in 97% (n=76) and acute dysphagia in 96% (n=75) of patients. Twenty-seven percent of patients (n=20) had skin changes while pneumonitis was seen in 24% (n=19). Late complications included mediastinal fibrosis in 3% (n=3) and post-radiation oesophageal stricture in 2% (n=1) of patients.
Four patients (5%) died during the course of the treatment program due to acute gastroenteritis (n=3) and acute pneumonia (n=1).
In Group B, patients with locally advanced or metastatic disease, no patient had complete clinical response. Twenty-three patients had a partial response to chemotherapy (33%) and 47 patients (67%) had the no response at the end of treatment course. Following chemotherapy, 12 patients (17%) remained with a static disease and by the end of the chemoradiation course 11 patients (16%) were static. Symptoms got worse in 18 patients (26%) who had only chemotherapy and this number increased to 43 patients (61%) after the chemoradiation course.
Complications following chemotherapy like nausea and vomiting were present in all patients. There were 91% (n=71) patients with renal impairment, 61% (n=43) with diarrhea, 53% (n=37) with peripheral neuropathy, 42% (n=29) with myelosuppression and alopecia in 7% (n=5) of patients.
Post-radiation related morbidities included oesophagitis which was observed in 96% (n=67), pneumonitis in 5% (n=4), skin changes in 30% (n=21) and oesophageotracheal fistulas in 3% (n=2) of patients. Late
complication like mediastinal fibrosis occurred in 4% \((n=3)\) and post-radiation stricture in 2% \((n=1)\) of patients. There were 17 deaths in the early phase of chemotherapy treatment (24%). Mortality has reached 55.7% \((n=39)\) by the end of CRT. Deaths were mainly due to acute severe gastroenteritis in 54% \((n=21)\) while acute pneumonitis was the cause of death in 28% \((n=11)\) and meningoencephalitis in 15% \((n=6)\) of patients. In one case, the cause of death could not be identified because of insufficient clinical data.

**Discussion**

The role of CRT in the management of oesophageal carcinoma could be definitive, palliative, neo-adjuvant or adjuvant treatment. As treatment course entails long stay within the vicinity of the compound, the majority of our patients found it unaffordable. There are currently only two radio-isotope centres in the Sudan, Khartoum and Medani. Surgical treatment is offered in one unit in Khartoum with a single case operated upon every week, entailing a long waiting list and necessitating the reference to CRT. Oesophageal stent and laser therapy are available in private settings and generally unaffordable by the majority of patients. In the current study using CRT, complete clinical response occurred in 9% and partial response in 45% of patients with early tumors. In patients with locally advanced or metastatic disease, no patient showed complete clinical response while 33% of patients had only partial response.

Courrech S et al\(^{(9)}\) evaluated the efficacy of a CRT regimen in form of radiotherapy of 66 Gy in 33 fractions with low-dose cisplatin and planned as neo-adjuvant or definitive treatment. Clinically complete and partial response was observed in 54% of patients. Nquyen NP et al\(^{(10)}\) reported a complete clinical response by CRT in 52% of patients with advanced tumors when continuous (rather than bolus) 5-FU administration was used combined with daily low-dose administration of cisplatin before each single or twice fraction of radiation. Independent studies revealed 2-year survival rates ranging from 28%-55%, which are comparable with results achieved with surgery alone and better than historical results achieved with radiation alone\(^{(11)}\). Bedenne L\(^{(12)}\) concluded that in advanced thoracic oesophageal carcinoma, patients who respond to neoadjuvant CRT, will not get more benefits from surgery compared with continued CRT. However, neoadjuvant CRT is being used in both squamous cell carcinoma and adenocarcinoma. A meta-analysis from Gebski et al\(^{(13)}\) that included data from 10 neoadjuvant CRT trials of 1209 patients has shown an absolute overall survival benefit of 13% when compared with surgery alone. This result prompted some investigators to consider neoadjuvant treatment as the standard of care in oesophageal cancer\(^{(14)}\).

Concurrent CRT toxicities were studied by Takashi Uno et al\(^{(15)}\) using a regimen of radiation in addition to 5-FU and cisplatin doses similar to what was given to our patients, except that graded cycles of chemotherapy were used instead of 5-6. Reported gastrointestinal, haematological and renal toxicities occurred in 25%, 35% and 20% of cases, respectively. Most of these toxicities were of grade 1 and 2, while life threatening toxicities occurred in 10% of patients with no treatment-related acute mortalities.

Our institutional findings showed severe side effects in 54%-100% of patients, and life-threatening complications in 28% of patients. Crosby et al\(^{(16)}\) reported toxicities of CRT when used as a definitive treatment by a planned dose of external beam RT more or equal to 45 Gy delivered with four cycles of cisplatin and 5-fluorouracil (5FU) in doses equivalent to our local regimen. Renal disturbances occurred in 11% of population, gastrointestinal toxicities in 7%, neurological toxicities in 11%, and
myelosuppression in 13% patients. In our study, the reported toxicities were 81% (renal impairment), 78-100% (gastrointestinal), 37%-41% (neurological) and 52% (myelosuppression), respectively. Crosby et al\(^{(16)}\) reported no deaths directly related to treatment when used in non-advanced tumours, though 5 patients died during or within 30 days of completing treatment used for advanced disease. Laurent et al\(^{(12)}\) studied the outcome of 5-FU continuous infusion and cisplatin with radiation dose of 30-45 Gy among 130 patients with advanced disease. The mean hospital stay was 24.7 days. Gastrointestinal toxicities occurred in 11% of patients and hematological side effects in 37% of patients. Only one patient died during the early (less than 3 months) post-therapeutic period and the six-month mortality rate was 6%.

In our series, 4 patients (5%) with early disease died during the course of the treatment and there were 39 (55.7%) deaths by the end of the CRT course for advanced tumours (55.7%).

The higher rates of toxicities and mortalities in our population could be attributed to the number of chemotherapy cycles used by most of the treating units (six cycles compared to four cycles in most of the revised studies). Dose adjustment (our patients received rather weight related constant doses and not graded cycle’s regimen) could also be an additive factor. Due to shortage of beds, our patients were admitted for a very short duration (51 hours in our centre versus 24.7 days in other studies). The majority of those patients were admitted from home to the general casualty with these complications which needed a multidisciplinary team to deal with rather than medical practitioners.

Upgrading of management varieties, decisive dose individualization, monitoring, amplification hospital bed capacity, incorporation of different medical specialties in the centre are needed to improve the overall outcome.

**Acknowledgement**

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**References**


