REVIEW ARTICLE

CANCER ESOPHAGUS: TREATMENT MODALITIES

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INTRODUCTION

Esophageal cancer was 1.15% of all tumors collectively in a study done in Lahore, Pakistan. In this males were 1.41% and females 0.86% [1]. From the same centre there was no significant change in the last two decades [2]. But as compared to this figure the latest figures from other part of the country have shown high incidence [3]. This regional difference may be due to etiological factors like smoking, chewing of tobacco and alcoholism [4]. In another study squamous cell carcinoma was noted in 81% of the cases, whereas adenocarcinoma was the second most common variety. At the time of diagnosis, early stage disease was found in 25%, locally advanced in 41% and metastatic in 34% of all cases. Median survival was 7 months [5]. High incidence of squamous cell carcinoma was found in another study from Pakistan as compared to the western studies where adenocarcinoma was high, and the majority was advanced stage [6]. Over the past 20 years in the United States esophageal cancer has shown the most rapid rate of increase of any solid tumor. Esophageal cancer is an aggressive disease, and poor survival is achieved with surgery, chemotherapy or radiotherapy alone.

There used to be only three treatment options for patients suffering from cancer esophagus i.e. surgery, radiotherapy, and intubation with plastic prosthesis. For those with terminal disease, a gastrostomy tube was the answer. This merely prolonged life without meaningful palliation. In the last two decades, there has been some progress in this disease. Surgical resection has been refined, techniques of radiation improved, neoadjuvant or adjuvant therapies with chemotherapy and/or radiotherapy added, and there are various methods of endoscopy for palliation. For each patient, best treatment has to be individualized. The present review describes the various treatment options currently available.

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STAGING

Accurate staging for cancer esophagus is gaining importance with the increase in the number of therapeutic options. Staging should include an endoscopic examination and bronchoscopy for lesion located in the middle or upper third of the esophagus. A computed tomography (CT) scan of the neck, thorax and abdomen is used to detect distant metastases. Endoscopic ultrasound (EUS) allows greater delineation of mucosal and submucosal cancers [7]. Such information is important when endoscopic mucosal resection is contemplated [8]. Use of EUS guided fine needle aspiration has increased its diagnostic accuracy [9].

PET scan detect organ metastases better than CT [10]. The PET scan is becoming more widely available, and its main value seems to be more effective in detecting distant lymph node and systemic metastases [11]. Thoracoscopy and laparoscopy with laparoscopic ultrasound are now part of staging system [12].

MANAGEMENT

Surgical

Surgical resection is the main treatment modality for cancer esophagus. An

improvement in the treatment of cancer esophagus is the reduction in mortality after surgical resection. In some centers, a low mortality rate of less than 5% has been reported [13]. The two most common surgical approaches are transhiatal (THE) and transthoracic (TTE) resections [14].

Combined Modality Therapy

Although immediate surgical results have improved, long term prognosis remains dismal. In unselected patients who undergo resection, the 5-year survival rate is approximately 20%. The past two decades have seen a proliferation of reports on the use of combination of therapies for cancer esophagus [15]. Combining different modalities of treatment seems to improve the result. The local treatment effects of radiotherapy and surgery are additive, and the systemic effects of chemotherapy, plus its radiosensitizing properties, can be exploited. With latest advances in radiotherapy equipment and radiobiological understanding there is improvement in treatment response. Three dimension conformational radiotherapy and intraluminal brachytherapy has improved the results [16,17]. Accelerated fractionation radiotherapy regimens has been used for palliation of dysphagia [18].

Randomized phase III trials on neoadjuvant radiotherapy have failed to show increased resection rate or improved survival compared with surgery alone [19]. Adjuvant radiotherapy has not shown any improvement in survival, although it could enhance local control by reducing tracheobronchial recurrence in the patients with residual disease in the mediastinum after palliative resection [20].

Major trials of neoadjuvant chemotherapy are limited [21]. In general, chemotherapy was well-tolerated. However, a clear survival advantage with neoadjuvant chemotherapy has not been demonstrated. Subgroup analysis showed that a survival benefit, if any, appeared to exist only in objective responders [22]. However the combination of gemcitabine, 5-FU and leucovorin have shown better activity in advanced esophageal cancer [23].

Some effectiveness of chemotherapy to palliate metastatic disease or to combine it with radiotherapy in locally advanced cancer has prompted the research for new systemic agents. The phase II evaluation of the combination of weekly irinotecan and cisplatin has shown encouraging response rates exceeding 30% to 50% in esophageal and gastric cancer. Irinotecan (CPT-11) is an active radiosensitizer, and trials have evaluated the combination of CPT-11with concurrent radiotherapy. Chemoradiotherapy as compared to radiotherapy alone has shown better survival [24].

Further phase I and II investigation of combined irinotecan, cisplatin, and concurrent radiation is ongoing with the addition of targeted agents, including celecoxib, cetuximab, and bevacizumab. Alternative combinations of CPT-11 with radiotherapy, including the addition of docetaxel and continuous infusion 5-FU, are also undergoing phase I and II evaluation [25]. Combination of docetaxel and CPT-11 resulted in a response rate of 30%. Another 40% achieved stable disease. This combination showed high rate of febrile neutropenia [26]. Paclitaxel and carboplatin combination is a safe and well tolerated regimen for esophageal cancer with comparable clinical response. This regimen may be especially suitable for patients with epidermoid cancer, who had a 25% pathological complete response in another report [27]. The most beneficial combination appears to be cisplatin and 5-flurouracil but its dosage is not clear [28].

Because there is marginal or no benefit when radiotherapy or chemotherapy is added alone to surgery, the strategy of chemoradiation therapy has been most intensely studied in the past decade. Several groups have explored its use as neoadjuvant therapy [29]. A survival advantage with neoadjuvant chemoradiation over surgery

alone was demonstrated in one trial for adenocarcinoma [30]. It was assessed that better patient selection for preoperative radiochemotherapy was needed [31].

Chemoradiation employing a combination of cisplatin and a continuous infusion of 5-FU has been the most commonly used therapy. The gastrointestinal toxicity of cisplatin/5-FU-based regimens has increased the need for new agents in combined modality therapy. In this context chemoradiation trials with weekly paclitaxel/cisplatin and CPT-11/cisplatin has been done, and the results suggest that this regimen has the potential to improve the therapeutic index without compromising efficacy. Randomized trials are under way to evaluate the tolerance and efficacy of paclitaxel/cisplatin in comparison with paclitaxel/5-FU combined with radiotherapy in locally advanced esophageal cancer [32].

Complete pathologic response with induction chemoradiation is associated with improved overall and disease free survival following surgery for adenocarcinoma of the distal esophagus. Because recurrent cancer still develops in many of these patients, even after complete pathologic response, the search for the optimal treatment continues [33]. In one study paclitaxel / carboplatin / 5-FU infusion along with radiotherapy was used. This combined modality was active in the treatment of localized cancer, producing an actuarial 3 year survival of 41%. Although acute toxicity was moderate, there was no treatment related deaths and the majority had surgical resection [34]. From the data available, chemoradiation can produce a pathological complete response of approximately 25% and is the best treatment option available [35].

The Radiation Therapy Oncology Group trial of chemoradiation versus radiotherapy alone was first reported in 1992 and updated in 1997 and 1999 [34]. It reported a 14-26% 5-year survival rate achieved with chemoradiation alone. Chemoradiation have become the preferred non-operative mode of treatment of cancer esophagus [36]. In esophageal cancer, the combination of low-dose weekly paclitaxel, platinum, and concurrent radiation therapy (RT) has substantial activity and is well tolerated. Preliminary efficacy data are encouraging [37,38]. Chemoradiation enabled better patient selection for curative resections and also resulted in more complete resections by tumor downstaging [39]. The resectability of tumor increased after chemoradiotherapy [40]. But it was further seen in one study that in advanced esophageal carcinoma there was no survival benefit on adding surgery to chemoradiotherapy [41]. Chemoradiation is by no means harmless [42]. Treatment related mortality was 9%. Whereas addition of surgery is expected to enhance local control [43]. Preoperative chemoradiotherapy is able to significantly reduce the tumor stage, and achieve substantially high clinical response rate and pathological complete response rate [44]. In one study chemoradiotherapy showed more benefit for squamous cell carcinoma [45].

Similarly postoperative adjuvant chemotherapy with cisplatin and fluorouracil is able to prevent relapse in patients with esophageal cancer than surgery alone [46]. Most clinical trials to date are cisplatin and fluouracil based even for patients undergoing postoperative chemotherapy. Efforts have been put into developing more agents and strategies in order to further improve outcome. Drugs under investigations for this purpose include the Taxanes (e.g. paclitaxel, docetaxel), CPT-11, topotecan, vinorelbine and gemcitabine [47].

Trimodality Therapy

There are conflicting results from studies on the effect of neoadjuvant and/or adjuvant treatment on long term survival [48]. Most patients with locally advanced esophageal cancer die from their disease, despite complete surgical extirpation of tumor or institution of aggressive, multimodality

treatment. However more treatment is good. Although this has proved to be aggressive, but trimodality therapy provides a survival advantage for patients with locally advanced esophageal cancer [49,50]. In patients with locoregionally advanced esophageal carcinoma, addition of postoperative adjuvant chemoradiotherapy to esophagectomy alone doubled survival time, time to recurrence, and recurrence-free survival [51].

Endoscopic Therapy

Endoscopic therapy can be used with radical or palliative aim. Endoscopic mucosal resection is employed in Japan to cure early stage disease [52]. This applies to tumors confined to mucosa only. Such cases are seen only under screening program, because most symptomatic patients have late stage disease. Endoscopic palliative treatments for more advanced tumors include placement of an esophageal prosthesis, laser therapy, intralesional injection of various substances, and photodynamic therapy (PDT). The two most commonly employed techniques are insertion of prosthesis and laser therapy. Insertion of self expanding metallic stents (SEMS) self expanding plastic stents (SEPS) has become the preferred method in many institutions [53]. However, esophageal plastic stents can be accurately and safely placed under direct endoscopic control with lower costs suitable to low socioeconomic conditions. Therefore, endoscopic intubation remains a useful and cost effective palliative treatment for patients with unresectable carcinoma of the esophagus [54,55]. PDT offers effective palliation for patients with obstructing cancer esophagus in 85% of treatment courses. Patients living more than 2 months may require reinterventions to maintain palliation of malignant dysphagia, and a multimodality treatment approach can be offered [56].

Management of Metastatic and Recurrent Disease

Large majority of patients have metastatic disease from the start and some develop later even after treatment. In one study Gemcitabine and Cisplatin was used. This regimen was tolerable and provided palliation to such patients [57]. Since CDDP was developed, it has become a key drug for combined chemotherapy. Nedaplatin and paclitaxel have shown favorable results either as a single agent or in combination with CDDP. The results of definitive chemoradiotherapy for advanced esophageal cancer have recently improved.

Trimodality therapy has been shown in preliminary studies to increase survival in metastatic esophageal cancer. Distant recurrence remains the main pattern of failure [58]. Ninety-six-hour paclitaxel in metastatic esophageal cancer is well tolerated with minimal toxicity; however, it is ineffective in previously treated patients. The same schedule of paclitaxel in combination with concurrent radiotherapy is ongoing in locally advanced esophageal cancer [59].

CONCLUSION

Therapeutic options for cancer esophagus have increased. Treatment for each patient should be individualized. Surgical resection is the mainstay of treatment for patients with curative intent. In those with more advanced disease where the aim of treatment is obviously palliative, surgical resection is less frequently performed, given the alternatives available. Successful resection however, still offers the most complete and lasting relief of dysphagia, providing it can be carried out safely in experienced centers. In selected patients, a bypass procedure is also an option. Chemoradiation therapy is widely adopted in patients who have good performance status. Good palliation can be obtained in those who respond without the development of a radiation stricture.

In selected patients who demonstrate a positive response, surgical resection is sometimes warranted, especially when tumor downstaging makes a curative resection possible. In patients without a chance of cure

or in poor health, placement of stents achieves rapid, safe and cost effective palliation.

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