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REVIEW ARTICLE

Advances in the management of esophageal cancer

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ABSTRACT

The management of clinical stage III and IVa esophageal cancer has evolved in the past 2 decades. Based on the Cross trial, neoadjuvant chemoradiation, followed by surgical resection has become standard. For medically inoperable, definitive chemoradiation is most commonly used. The standard radiation dose is 50.4 Gy although trials of dose-escalation are ongoing. At the current time, there are no definitive biomarkers to predict response.

Keywords: Esophageal cancer, Radiation therapy, Chemotherapy, Dose-escalation

NONOPERATIVE THERAPY

Radiation therapy alone

Radiation therapy alone is limited to palliation or for patients who are medically unable to tolerate chemotherapy. The 5-year survival rate for patients treated with conventional doses of radiation therapy alone is 0-10% [1-3]. In the radiation therapy alone arm of the RTOG 85-01 trial in which patients received 64 Gy at 2 Gy/day with conventional techniques, all patients were all dead of disease by 3 years [4,5]. Shi and colleagues reported a 33% 5-year survival rate with the use of late course accelerated fractionation to a total dose of 68.4 Gy [6-12].

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Dose intensification with brachytherapy

Brachytherapy can be delivered by low or high dose rates and has previously been used as a boost following external beam radiation therapy or chemoradiation [7-16]. This technique is limited by the effective treatment distance. The primary isotope is 192Ir, which is usually prescribed to treat to a distance of 1 cm from the source. Therefore, as confirmed by pathologic analysis of treated specimens, any portion of the tumor which is >1 cm from the source will receive a suboptimal radiation dose [17].

Retrospective and single institution trials suggest that there is no advantage of adding brachytherapy to external beam radiation. Chemoradiation plus brachytherapy was tested prospectively by the RTOG 92-07 trial. A total of 75 patients with cancers of the thoracic esophagus (92% squamous cell, 8% adenocarcinoma) received the RTOG 85-01 50 Gy chemoradiation regimen followed by a boost during cycle 3 of chemotherapy with either low dose rate or high dose rate intraluminal brachytherapy [22]. Due to low accrual the low dose rate option was discontinued and the analysis was limited to patients who received the high dose rate treatment. High dose rate brachytherapy was delivered in weekly fractions of 5 Gy during weeks 8, 9, and 10. Several patients developed fistulas and the fraction delivered at week 10 was discontinued. The complete response rate was 73%. With a median follow-up of only 11 months, local failure as the first site of failure was 27%. Acute toxicities were high. These included 58% grade 3, 26% grade 4, and 8% grade 5 (treatment-related death). The

cumulative incidence of fistula was 18%/year and the crude incidence was 14%. Of the 6 treatment related fistulas, 3 were fatal. Given the significant toxicity and lack of efficacy there is limited interest in this technique.

However, if brachytherapy is to be used, guidelines for esophageal brachytherapy have been published by the American Brachytherapy Society are available [23]. For patients treated in the curative setting brachytherapy should be limited to tumors ≤ 10 cm with no evidence of distant metastasis. Contraindications include tracheal or bronchial involvement, cervical esophagus location, or stenosis which cannot be bypassed. The applicator should have an external diameter of 6-10 cm. If chemoradiation is used (defined as 5-FU based chemotherapy plus 45-50 Gy) the recommended doses of brachytherapy are 10 Gy in 2 weekly fractions of 5 Gy each for high dose rate and 20 Gy in a single fraction at 4-10 Gy/hr for low dose rate. The doses should be prescribed to 1 cm from the source. Lastly, brachytherapy should be delivered after the completion of external beam and not concurrently with chemotherapy.

Primary chemoradiation

Although there are 6 randomized trials comparing definitive radiation therapy alone with chemoradiation, the only trial which designed to deliver adequate doses of systemic chemotherapy with concurrent radiation therapy was the RTOG 85-01 trial reported by Herskovic and colleagues [23-26]. As was common in the 1980s, most patients had SCC. Treatment included four cycles of 5-FU (1000 mg/m2/24 hr x 4 days) and Cisplatin (75 mg/m2, day 1). Radiation therapy (50 Gy at 2 Gy/day) was given concurrently with the first day of cycle 1 of chemotherapy. Cycles 3 and 4 of chemotherapy were delivered every 3 weeks rather than every 4 weeks. Only 50% of the patients finished all 4 cycles of the chemotherapy. The control arm was radiation therapy alone, albeit a higher dose (64 Gy) than the chemoradiation arm.

Patients treated with chemoradiation had a significant improvement in both median (14 months vs. 9 months), and 5 year survival (27% vs. 0%, p< 0.0001) [25]. The 8 year survival was 22% [26]. Histology did not significantly influence the results. The 5-year survival was 21% for the 107 patients with SCC vs. 13% of the 23 patients with adenocarcinoma, (p=NS). Local failure (defined as local persistence plus recurrence) was also lower in the chemoradiation arm (47% vs. 65%). Although African Americans had larger primary tumors of which all were SCC, there was no difference in survival compared with Caucasians [27].

Dose intensification with external beam escalation

This concept was prospectively examined in INT 0123 (RTOG 9405) [29]. In this trial, patients selected for a non-surgical approach were randomized to a slightly modified RTOG 85-01 chemoradiation regimen with 50.4 Gy versus the same chemotherapy with 64.8 Gy, based on INT 0122. As with RTOG 85-01, the majority of patients (85%) had SCC. The trial opened in late 1994 and was closed in 1999 when an interim analysis revealed that it was unlikely that the high dose arm would achieve a superior survival compared to the standard dose arm.

For the 218 eligible patients, there was no significant difference in median survival (13.0 months vs. 18.1 months), 2-year survival (31% vs. 40%), or local/regional failure and/or local/regional persistence of disease (56% vs. 52%) between the high dose and standard dose arms. Although 11 treatment-related deaths occurred in the high dose arm compared with two in the standard dose arm, seven of the 11 occurred in patients who had received ≤ 50.4 Gy.

An alternative approach to dose escalation is altered fractionation. This has revealed mixed results. Zaho and colleagues treated 201 patients with squamous cell cancer using 41.4 Gy followed by late-course accelerated hyperfractionation to 68.4 Gy [30]. The results were similar to RTOG 85-01 (38% local failure and 26% 5-year survival). Choi and colleagues treated 46 patients with 5-FU/cisplatin and BID radiation using a concurrent boost technique and reported a 37% 5-year survival [31]. Additionally, Lee et al reported on a trial of 102 patients with LAEC, limited to SCC, randomized to surgery alone versus preoperative therapy with 45.6 Gy (1.2 Gy BID) plus 5-FU/cisplatin [32]. There was no difference in median survival (28 vs. 27 months). Thus, although these approaches may appear to be reasonable, there appears to be a significant increase in acute toxicity without any clear therapeutic benefit.

The above trials used 2D and 3D techniques. Newer techniques such as IMRT and protons may be able to deliver higher doses of radiation with a more tolerable toxicity profile. Multiple dosimetric studies comparing standard 3D-conformal radiotherapy and IMRT, generally have found improved sparing of the heart, lung or both using either static field or arc-based IMRT [33-44]. Retrospective data do not suggest inferior outcome and may provide decreased toxicity vs. non-IMRT treatment techniques [45-47]. Investigators at the MD Anderson reported the results of 676 patients treated with either IMRT (263) or 3DCRT (413) [45]. On multivariate analysis, IMRT was associated with improved survival (p=0.004), but not cancer specific survival (p=0.86). The survival difference between 3DCRT and IMRT was thought to be due to a higher

level of cardiac (p=0.05) and unexplained deaths (p= 0.003) in the 3DCRT patients, suggesting that decreased cardiac dose may have a direct impact on patient outcome. A randomized trial is unlikely, therefore the available data may represent the best comparison.

Another theoretical advantage of IMRT is the possibility of dose escalation. With the use of IMRT, a simultaneous integrated boost (SIB) may be performed while maintaining commonly used lung and heart dosimetric constraints. Retrospective data from Zhang and colleagues suggest a positive correlation between radiation dose and locoregional control [48].

Neoadjuvant chemotherapy

A potential advantage of neoadjuvant chemotherapy is the early identification of those patients who may or may not respond to the chemotherapeutic regimen being delivered concurrently with chemoradiation. Data from Ilson et al suggest that the change in SUV on FDG-PET scan was able to predict which patients showed a response to chemotherapy [49]. Weider and associates reported similar findings in 38 patients with squamous cell cancers [50]. Although this approach is investigational, if the non-responders can be identified early, changing the chemotherapeutic regimen may be helpful. However, in the context of induction chemotherapy prior to definitive chemoradiation, the data do not support its routine use. For example, Ruhstaller and colleagues report the outcomes from a phase II trial using cisplatin/docetaxel followed by chemoradiation [51]. The median survival was 16 months, with 29% of patients surviving long term suggesting no benefit over chemoradiation alone.

NEOADJUVANT THERAPY

Preoperative chemoradiation

There are seven randomized trials comparing preoperative combined modality therapy with surgery alone in patients with clinically resectable disease, the most recent being the CROSS trial [32, 55-60].

The CROSS trial randomized 366 patients (75% adenocarcinoma, 23% squamous cell) to receive either neoadjuvant chemoradiation with 41.4 Gy and carboplatin/ paclitaxel followed by surgical resection versus surgical resection alone [60]. In median survival was 49.4 vs. 24 months, p=0.003, respectively. Improved survival was seen in both adenocarcinoma and SCC, although the magnitude was slightly greater in squamous cell. The R0 resection was 93% in the chemoradiation arm, compared to 69% in the surgery alone arm (p<0.001) and the pCR rate was 29%. There was no significant difference in perioperative complications was seen between treatment arms.

Prior to the publication of the CROSS trial the role of preoperative chemoradiation was controversial. The first 6 trials (Urba [55], Walsh [56], EORTC [57], Australasian [58], Korea [32], and CALGB 9781 [59]) had limited patient numbers, heterogeneous treatment regimens, and in some the dose of radiation was insufficient based. With the publication of the CROSS trial the standard of care for patients with locally advanced but medically resectable adenocarcinoma of the esophagus is now preoperative chemoradiation.

Is surgery necessary following chemoradiation?

Given the response rate to chemoradiation and the morbidity of surgery, two randomized trials have examined whether surgery is necessary after chemoradiation. In the Federation Francaise de Cancerologie Digestive (FFCD) 9102 trial, 445 patients with clinically resectable T3-4N0-1M0 SCC or adenocarcinoma of the esophagus received initial chemoradiation [64]. Patients initially received 2 cycles of 5-FU, cisplatin, and concurrent radiation (either 46 Gy at 2 Gy/day or split course 15 Gy weeks 1 and 3). The 259 patients who had at least a partial response were then randomized to surgery versus additional chemoradiation which included 3 cycles of 5-FU, cisplatin, and concurrent radiation (either 20 Gy at 2 Gy/day or split course 15 Gy). There was no significant difference in 2-year survival (34% vs. 40%, p=0.56) or median survival (18 months vs. 19 months) in patients who underwent surgery versus additional chemoradiation. These data suggest that for patients who initially respond to chemoradiation, they should complete chemoradiation rather than stop and undergo surgery. Using the Spitzer index, there was no difference in global quality of life however, a significantly greater decrease in quality of life was observed in the surgery arm during the postoperative period (7.52 vs. 8.45, p<0.01, respectively) [65]. A separate analysis revealed that compared with split course radiation, patients who received standard course radiation had improved 2-year local relapse free survival rates (77% vs. 57%, p=0.002) but no significant difference in overall survival (37% vs. 31%) [66].

The second trial, from the German Oesophageal Cancer Study Group, compared preoperative chemoradiation followed by surgery versus chemoradiation alone [67]. In this trial, 172 eligible patients < 70 years old with uT3-4N0-1M0 SCC were randomized to preoperative therapy (3 cycles of 5-FU, leucovorin, etoposide, and cisplatin,

followed by concurrent etoposide, cisplatin, plus 40 Gy) followed by surgery versus chemoradiation alone (the same chemotherapy but the radiation dose was increased to 60-65 Gy +/- brachytherapy). The pCR rate was 33%. Although there was a decrease in 2-year local failure (36% vs. 58%, p=0.003) there was no significant difference in 3-year survival (31% vs. 24%) for those who were randomized to preoperative chemoradiation followed by surgery vs. chemoradiation alone.

Despite the above data, the current standard of care is to perform esophagectomy following chemoradiation in patients that can tolerate this approach. However, it is known that a subset of patients will have a complete response to chemoradiation. Further, it is known that patients with pCR have improved survival. Data from both Berger et al [68] and Rohatgi et al [69] suggest that patients who achieve a pCR had an improvement in survival compared to those who do not (5-year: 48% vs. 15%, and median: 133 months vs. 34 months, respectively). In these patients, surgical resection may not be necessary and has led to the concept of "selective" surgery after preoperative chemoradiation. Swisher and colleagues reported a retrospective analysis of patients who underwent a salvage compared with a planned esophagectomy [70]. The operative mortality was higher in those who underwent salvage vs. planned surgery (15% vs. 6%) but there was no difference in survival (25%).

However, only 13 patients were identified who had salvage, limiting the broad interpretation of these findings. However, a recent phase II trial, RTOG 0246, prospectively examined the approach of preoperative paclitaxel/CDDP and 50.4 Gy followed by selective surgery in patients with either residual disease or recurrent disease in the absence of distant metastasis. In this trial of 43 patients with LAEC, 21 patients required surgical resection after chemoradiation due to residual (17 patients) or recurrent (3 patients) disease [71]. This approach led to a one year overall survival of 71%, lower than the predetermined survival rate (77.5%). Since all patients do not undergo surgery after neoadjuvant therapy, the use of a definitive does of radiation (50.4 Gy) rather than 41.4 Gy, is recommended.

Conclusions

The management of esophageal cancer continues to evolve. Approaches include both preoperative and non-operative approaches, based on resectability, histology and location. In patients with resectable disease, who are medically fit for this procedure, we recommend preoperative chemoradiation to 50.4 Gy. One possible exception to this recommendation is SCC of the cervical esophagus, for which definitive chemoradiation should be considered. Additionally, in non-operative patients, definitive chemoradiation to 50.4 Gy is standard; however enrollment of these patients on dose-escalation or other protocols is encouraged. Future directions include evaluation of tumor biomarkers of response to chemoradiation with a goal of possibly omitting surgery in favorable patients, while targeting non-responders for protocol based chemotherapy and radiosensitizers.

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