REVIEW ARTICLE

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Chemoradiotheraphy of Esophageal Cancer

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Esophageal cancer is a disease with a poor prognosis and high biological aggressiveness. The disease used to be considered a mainly local problem, and palliative care with relief of dysphagia was the goal for most of those concerned with the disease. When surgical techniques were improved and parallel progress was made in intensive care and postoperative care, some patients could be cured of the disease. The development of pre- or postoperative radiotherapy also improved local control. Partly because of the interest that began to be focused on improving survival for this diagnostic group, chemotherapy combined with radiotherapy has been incorporated into the therapeutic arsenal. The aim of this review is to shed light on current treatment principles for esophageal cancer. However, treatment results from studies utilizing combination chemotherapy given concurrently with radiotherapy support the conclusion that well-designed randomized trials with long-term follow-ups should be performed.

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BACKGROUND

Concurrent radiation and chemotherapy has already shown promising results for different gastrointestinal tumors, e.g. anal cancer. The addition of chemotherapy to radical radiotherapy has improved local tumor control, as shown by a 46% reduction in the risk of local failure after a median follow-up of 42 months (1). Promising results have also been achieved in head and neck melanoma (2). An overview analysis by Munro (3) including 54 randomized, controlled clinical trials in head and neck cancer where chemotherapy was given synchronously with radiotherapy indicated a therapeutic gain from combined therapy. This was confirmed in a meta-analysis of randomized data (4).

Other reports also show survival benefits from the combination of these two therapies given together, but it is unclear whether the survival benefit is due to a synergistic effect between the radiotherapy and the chemotherapy, as local control is not always improved, or if they provide spatial cooperation (5, 6).

The differential effects on tumor and normal tissues from the esophagus of combined radiation-chemotherapy in man and animals have been reported elsewhere (7–11).

Esophageal cancer is a difficult problem. Neither surgery nor radiation therapy reliably provides long-term control for patients, even with apparently localized disease (12). Tumor stage, lymph node spread and response to preoperative treatment have been identified as relevant prognostic markers. The purpose of concomitant chemotherapy and radiation therapy is to improve local control while simultaneously treating micrometastases. While 5-fluorouracil (5-FU) as a single agent has relatively limited activity in squamous cell carcinoma of the esophagus, tissue culture studies have suggested increased cytotoxicity when radiation and 5-FU are combined (13, 14). Increased drug concentrations and exposure have yielded better results. A combination of fluorouracil, mitomycin and radical radiotherapy has been used for the management of carcinoma of the esophagus for some considerable time now (15). However, the comparability of clinical trials is limited by differences in tumor staging before treatment, and varying precision in the diagnostic procedures. The number of patients within the trials is also often small, even though worldwide, esophageal cancer is among the 10 most frequent cancers. The rate of esophageal cancer is 20–30 times higher in China than in the Western world (16). The Nordic countries are a low-incidence area with about 1000 new cases diagnosed each year in a population of about 24 million. Of these, about 50% are considered resectable at the time of diagnosis. The disease is more common in men, with a male versus female ratio of 2 : 1. The incidence increases with age and peaks in the seventh decade of life. The most common histologic type is squamous cell carcinoma, but there seems to be an increasing incidence of adenocarcinoma affecting younger persons, predominantly

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men (17). So far, there do not seem to be any statistically significant differences in response to therapy or prognosis between squamous cell carcinoma and adenocarcinoma, which is why the majority of studies combine the two types.

SURGERY

Only 40–60% of patients with esophageal cancer present with clinically localized disease. This group of patients has so far been treated predominantly with surgical resection as the primary therapy.

Surgery can provide good palliation and also a chance of cure. With improved surgical techniques and improved postoperative and intensive care, the survival rates have improved from the 1970s to the 1990s (12, 18). In a controlled clinical trial significantly higher 5-year survival rates were demonstrated for en-bloc esophagectomy compared with transhiatal esophagectomy (19). However, the number of patients in the study was low (n = 60). Otherwise, surgical techniques have not been subject to controlled clinical trials. Since most patients with esophageal carcinoma present with lymph node metastases at the time of surgery (20), interest has focused on three-field lymphadenectomy compared with two-field lymphadenectomy. A 34% 5-year survival (1800 patients) was reported from Japan (21), when three-field dissection was performed, compared with 27% for 2800 patients undergoing two-field dissection. The data in favor of extended field lymphadenectomy are not conclusive (22, 23). Although radical surgery is now safer than in the past, it is still associated with both morbidity and mortality.

RADIOTHERAPY

Esophageal cancer is radiosensitive and radiotherapy has often been successfully used for palliation, providing good symptomatic relief of the dysphagia in 50–75% of cases (24, 25). External beam irradiation is commonly used. It has traditionally been one of the standard treatment arms of esophageal cancer trials, either alone or in combination with surgery. Many of the radiotherapy patient materials are selected in the sense that the patients comprise a group with especially poor outcome, with high age or other conditions that do not allow extensive treatment. Radiotherapy alone was inferior to radiotherapy plus chemotherapy with 5-FU and cisplatin in a phase III trial by Herskovic et al. (26). Radiotherapy alone versus surgery alone can only be compared indirectly since there are no randomized clinical trials. Controlled clinical trials do not show any survival benefit for patients treated postoperatively with 30 Gy (27) or 49–56 Gy (28, 29). Radiotherapy can thus not be recommended as a single modality treatment or as the only adjuvant therapy with surgery in a curative approach. Radiotherapy has been of little value in converting unresectable cancers into resectable ones (30). However, it decreases the incidence of locoregional recurrence (31). A recently published article showed a significant survival advantage with postoperative chemoradiation therapy for lymph-node-positive esophageal carcinoma (32).

PREOPERATIVE CHEMORADIATION

Randomized trials

In randomized studies, the effects of preoperative chemoradiation versus those of surgery alone have been compared. In some studies chemotherapy was given sequentially with radiation in the preoperative setting, while in other studies it was administered concomitantly.

A Scandinavian study by Nygaard et al. (33) was a four-arm study in which two of the arms represented surgery alone and preoperative chemoradiation. Cisplatin and bleomycin were given before radiation, followed by surgery. There was no significant difference in median, 3-year, or 5-year survival rates when the three-modality treatment was compared with surgery alone. The results indicate that preoperative irradiation had a beneficial effect on intermediate term survival, whereas the chemotherapy regime used did not influence survival. Le Prise et al. (34) reported a trial in which 86 evaluable patients were randomized to receive surgery alone, or chemotherapy with cisplatin and 5-FU before and after 20 Gy radiation, followed by surgery. There was no difference in survival at 1, 2 or 3 years.

Urba et al. (35) randomized patients to surgery alone or cisplatin, 5-FU and vinblastine concurrent with 45 Gy radiation followed by surgery. In this study there was a survival advantage for the patients who received combined modality therapy.

In 1997 Bosset et al. (36) published a study in which 134 out of 277 patients with resectable tumors were treated with surgery alone and 143 had preoperative treatment with cisplatin and radiation. There were no differences between the groups with regard either to median survival or 5-year survival, but an 8% greater in-hospital and treatment-related mortality rate was reported in the combination arm. Correcting for this, a significant improvement in treatment results in the combination arm was obtained. Moreover, a longer disease-free survival and survival free of local disease was found for the multimodal group.

A trial from Ireland (37) compared surgery with preoperative cisplatin, 5-FU, and concurrent radiation followed by surgery; 113 patients with adenocarcinoma were enrolled. Survival analysis based on intention-to-treat showed a survival advantage for the combined modality group. Median survival was 16 months compared with 11 months for the patients treated with surgery alone. The 1-, 2- and 3-year survival rates were 52%, 37% and 32%, respectively, for the patients who received multimodality

treatment, and 44%, 26% and 6%, respectively, for those who underwent surgery only. This difference was statistically significant at 3 years.

The most widely tested chemotherapy regimen is cisplatin and 5-FU. This chemotherapy in combination with 30 Gy of radiation has been tested in the preoperative setting by different investigators. The first study reported from Wayne State University appeared promising, achieving a histologic complete response rate of 26% and a median survival of 18 months. Moreover, all complete responders were alive after two years (38). Similar results have been reported from other groups (39). In our own study published in 1991, 20% received a histologically complete response, and in this group all patients were long-term survivors. In all studies so far reported, improved survival is observed for patients who are pathologically complete responders (40–47). A recently reported abstract of a Medical Research Council trial of chemotherapy before surgery versus surgery alone shows a statistically significant improvement in survival (48).

NON-SURGICAL TREATMENT

Primary radiation therapy is usually reserved for patients with extensive locoregional esophageal carcinoma that is not resectable or for patients who are not candidates for surgery because of the medical risks. The results are generally poor, with a median survival of less than 12 months. In an effort to improve these discouraging results and to avoid the morbidity and mortality associated with esophagectomy in operative candidates, several investigators have combined chemotherapy with radiation. There are several advantages with the concurrent application; e.g. treatment of both the locoregional and systemic disease as early as possible, and also potentially an enhanced tumor activity. Both cisplatin and 5-FU seem to be synergistic with radiation. There is also less risk of accelerated repopulation of tumor cells during treatment, which is an important cause of local failure in cancer of the head and neck (49) and cervix (50). Even if the acute esophageal toxicity is greater with the concurrent treatment, late toxicity seems to remain the same (51, 11). The swallowing function is often well restituted for responding patients and for those with remaining tumors surgical salvage is still possible. Several studies with preoperative chemoradiation have shown that a pathologically complete remission is predictive of those who will be long-term survivors (40–47). This also stresses the need for a surgical resection.

One of the first randomized trials demonstrating a survival benefit with combined modality treatment of esophageal carcinoma was the intergroup trial, in which radiation alone (64 Gy) was compared with combination therapy with 4 courses of cisplatin and 5-FU administered concomitantly with radiation to a total dose of 50 Gy (52). A significant difference was noted in median survival, 8.9 months vs. 12.5 months, ($p = 0.0009$), and 24-month survival (10% vs. 38%), favoring the chemotherapy/radiation therapy arm. There was also a significant difference in the percentage of patients developing distant metastases (22% vs. 38%, $p = 0.005$), and local recurrence (16% vs. 24%). In a non-randomized, single-institution trial, patients with stages I or II were treated with 60 Gy concurrent with fluorouracil (5-FU) and mitomycin-C. Median disease-specific survival rate was 20 months, with a 5-year actuarial disease-specific survival of 29%. Most patients had excellent preservation of swallowing function after treatment. Surgical resection as salvage was successful in patients with local failure only (51).

Within Scandinavia a randomized trial is in progress for resectable esophageal tumors (adenocarcinoma, squamous cell carcinoma) (53). So far, 55 patients have been enrolled. The primary objective is to investigate whether concomitant chemoradiotherapy improves survival as compared to surgery alone. The second objective is to compare the treatments with regard to quality of life.

METASTATIC DISEASE

Metastatic carcinoma of the esophagus has a median survival of 6 months, and therefore most treatment options are directed towards palliation.

Radiation to the primary tumor is usually indicated and also for relief of pain from bone metastases. Other approaches include external beam radiotherapy alone, intracavitary brachytherapy, simple dilatation, placement of stents, laser recannulation of the esophageal lumen and photodynamic therapy. The newest but already relatively well-established modality in the treatment of dysphagia is the insertion of an expandable stent. Substantial relief from dysphagia is rapid, often as early as the day after stent insertion, and the incidence of complications is low (54). Laser treatment must often be repeated because of the relatively short duration of its effect. In a prospective, randomized multicenter trial PDT (Photofrin) was compared with neodymium/yttrium-aluminum-garnet (Nd : YAG) laser therapy in 236 patients with advanced esophageal cancer. Improvement of dysphagia was equivalent with the either of the treatments (55). Objective tumor response at 1 month was superior with PDT, although it produced more toxicity, but fewer perforations (1% vs. 7%).

Investigational protocol chemotherapy is the best option for a patient who has a good performance status and desires treatment.

NEW AGENTS FOR RECURRENT DISEASE

Taxanes

Taxanes promote stabilization of microtubules, and are potent radiosensitizers. Docetaxel and paclitaxel have been

tested in metastatic disease with overall response ratess for paclitaxel of 17% (56) and 23% for docetaxel (57).

Within the Scandinavian esophageal group, one protocol is in progress for locally advanced inoperable cancer: a phase I–II study on treatment with taxotere in combination with cisplatin, 5-FU, and radiotherapy (50 Gy). The protocol includes patients with locally advanced but non-metastatic esophageal cancer or cancer in the cardia region. So far, 28 patients have been enrolled.

Vinorelbine

Vinorelbine is a vinca alkaloid that disrupts microtubules by reversibly binding to tubulin, and is active in lung cancer and breast cancer. For esophageal cancer, overall responses have been reported to be 15% (58). This drug may be combined with others in the future for further testing.

Gemcitabin

Gemcitabin is undergoing early evaluation for its activity in esophageal carcinoma. Its potent radiosensitization capabilities will need to be investigated carefully (59). For metastatic esophageal cancer, a Scandinavian protocol is ongoing: a phase I–II study on treatment with Taxotere in combination with Gemzar in patients with esophageal cancer or cancer in the cardia region. So far 49 patients have been enrolled. The treatment is well tolerated.

CONCLUSION

Newer staging procedures in esophageal carcinoma, such as EUS and laparoscopy, improve the clinician's ability accurately to stage esophageal carcinoma. Patients with higher-stage disease, although still localized, fare poorly and are the most appropriate for multimodality clinical trials.

Preoperative chemotherapy does not provide survival advantage to patients, and therefore should not be used outside clinical trials.

Preoperative chemotherapy combined with radiotherapy has demonstrated a survival benefit over surgery (37) and radiotherapy alone (26) and seems to constitute an alternative to surgery. The results of concomitant chemoradiotherapy given either preoperatively or as definitive treatment appear promising. Based on the results of a phase III intergroup trial comparing chemoradiation therapy with radiation therapy alone (52), we recommend this combined modality approach for patients with locally unresectable disease. For resectable tumors, randomized studies are ongoing comparing preoperative chemoradiation and surgery versus surgery alone or chemoradiotherapy alone versus surgery alone (53).

For optimal management of patients with esophageal cancer, they should be offered the opportunity to participate in well-designed clinical trials. Incorporation of novel chemotherapy agents that have demonstrated activity in upper aerodigestive tract malignancies such as the taxanes, vinorelbine or gemcitabin is indicated. A critical approach to the literature-based knowledge is, however, required both when suggesting therapy to patients and when designing new trials (60).

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