CONCURRENT CHEMORADIATION FOR ESOPHAGEAL CARCINOMA: PRELIMINARY RESULTS

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Abstract- Despite all advances, treatment of esophageal carcinoma is still unsatisfactory. Currently the standard non-surgical treatment of esophageal cancer is concurrent chemotherapy and radiotherapy (chemoradiation), with results comparable to best surgical series. A few years ago, we started a chemoradiation protocol for the cancer of esophagus as a curative treatment, of which we present the preliminary results here. Files of all esophageal carcinoma patients treated in our department since 1996 until mid 2001 were checked, and those treated by chemoradiation were selected and reviewed. Overall survival was measured from the start of radiotherapy to the time of last follow-up or death. Results were compared to historical controls treated by radiotherapy alone in our department, reviewed in a recent study. Twenty-eight patients (17 males and 11 females, mean age 59 years, tumor location in the middle-third of esophagus in 54%, all squamous carcinoma except one adenocarcinoma) were treated by two courses of cisplatin and 5-FU chemotherapy with concurrent radiotherapy. Radiation dose was mostly 50 Gy in 25 fractions. Mean overall survival was 17 months and median survival was not reached yet due to relatively short follow-up. Compared to 283 patients treated by radiotherapy alone with a mean and median survival of 12 and 8 months, chemoradiation was significantly superior (P=0.0004). Concurrent chemoradiation as used in our department offers a definitely better chance of survival compared to radiotherapy alone. To improve the results, we are pursuing the combination of neoadjuvant chemoradiation and surgery in a clinical trial.

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INTRODUCTION

Despite all advances, treatment of esophageal carcinoma is still unsatisfactory, and most of the patients with this cancer die of local or distant tumor effects. Currently the standard non-surgical treatment of esophageal cancer is concurrent chemotherapy and radiotherapy (chemoradiation) with results comparable to best surgical series, though head to head comparison between chemoradiation and surgery alone in treatment of esophageal cancer is somewhat difficult due to lack of well-controlled randomized data (1). In addition, combination of pre-operative (neoadjuvant) chemoradiation and surgery is now being tested in many clinical trials around the world (including our department) to improve the relatively dismal survival results. A few years ago we started a chemoradiation protocol for the cancer of esophagus as a curative treatment, of which we present the preliminary results here. We hope to be able to report the mature results again after suitable longer follow-up, and also present the findings of our neoadjuvant chemoradiation trial in the near future.

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MATERIALS AND METHODS

Files of all esophageal carcinoma patients treated in our department since 1996 until mid 2001 were

checked, and those treated by chemoradiation were selected and reviewed. Overall survival was measured from the start of radiotherapy to the time of last follow-up or death, and mean and median survivals were calculated by Kaplan-Meier method. Survival results were compared by log-rank test to historical controls treated by radiotherapy alone in our department, reviewed in a recent study (2). Multifactorial analysis of overall survival was performed by Cox-regression method. *P* values of <0.05 were considered significant. All statistical analyses were performed by SPSS statistical software version 9.0.

Chemoradiation protocol

Concurrent chemotherapy and radiotherapy was prescribed to the patients; radiation treatment was 50 Gy in 25 fractions administered during 5 weeks as definitive treatment, reduced to 45 Gy in 25 fractions in the preoperative (neoadjuvant) setting. Neoadjuvant treatment was given at the discretion of the referring surgeon to patients considered operable with a suitable performance status for preoperative treatment. During weeks 1 and 5 of radiotherapy, concurrent chemotherapy was given as cisplatin 60-75 mg/m^2 bolus infusion on day 1 of chemotherapy and 5-fluorouracil (5-FU) 750-1000 mg/m^2 per day continuous 24-hour infusion on days 1-4 of chemotherapy. Patients were hospitalized for the concurrent chemotherapy periods.

RESULTS

Twenty-eight patients were treated according to the concurrent chemoradiation protocol, all by the first two authors.

The patients were 17 males and 11 females, and their mean age was 59 years, with a range of 37-74 and standard deviation (SD) of 9 years. The tumors were located in the middle esophagus in 15 patients (54%), in the upper esophagus in 6 (21%) and in the lower esophagus in 7 patients (25%). All histologies were squamous carcinomas except one, which was adenocarcinoma. The tumors length (radiologic measurement) was 5-15 cm, with a mean of 8.6 and SD of 2.7 cm.

Radiation dose was 50 Gy in 25 fractions in 21 patients and 45 Gy in 25 fractions in 7 patients (both during 5 weeks). All patients received the two planned courses of concurrent chemotherapy, except one who could not tolerate the second course because of side effects. Chemotherapy courses were all given with the full dose of drugs.

Of the 7 patients treated in the pre-operative setting (receiving 45 Gy of radiation), 4 patients unfortunately did not return and/or accept surgery after the chemoradiation mostly because of improvement in their symptoms, and only 3 patients were actually operated on. In these 3 patients who underwent surgery, two pathologic complete responses (no tumor seen in the operative specimen) and one partial response (islands of tumor only left in the muscularis layer) were seen. One of the pathologic complete responses was seen in a patient whose pathologic diagnosis at the endoscopic biopsy was microinvasive squamous carcinoma, though her radiologic tumor length was 5 cm.

Side effects of treatment included nausea and vomiting (especially after cisplatin infusions), mucositis, and drops in white blood cell counts. Nausea and vomiting were mostly well controlled by suitable antiemetic drugs. Mucositis occurred in nearly all patients, mostly in the last 2 weeks of the treatment; due to this, dysphagia usually improved in the early phase of treatment, but worsened in the last weeks of treatment and improved again after the end of treatment with subsidence of mucositis. None of the side effects was life-threatening.

Sixteen recurrences were found after treatment by radiology and/or endoscopy; also 7 deaths were recorded during the follow-up, all due to esophageal cancer. With a mean follow-up of 1 year (range 1-23 months), mean overall survival was 17 months by Kaplan-Meier method and median survival was not reached to this date due to the relatively short follow-up. In Cox-regression multifactorial analysis, age, sex, and tumor length and location did not have a significant effect on overall survival of chemoradiation patients, though tumor length was close to statistical significance with a *P* value of 0.06.

The above results were compared to 283 patients (historical controls) treated in 1989-1999 by radiotherapy alone in our department, reviewed in a

recent study (2). These patients were 54% male, and their mean age and tumor length, location and histology were similar to our chemoradiation patients. Mean and median overall survivals in historical controls were 12 and 8 months respectively; by log-rank test, overall survival (Fig. 1) in chemoradiation patients was significantly superior (P=0.0004). In Cox-regression mutifactorial analysis of age, sex, tumor length, location, and prescription of concurrent chemoradiation, the only factor with a significant effect on overall survival in the total patient population was chemoradiation (P=0.006), though tumor length was very close to statistical significance with a P value of 0.053.

To exclude the effect of surgery on survival, all the 3 patients who had actually received surgery were removed from the analysis and the survival comparison with log-rank test was repeated; again chemoradiation was superior to radiotherapy alone (P=0.004).

DISCUSSION

The treatment of choice for patients with esophageal cancer is controversial. Esophagectomy has long been the standard of care; however, its role has been challenged due to the generally poor outcome following surgical resection alone in patients who typically have locally advanced disease (1). A survey of community care practice patterns between 1988 and 1993 revealed an increase in the use of chemoradiotherapy relative to surgery as primary management of esophageal cancer in the United States (3). Currently, in many institutions, primary resection is deferred in favor of combined modality therapy with or without adjuvant esophagectomy. Radiation alone has always had an established role in the treatment of esophageal cancer too, but overall survival after radiation alone is approximately 18% at 1 year and 6% at 5 years (4). Similarly, single-modality radiotherapy in our centre in 283 patients showed a 2-year survival of 8.4%. The use of radiation therapy as a potentially curative modality requires doses of at least 50 Gy at 1.8 to 2.0 Gy per fraction. Furthermore, given the large size of many unresectable esophageal cancers, doses of 60 Gy or greater are probably required.

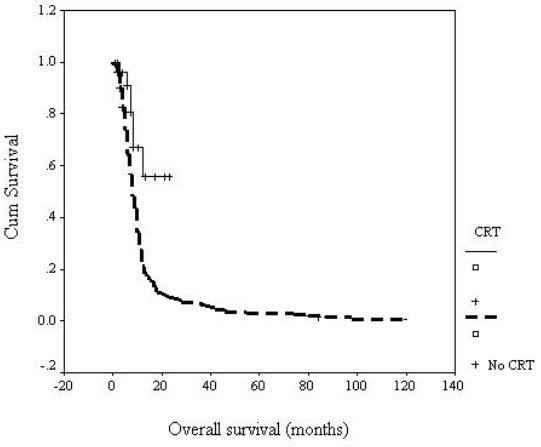

Fig. 1. Overall survival in chemoradiation (CRT) versus radiotherapy alone (No CRT).

Given the poor results of radiation alone in treatment of esophageal carcinoma, concurrent use of chemotherapy with radiotherapy (chemoradiation) has been enthusiastically pursued. Two important multi-center clinical trials from the United States, the Radiation Therapy Oncology Group (RTOG) 85-01 study (5,6) and the Eastern Cooperative Oncology Group (ECOG) study (7), have shown the superiority of chemoradiation over radiotherapy alone in the improvement of survival in esophageal cancer patients. In the randomized part of the RTOG trial, at 5 years of follow-up the overall survival for combined therapy (5-FU and cisplatin with radiation) was 26% compared with 0% following radiotherapy alone. Interestingly, the dose of radiation in the combined therapy arm of the trial was 50 Gy in 25 fractions versus 64 Gy in 32 fractions in the radiotherapy-only arm. In the ECOG study, which used 5-FU and mitomycin C with radiation, two- and 5-year survivals were 12% and 7% in the radiation alone arm and 27% and 9% in the chemoradiation arm. Patients treated with chemoradiation had a longer median survival (14.8 months) compared to patients receiving radiation therapy alone (9.2 months). This difference was statistically significant. The same pattern of survival was noted in almost all subgroups independent of whether surgical resection was performed or not.

Based on the positive results from the RTOG 85-01 trial (and also the ECOG trial), the conventional nonsurgical treatment for esophageal carcinoma is combined modality therapy. Collectively, these and other data indicate that radiation therapy alone should be reserved for palliation or for patients who are medically unfit to receive chemotherapy. Combined modality therapy should be the standard of care (1). Notwithstanding, the local failure rate in RTOG 85-01 combined modality therapy arm was 45%; therefore, new approaches such as intensification of combined modality therapy, including escalation of the radiation dose, have been pursued in an attempt to help improve these results.

Our findings, though preliminary and immature, further confirm the superiority of concurrent chemoradiation over radiotherapy alone in the treatment of esophageal cancer, and also demonstrate the feasibility of this type of combined-modality treatment in Iran. Our combined therapy patients had a better overall survival than patients treated by radiotherapy alone in our department (historical controls); the survival difference was statistically significant (P=0.0004). In mutifactorial analysis, the only factor with a significant effect on overall survival in the total patient population was prescription of concurrent chemotherapy (P=0.006), though the effect of tumor length was very close to statistical significance with a P value of 0.053.

It should be noted that concurrent chemoradiation is an intensive treatment with potentially severe acute side effects; in the RTOG trial, 10% had life-threatening toxic effects with combined therapy versus 2% in the radiotherapy only group (5). But with careful attention to the nutritional status of the patients and their symptoms during treatment and also hospitalization for the concurrent part of therapy, we could keep our acute effects in a manageable state, and we could prescribe the full treatment according to the protocol to all but one of the patients. Our somewhat lower dose of chemotherapy in some patients compared to the RTOG trial may have contributed to the relatively lower rate of acute side effects. Our study has a short follow-up, and thus we have not recorded the late effects of treatment. But it should be borne in mind that concurrent use of chemotherapy does not seem to add to late effects of radiation; in RTOG trial, there were no significant differences in severe late toxic effects between the groups (5). Pre-operative treatment is not the topic of discussion here; our results in this setting will be hopefully reported in future. But it is worth to notice that of the 3 patients who actually underwent surgery after neoadjuvant chemoradiation in our department, two had pathologic complete responses, and the other had only islands of tumor left (one of the complete responses was seen in a patient whose pre-treatment endoscopic biopsy showed microinvasive carcinoma, but in this patient the radiologic tumor length was 5 cm). To exclude the effect of surgery on survival of the chemoradiation patients, we removed the 3 patients with surgery from analysis and repeated the survival comparison, which showed again a significant superiority for chemoradiation over radiotherapy alone (P=0.004). We hope to be able to report the mature results of the present study after longer follow-up. As this study and others have shown, even with concurrent chemoradiation the treatment of esophageal carcinoma is not very successful. Given the improved results of combined-modality therapy, various combinations of pre-operative (neoadjuvant) chemoradiation and surgery are being tested in many trials around the world (8) to increase the survival of esophageal cancer patients; we have also begun a randomized clinical trial in this setting, for which we hope a better accrual. In conclusion, concurrent chemoradiation as used in RTOG trial and our department offers a definitely better chance of survival compared to radiotherapy alone. Mean overall survival was 17 months (median not reached yet) in our combined therapy patients versus 12 months (median 8 months) in historical controls treated by radiation alone in our department. To improve the results, we are pursuing the combination of neoadjuvant chemoradiation and surgery in a clinical trial.

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