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Extended vs. Small Field Irradiation in High Risk Post Esophagectomy Patients Receiving Combined Chemoradiation Therapy: A Decade Experience in Treatment of Esophageal Cancer

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EXTENDED vs. SMALL FIELD IRRADIATION IN HIGH RISK POST ESOPHAGECTOMY PATIENTS RECEIVING COMBINED CHEMORADIATION THERAPY: A DECADE EXPERIENCE IN TREATMENT OF ESOPHAGEAL CANCER

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Extended vs Small field irradiation in High Risk Post Esophagectomy Patients Receiving Combined Chemoradiation Therapy : A Decade Experience In Treatment Of Esophageal Cancer.

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OBJECTIVE: To assess the impact of extended field irradiation with anastomotic coverage on local recurrence in high risk resected esophageal cancer patients.
METHODS: From 1989-1999, high risk resected esophageal cancer cases receiving post-resection chemoradiation were reviewed. Adjuvant chemotherapy consisted of four cycles of fluorouracil - based regimens. Loco-regional irradiation with or without coverage of anastomotic site had radiation a dose range from 45-60 Gy at 1.8-2.0 Gy / fraction given with initial anterior-posterior / posterior-anterior arrangement with either extended (with anastomotic coverage), or small (without anastomotic coverage) field followed by oblique fields for boost.
RESULTS: One hundred eighty-eight charts were reviewed. Seventy-two patients were eligible for post-resection chemoradiation. Three patients had disease progression prior to therapy, and 69 patients were analyzed. The median age was 60 years (range 35-82years) with 94 % T_{2-3} N_1 and 65% were adenocarcinoma. As of January 2005 median follow up was 30.5 months (range 3-142 months), the two - and five- year overall survival rates were 50% and 31%, respectively . First relapse rate after adjuvant therapy was 71% (n=49) and median time to relapse was about 30 months. Loco-regional relapse with small field was 25/35 (71.4%) and 2/14 (14.2%) with extended field (P < 0.001). Recurrence locally to anastomosis or adjacent site was 10/35 (28.6%) with small field and 0/14 (0%) with extended field (P=0.04).
CONCLUSION: At a minimum of 5-year follow up, there is significant decrease in loco-regional relapse with the use of extended field in high risk resected esophageal cancer patients. This important improvement trend deserves further exploration in prospective randomized clinical trials.

Introduction

- Post-operative radiation therapy (RT)[1] and post-operative chemoradiation[2] have been used for esophageal cancer patients deemed high risk for recurrence after esophagectomy. Defining optimal RT target voulme after esophagectomy is difficult due to significant changes in patient anatomy and function.
- Some radiation oncologists advocated the inclusion of the anastomotic site within the irradiation volume due to concerns for potential increased relapse risk, while others did not subscribe to this practice due to concerns for increased treatment-related toxicity. We performed a review of patient outcomes in a single institution to investigate the impact of anastomotic coverage in high risk esophageal patients who underwent esophagectomy.

[1] Fok et al, Surgery: 113, 1993

[2] Bedard et al, Cancer: 91, 2001

Methods and Materials

- Data were analyzed for patients treated at London Regional Cancer Center (LRCC) from 1989 to 1999 with a diagnosis for "high risk" resected esophageal cancer. "High risk" pathologic findings were defined as T_3 or T_4 disease and/or regional nodal involvement.
- Adjuvant therapy consisted of chemotherapy followed by concurrent chemoradiation. Chemotherapy consisted of 4 cycles of either ECF (epirubicin 50mg/m^2 day 1 and q21 days, 5 fluorouracil 200mg/m^2 continuous infusion for 21 days, and cisplatinum 60mg/m^2 day 1 and q21 days), with epirubicin omitted during the concurrent phase with RT, or 4 cycles of CF (cisplatinum 100mg/m^2 day 1 and q21 days), and 5 fluorouracil 1000mg/m^2 days 1-4 continuous infusion and q21 days). Total RT dose ranging from 45-60 Gy at 1.8-2.0 Gy fraction. In general 45-50 Gy was used for microscopic disease while higher doses up to 60 Gy were reserved for patients with margin involvement or residual disease.
- The first phase of RT involved APPA beam arrangement to 30-45 Gy, with either extended field (including anastomotic site with field size range 22x12-28x12cm, median 24x12cm) or small field (excluding anastomotic site with field size range 12x10-22x12 cm, median 19x12cm) followed by second phase cord-sparing, oblique fields for boost with an additional 15-30 Gy.
- The initial target volume defined by margins of 5 cm above and below the pre-surgical gross tumor volume, as well as a 2 cm margin to cover the mediastinal lymph nodes medially and laterally. For "extended field" the superior margin extended 2 cm above the anastomotic site (Figure 1).
- Boost fields were CT- planned with 2 cm margins around the target volume. All patients were treated with high energy mega voltage photon (>6 MV) in supine position. Close margin was defined as microscopic tumor cells presented within 2 mm of the resection margin.
- Local relapse was defined as recurrence at or immediatley adjacent to the anastomotic site. Regional relapse was recurrent at the mediastinum and/or peri-esophageal region excluding local relapse.
- Distant relapse was tumor recurrence at the distant site, i.e. brain, liver, and lung etc. Acute treatment toxicities included chemotherapy/RT interruption, and late gastrointestinal RT morbidity (RTOG grading system) Grade 2 toxicity were also analyzed. Grade 2 was described as moderate diarrhea and colic with bowel movement > 5 times daily, or intermittent bleeding. The marker for any toxicity-related treatment break was measured by the length (in days) of the interruption in the chemotherapy or RT schedule arising during the concurrent phase of the treatment.
- Hematological criteria for interruptions during concurrent chemotherapy RT including absolute neutrophil count < 1,000 mm^{-3} , sepsis or neutropenic fever, thrombocytes <80,000 mm^{-3} .
- Loco-regional symptomatology including severe esophagitis (i.e. severe odynophagia/dysphagia, intolerable pain), impaired nutrition with nausea/vomiting; and dehydration require hospitalization.

Results

- 188 esophageal cancer patients eligible for review were identified. 72 had thoracic esophageal and GE junction cancer with high risk features post-surgery. Three patients had disease progression prior to treatment, leaving 69 patients for analysis. The median age of the patients was 60 years (range 35-82years). Table 1 shows the patient characteristics of the study group.
- As of Jan 2005, follow-up ranged from 3-142 months with median 30.5 months. The 2-yr and 5-yr overall and disease specific survivals were 50 and 31%, 62 and 37.4% respectively (Figure 2).
- For small field RT the median, 2 yr and 5-yr overall survivals were 32.5 months, 60.5 and 29.2% respectively; 27.6 months, 42.5 and 34.6% respectively for the extended field RT (P= 0.950).
- The median, 2-yr and 5-yr disease specific survivals, were 36.4 months, 66.1 and 31.9%, respectively, for small field RT; 35.2 months , 59.7 and 49.7% respectively, for the extended field RT (P= 0.50) (Figure 3). The first relapse rate after adjuvant therapy was 71% (n=49) and the median time to relapse was about 30 months. Loco-regional relapse with small field was 25/35 (71%) and 2/14 (14.2%) with extended field (P<0.001) (Table 2).
- The difference between small and extended field remained statistically significant (P=0.003) when adjustment was made for the effect of margin status. Recurrence locally to anastomosis or adjacent site was 10/35 (28.6%) with small field and 0/14 (0%) with extended field (P= 0.04) (Table 3). Complications of extended field RT were reviewed including RT treatment interruption (P=0.71), chemotherapy delays (P=0.26), and late gastrointestinal Grade 2 toxicity (P=0.26) were not statistically significant when compared with patients treated with small field RT.

Conclusion

- Esophageal cancer patients with high risk features of regional nodal involvement, positive or close resection margins and T_3 or T_4 disease, post-operative RT with extended field to include the anastomotic site, improved local-regional disease control without added late toxicity upon retrospective analysis.
- Confirmation of these findings and evaluation of acute and chronic toxicity and patient quality of life associated with this treatment regimen, require prospective investigation.

Figure 1a: Small Field RT

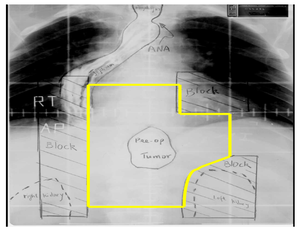

Figure 1b: Extended Field RT

Figure 2a

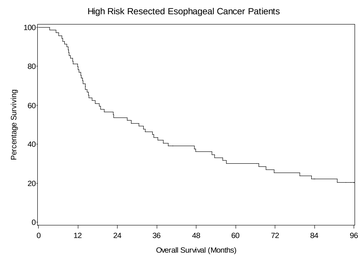

Figure 2b

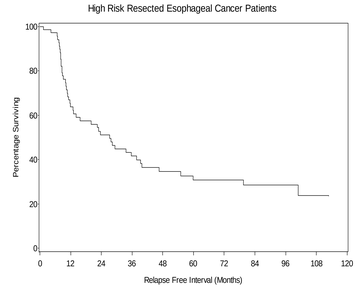

Figure 3a

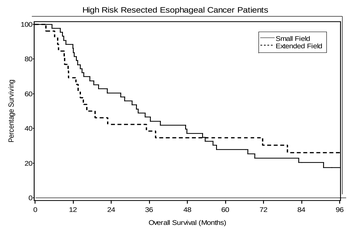

Figure 3b

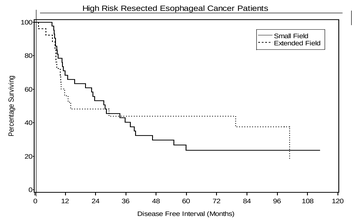

Table 1: PATIENT CHARACTERISTICS

Patient	Characteristics	All (n=69)	SM (n=43)	EX (n=26)	[a]P-value
Age	< 65	41(59%)	25	16	
	≥ 65	28(41%)	18	10	P=0.781
Sex	Male	62(90%)	38	24	
	Female	7(10%)	5	2	P=0.598
Pathological	$T_{2,3}$ N_1	65(94%)	41	24	
Stage	$T_{3,4}$ N_0	4(6%)	2	2	P=0.601
Type of	Transhiatal	59(86%)	35	24	
Surgery	Transthoracic	10(14%)	7	3	P=0.523
Tumor	Squamous	24(35%)	15	8	
Pathology	Adenocarinoma	45(65%)	27	18	P=0.676
Margin	Positive/Close	34(49%)	14	20	
Status	Negative	35(51%)	29	6	P<0.01

SM- Small field RT
EX- Extended field RT
[a]Chi-Square

Table 2: TREATMENT VOLUME

TREATMENT VOLUME	LOCAL REGIONAL	DISTANT	TOTAL (%)
Small field	25(71.4%)	10(28.6%)	35(100%)
Extended field	2(14.3%)	12(85.7%)	14(100%)

([a] P<0.001) , [a] Chi- Square
([b] P<0.001) , [b] Fisher's Exact (two- tails)

Table 3: TREATMENT VOLUME RELAPSE

Treatment Volume	Relapse Pattern		TOTAL (%)
	ANA	NANA	
Small field	10 (29%)	25 (71%)	35 (100%)
Extended field	0 (0%)	14 (100%)	14 (100%)

([b] P =0.04) , [b] Fisher's Exact(two-tails)
ANA - Anastomotic
NANA- Non-Anastomotic