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Post-Operative Extended Volume External Beam Radiation Therapy Is Safe for High Risk Esophageal Cancer Patients

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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 opitmal RT target volume 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 have previously reported patient outcome benefit using extended volume RT In management with high risk esophageal cancer patients underwent esophagectomy (3).

We have performed a Phase I study to evaluate the safety of subscription to this practice.

1. Folk et al, Surgery, 113:1993
2. Bedard et al, Cancer, 91;2001
3. Yu et al, Radiother & Oncol, 73;2004

METHODS

From 2001 to 2006, a prospective phase I study to evaluate extended volume RT covering anastomotic site post-esophagectomy was performed.
Eligible patients had resected esophageal cancer with high risk features, ie, pathological findings as T3 or T4 disease and/or regional nodal involvement, with or without surgical margins involvement.
Patients with distant metastasis (M1) or previously received RT were excluded.
Adjuvant therapy consisted of chemotherapy followed by concurrent chemoradiation. Chemotherapy consisted of 4 cycles of ECF (epirubicin 50 mg/m2 day 1 and q 21 days, and cisplatinum 60 mg/m2 day 1 and q 21 days) with epirubicin omitted during the concurrent phase with RT.
External beam RT utilized conformal CT planning, with multi-fields arrangement tailored to the pathological findings and encompassed the primary tumor bed and anastomotic site.
The initial target volume defined by margins of 5 cm above and below the pre-surgical gross tumor volume, as well as 2 cm margin to cover the mediastinal lymph nodes medially and laterally with superior margin extended 2 cm above the anastomotic site (3).
The boost fields were 2 cm margins around the target volume.
The total RT dose was 5040 cGy at 180 cGy per fraction (the initial target volume of 3060 cGy/17 fractions followed by 1980 cGy/11 fractions), delivered concurrently with the third cycle of chemotherapy.
Treatment – related toxicities were assessed using NCI-CTC grading.
Patient outcomes were disease free survival (DFS) and overall survival (OS), calculated by Kaplan-Meier method.

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Table 1: Patient Demographics

Patient Demographic		
Age	Median	Range (48-80 years)
Sex	Male Female	10 5
Pathological Stage	T3N0 T2N1 T3N1 T4N1	1 2 11 1
Tumor Pathology	Squamous Adenocarcinoma	10 5
Margin Status	Clear Close/positive	10 5

Table 2: Chemotherapy Delay and Dose Reduction

Chemotherapy								
Patient No.	Cycle 1		Cycle 2		Cycle 3 + RT		Cycle 4 + RT	
	Delay	Dose Reduction	Delay	Dose Reduction	Delay	Dose Reduction	Delay	Dose Reduction
1	-	-	-	-	-	-	-	-
2	-	-	-	-	+	-	+	+
3	-	-	-	-	-	-	-	-
4	-	-	-	-	+	-	+	-
5	-	-	-	-	-	+	-	-
6	+	-	-	+	-	-	-	-
7	-	-	+	-	-	+	-	-
8	-	-	-	-	-	-	-	-
9	-	-	+	+	-	-	+	-
10	-	-	+	-	+	-	-	-
11	-	-	-	-	-	+	-	-
12	-	-	-	-	-	-	-	-
13	-	-	-	-	-	-	-	-
14	-	-	-	-	-	-	-	-
15	-	-	-	-	-	-	-	-
%	6.6%	0%	20%	13.3%	20%	20%	20%	6.6%

RESULTS

Out of 15 accrued patients there were 10 males and 5 females, age ranging from 48 to 80 years, with median age of 64 years. The TNM stages included one T3N0, two T2N1, eleven T3N1, and one T4N1. The histo-pathology included 5 adenocarcinoma and 10 squamous cell carcinoma. Resection margins were clear in 10 patients (Table 1).
Follow-up ranged from 3.5 to 53.4 months with median of 19 months.
Table 2 showed chemotherapy delay in 20% and dose reduction in 13.3% of the patients prior to RT was needed while with concurrent RT it was 20% and 6.6%, respectively.
The reasons for chemotherapy delay and dose reduction were as follows: for chemotherapy delay including physician and patient's choice in cycle 1; febrile neutropenia, diarrhea in cycle 2; neutropenia in cycle 3 with RT; and neutropenia and patient's choice in cycle 4 with RT. For chemotherapy dose reduction there was no dose reduction in cycle 1; febrile neurtopenia, diarrhea and physician's choice in cycle 2. Febrile neutropenia, mucositis, handfoot syndrome in cycle 3 with RT and patient's choice in cycle 4 with RT. There were no RT delayed and dose reduction in the patient cohort.
During the follow-up period, there were 2 patients with Grade 1 for cough, one patient with Grade 1 for nausea and vomiting, one patient with Grade 2 nausea and vomiting, one patient with Grade 2 diarrhea and abdominal cramps, 2 patients with taste alteration and 3 patients with poor appetite and low energy level.
There was no patient experienced treatment related esophagitis or pneumonitis of greater than Grade 2 during treatment and in the follow-up assessments.
There was no chemoradiation treatment related mortality in the study cohort.
Disease recurrence occurred in 38% and the median time to relapse was 24 months (Figure1).
There was no tumor recurrence at the anastomotic site.
The median OS was 21 months (Figure 2).

CONCLUSION

Extended volume RT covering the anastomotic site in high risk patients post esophagectomy is feasible and safe.

Figure 1: Disease Free Survival

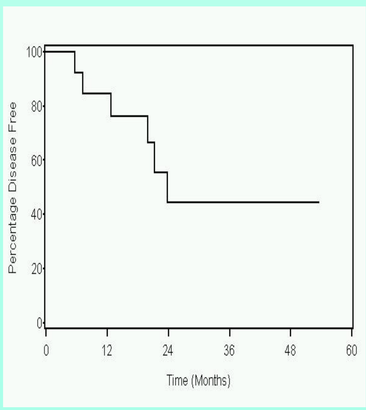

Figure 2: Overall Survival