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A Study of Concurrent Chemo Radiation in Carcinoma of Esophagus

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Abstract:
Background: *The efficacy of conventional treatment with surgery and radiation for cancer of the esophagus is limited. The median survival is less than 10 months, and less than 10 percent of patients survive for 5 years. Recent studies have suggested that combined chemotherapy and radiation therapy may result in improved survival.*
Aim: *Concurrent chemo radiation in carcinoma of esophagus with 50.4 Gy of 28 fractions 180 cGy / fraction, 5 fractions / week with concurrent chemotherapy with Inj.Cisplatin and Inj. 5 FU total 2 cycles with a gap of 3 weeks duration in 15 patients compared with who received 66 Gy and kept on follow-up from our institution with similar tumor patient.*
Methods: *30 patients (15 patients from each group) were selected to evaluate the efficacy of 2 courses of combined fluorouracil (500 mg/m^2 of BSA daily for 3 days) and Cisplatin (50 mg / m^2 on the day 1 and day 2) plus 5040 cGy of radiation therapy, as compared with 6600 cGy of radiation therapy with weekly Inj.Cisplatin 50Mg/m^2 in patients with squamous cell carcinoma of the esophagus.*
Results: *Acute toxicity was recorded during the entire course of treatment. The most common acute toxicity was observed was vomiting and dysphagia in 13 patients (86.67%) followed by Gr.I mucositis in 12 patients (80%) and Gr.I neutropenia in 12 patients (80%), 4 patients relapsed during follow-up period, 4 patients had locoregional recurrence, 1 patient developed retroperitoneal lymphadenopathy and 1 patient developed TEF. The median time to relapse from the end of the radiation was 3 months. The locoregioal control rates were 11 out of 15 patients (73.33%).These results are compared with 15 patients in control arm, who received 66 Gy and kept on follow-up, 7/15 patients (46.67%) relapsed locoregionally, and 1/15 (6.67%) relapsed distantly. All the patients who relapse during follow-up period mostly were stage-IIB & III.*
Conclusion: *Higher radiation doses did not increase survival or locoregional control. The results of 50.4 Gy with 3 weekly Inj.Cisplatin and Inj.5FU are equally efficacious to high dose arm with 66 Gy with weekly Inj.Cisplatin. In conclusion, that combination of chemotherapy and radiotherapy improves the local control and palliation and hence translates to better survival rates of the patients suffering from carcinoma esophagus.*
Keywords: *concurrent chemoradiation, Cisplatin, 5-flouorouracil.*

I. Introduction

In Carcinoma Esophagus squamous cell carcinoma is the principal type. Adenocarcinoma occurs in thelower end of esophagus.

Radiotherapy plays a dominant role in its management especially in upper and middle thirds and can produce cure rates ranging from 10 to 23% which is comparable treatment by radical surgery.The contributing factors like drinking local alcoholic brews, smoking beedies and cigarettes, chewing tobacco, beetlenut chewing and gross dental sepsis for the causation of carcinoma of esophagus can easily be prevented.

Dietary factors associated with Carcinoma esophagus:

Alcoholic drinks and Tobacco are the major risk factors, associated with 80 to 90% of all cases. 81 gms or more of Whisky per day show greater risk than the same quantity of beer or wine.Tobacco smoking is major carcinogenic factor.Nutritional deficiencies, Occupations at risk include waiters, bartenders. Metal workers and construction workers.

II. Objectives Of The Study

The Principle objectives of concurrent Chemo Radiotherapy in carcinoma esophagus are : (a)To increase locoregional tumor control, (b)To decrease distant metastasis,(c)To improve overall survival.

Pathology of Carcinoma Esophagus

Carcinoma of esophagus can occur in any portion of esophagus but it is common in the middle and lower third of the esophagus. The lesion may be squamous cell carcinoma or adenocarcinoma. The Adenocarcinoma occurs essentially at the lower end; as the lower 3 cms lined by columnar epithelium or it may be secondary to carcinoma of the stomach.

More than 90% of malignant esophageal tumors are squamous cell carcinomas, arising from the squamous cell lining the lumen of the esophagus.

About 50%occur in middle third of esophagus and are mostly squamous cell carcinomas.

About 30% occur in lower third of esophagus and are mostly adenocarcinomas.

Spread Of Carcinoma Esophagus:

(a) Direct Spread invade the important structures of the neck and posterior mediastinum, as well as the lungs and trachea.

(b) Lymphatic Spread lead to satellite nodules away from the main tumor.

Diagnosis:

Biopsies and Cytological examination has been 90% accurate in patients with very early cancer of the esophagus.

III. Materials & Methods

Target population: In our prospective study consists of 30 patients with esophageal carcinoma with squamous cell histology of stage II & III, 15 patients on either arms with a mean age of 60 years with PS 0 or 1 registered at GGH, Guntur Medical College with confirmed diagnosis of squamous cell carcinoma of esophagus.

In Arm-A received 50.4 Gy of 28# 180 cGy/#, 5#/week with concurrent chemotherapy with 2 cycles of Inj.Cisplatin 50 mg/m^2/on D1, D2, Inj.5FU 500 g/m^2 D1, D2,D3 with a gap of 3 weeks.

In Arm-B, patients received 66 Gy of 33# 200 cG/#, 5#/week with weekly Inj.Cisplatin 50 mg/$m^{2.}$

Inclusion criteria :

- Age younger than 70 years.
- Good general condition with ECOG 1 or 2
- Histopatholgically confirmed Squamous cell carcinoma of esophagus
- No H/o other malignancies
- No prior radiotherapy or chemotherapy
- Ca.Esophagus stage with M0 status
- Adequate function of major organs confirmed by WBC >4000/cumm, PC >150000/ cumm, Hb% > 10 gm%, Sr. Creatinine <1.2 mg/dl, LFT – WNL
- No co-morbid illness such as heart, renal, hepatic failures and uncontrolled infections, Informed consent.

Exclusion criteria :

- Age more than 70 years, ECOG PS 3 or more, Any evidence of distant metastasis, Co morbid conditions HTN, COPD and cirrhosis, Hematological parameters :WBC < 4000/ cumm, PC < 150000/ cumm, Sr-creatinine >1.5 mg/ cumm
- Histologies other than squamous cell carcinoma, Pregnant women., Recurrent disease

Pre-treatment evaluation : Routine Blood Tests, Radiological Examinations are necessary.

Protocol Design :

- Stage I to IV with M0 status
- Squamous cell carcinoma of esophagus
- Definitive chemoradiotherapy
- Concurrent chemoradiation.

Arm-A:

Radiation	:	Total dose 50.4 Gy, of 28# 180cGy/#, 5# / week
		After 4500 cGy; spinal cord sparing should be done Chemotherapy
1s cycle CT	:	Inj. Cisplatin 50mg/m^2, D1, D2
Day -1	:	Inj. 5 FU 500 mg/m^2, D1, D2, D3

(After 3 weeks)

2^{nd} cycle CT	:	Inj. Cisplatin 50mg/m^2, D1, D2
Day -21	:	Inj. 5 FU 500 mg/m^2, D1, D2, D3

ARM –B :

Radiation	:	Total dose 66 Gy, of 33# 200cGy/#, 5# / week with 4 to 5 cycles of Inj. Weekly. Cisplatin 50 mg / m^2
Tumors	:	Above carina treat SCV + mediastinal lymphnodes

Tumors at or below the carina : treat mediastinal lymphnodes and include celiac lymphnodes for lower 1/3 and gastresophageal junction tumors.

When radical treatment is given, the vogue is usually 15-18 cm is length. To encompass potential submucosal spread a margin of 5 cm is allowed above and below the tumor limits as determined by barium swallow and esophagoscopy.

Lateral and A-P boarders are chosen using a diagnostic barium swallow or CT scan and localized on simulator film. The width and depth of the target volume are usually 6-8 cm in order to include all soft tissue disease in the esophageal wall. Reduction in the length of the volume may be made to allow a 1-2 cm margin for a second phase of treatment.

Lesions in lower Two thirds of esophagus :

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Radiation Portals

Treatment on Linear Accelerator

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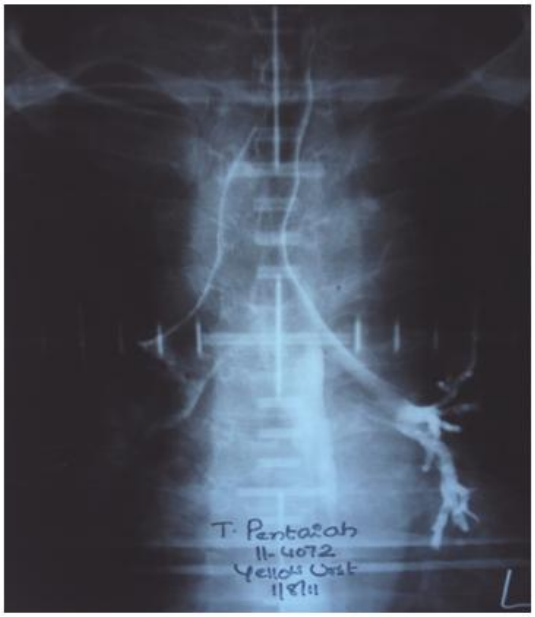
Treatment Planning check film



Tracheoesophageal Fistula

Conventional RT fields[2]:

ervical esophagus RT

Superior : 5 cm proximal to tumor +SCLN + Upper mediestal 2 N
Inferior : 5 cm distal to tumor
Lateral : Tumor + 2.5 to 3 cm + mediastinal LN + medial 2/3rd of clavicle for S.C.F.LN

Middle Esophagus RT:

Superior : 5 cm proximal to tumor + Upper mediastinal LN
Inferior : 5 cm distal to tumor + mediastinal LN
Lateral : Tumor + 2.5 to 3 cms + mediastinal LN

Lower Esophagus:
Superior : 5 cm Proximal to tumor + mediastinal LN
Inferior : 5cm to distal to tumor + mediastinal LN + celiac LN[until L 1-2 vertebra]
Lateral : Tumor + 2.5 to 3 cm + mediastinal LN s
A-P field is used until 45 Gy then 50.4 Gy oblique or three fields (one ant, Two posterior oblique fields) by sparing the spinal cord.

Conformal Radiotherapy volumes :
GTV: Tumor + involved lymphnodes (nodal GTV may be separately delineated)
CTV : GTV + 1 cm(lateral) + 3 cm (Superior + inferior), PTV : CTV + 1 cm.

Dose prescription : 1.8 Gy / # to 50.4 Gy.
IF the stomach is in the field consider reducing lower border to block stomach at 45 Gy if clinically possible.

Dose limitations :
Spinal cord D max < 45 Gy at 1.8 Gy#
Lung : Limit 70% of both lungs < 20 Gy
Heart : Limit 50% ventricles < 25 Gy

Complications :
Esophagitis, weight loss, fatigue, anorexia, Pneumonitis, Esophageal perforation occurs rarely.
Follow up : 1st follow-up after 6 weeks then 4 months for 1 yr, then every 6 months for 5 yrs.
Chemotherapy details :

Cycle	Drug	Dose	Day of administration
1.	Inj. Cisplatin	50mg / m^2	D1, D2
	+ Inj. 5 FU	500mg / m^2	D1, D2 & D3
2.	Inj. Cisplatin	50mg / m^2	D1, D2
	+ Inj. 5 FU	500mg / m^2	D1, D2 & D3

IV. Observations

Age distribution :

Arm-A

Age group	No. of patients	%
40-49	2	13.33%
50-59	3	20.00%
60-69	10	66.67%
70-79	0	0

Arm-B

Age group	No. of patients	%
40-49	0	0
50-59	6	40%
60-69	6	40%
70-79	3	20%

Sex distribution

Arm-A

Sex	No. of patients	%
Male	9	60%
Female	6	40%

Arm-B

Sex	No. of patients	%
Male	9	60%
Female	6	40%

Addiction :

Arm-A

Addiction	No. of patients	%
Smokers & Alcoholics	9	60%
No addiction	6	40%

Arm-B

Addiction	No. of patients	%
Smokers & Alcoholics	11	73.33%
No addiction	4	26.67%

Tumor Location:

Arm-A

Location	No. of patients	%
Upper 1/3	2	13.33%
Middle 1/3	12	80%
Lower 1/3	1	6.67%

Arm-B

Location	No. of patients	%
Upper 1/3	1	6.67%
Middle 1/3	11	73.33%
Lower 1/3	3	20%

Grade :

Arm-A

Grade	No. of patients	%
W.D	2	13.33%
M.D.	11	73.33
P.D.	2	13.33%

Arm-B

Grade	No. of patients	%
W.D	8	53.33%
M.D.	7	46.67%
P.D.	0	0

V. Results

15 patients in Arm-A received 50.4 Gy of 28 fractions 180 cGy / fraction, 5 fractions / week with concurrent chemotherapy with Inj.Cisplation and Inj. 5 FU total 2 cycles with a gap of 3 weeks duration.

The most common acute toxicity observed was vomiting and dysphagia.

The mean follow-up was 13 months. Among 15 patients who completed the treatment, few patients relapsed during follow-up period (documented by endoscopy and ultrasound), some patients had loco-regional recurrence.

These results are compared with 15 patients in control arm, who received 66 Gy and kept on follow-up from our institution with similar tumor patient characteristics as study group few patients relapsed and some patients had loco-regional recurrence.

VI. Discussion

In India, esophageal carcinoma incidence is about 10-50 per 1,00,000. Usually male to female ratio is about 6:1.

Surgery may be curative in early stages < 30% 5 year survival in locally advanced esophageal cancers. Surgical resection is the standard treatment for operable esophageal cancer i.e. stages I, II and most cases of III. Local failure after surgery 12% to 67% (mei et al Gignoux et al). 5 year survival with surgery is 20-25% and the median survival is about 15-18 months. Local recurrences are common in upper and middle third squamous cell carcinoma, distant recurrence more common in lower third adenocarcinomas.

In a report by Pearson in 1977, 208 patients were treated with radiation alone. Patients received 50 Gy and had an unduplicated 5 year reported survival rate of 20%.

The landmark trial establishing the superiority of concurrent chemoradiation to radiation therapy alone was RTOG 8501[10]

Newaishy et al conducted a study on 444 patients were treated with 50-55 Gy /4 week 92.5 to 2.75 Gr/ Fr.) reported 2 and 5 survival rates of 19% and 9% respectively.

Results with external beam radiation therapy alone for esophageal cancer.

VII. Conclusion

Higher radiation doses did not increase survival or locoregional control. The results of 50.4 Gy with 3 weekly Inj.Cisplatin and Inj.5FU are equally efficacious to high dose arm with 66 Gy with weekly Inj.Cisplatin.

In conclusion, that combination of chemotherapy and radiotherapy improves the local control and palliation and hence translates to better survival rates of the patients suffering from carcinoma esophagus.

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