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A Study of Chemotherapy and Radiotherapy in Carcinoma Stomach

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Abstract:
Background: *The use of adjuvant therapy with chemotherapy an attractive strategy to improve local control rates and decrease distant failures in resected gastric cancer patients.*
Aim: *The aim of the present study is to determine the efficacy of adjuvant concurrent chemoradiation in resected gastric cancer patients.*
Methods: *In our prospective study we have included 40 patients registered at GGH, Guntur with confirmed diagnosis of adenocarcinoma of stomach post-op, the intention was curative resection. 20 patients undervent surgery alone compared with 20 patients undervent surgery followed by chemoradiation.*
Results: *These results were compared with 20 patients of carcinoma stomach who underwent curative resection and kept on follow up from our institute and with similar tumor another 20 patients characteristics as study group, 10/20 patients (50%) relapsed locoregionally and 2/20 (10%) relapsed distantly. All the patients who relapsed during follow up period had D2 lymphnode dissection mostly were stage III and IV. In surgery followed by chemoradiation group patients survival rate increased and decreased local recurrence.*
Conclusion: *Adjuvant treatment with fluoro-pyrimidines plus leucovorin and radiotherapy has shown definite benefits for all patients with high risk gastric cancer who underwent curative surgery.*
Keywords: *Adjuvant chemoradiation, resected gastric cancer, 5-fluoro uracil, external beam radiotherapy.*

I. Introduction:

Gastric cancer is the fourth common malignancy in the world behind the lung, breast and colorectal malignacies[1] and second leading cause of cancer related deaths in the world in both sexes[2,3]. M:F = 2:1.

Consumption of red chilies, food at very high temperatures and alcohol are the main risk factors for stomach cancers in India[4]. The only proven curative treatment for gastric cancer is surgical resection of all gross and microscopic diseases[5]. In this relapses were frequent. To decrease relapses adjuvant therapy with chemotherapy an attractive strategy to improve local control rates and decrease distant failures in resected gastric cancer patients.

Recently post-operative chemo radiotherapy became the standard of care in the USA when MacDonald et al[7] reported the results of GI INT 0116 trail comparing the effects of post-operative chemo radiotherapy with surgery alone.

II. Objectives Of The Study

1. To evaluate the efficacy of adjuvant concurrent chemo-radiation on (RO) resected gastric cancer patients.
2. To evaluate the toxicity profile of adjuvant chemo-radiation in patients with carcinoma stomach.

Pathogenesis

1. Cell of origin is mucus producing cells
2. A model for gastric carcinogenesis[8] has been developed which has a sequential progression of following events:

1. Chronic superficial gastritis
2. Chronic atrophic gastritis
3. Intestinal metaplasis
4. Dysplasia

1. Ooi et al. identified 3 oncogenic pathways that are deregulated in the majority (>70%) of gastric cancers: the proliferated/ stem cell, NF-KappaB and Wnt/ beta-catenin pathways. Their study suggests that interactions between these pathways may play an important role in influencing disease behavior and patient survival[9].

Stomach cancer is one of the common GI cancers at our institution. The annual incidence rate ranges from 3.060 to 4.02%. The average male to female ratio is 2.47:1.

III. Materials And Methods

Target population

In our prospective study we have included 20 patients in each group registered at GGH, Guntur with confirmed diagnosis of adenocarcinoma of stomach post-op, the intention was curative resection.

Inclusion criteria

2. Age younger than 70 years.
3. Histopathologically confirmed adenocarcinoma of the stomach
4. ECOG PS 0,1,2
5. Resected gastric cancer with RO resection.
6. No H/O other malignancies
7. No H/O previous evidence of treatment such as chemotherapy or radiotherapy
8. Ca.Stomach stage IB-IV with MO status
9. Adequate function of major organs confirmed by

WBS>4000/ cumm, PC>15000/ cumm, Hb% >10 GM%, Sr.Creatinine <1.5 MG/ dl, LFT – WNL

1. No co-morbid illness such as heart, renal, hepatic failures and uncontrolled infections.
2. Informed consent

Exclusion criteria:

1. Age more than 75 years
2. ECOG PS 3 or more
3. Any evidence of distant metastasis
4. Comorbid conditions like hypertension, COPD and cirrhosis
5. Patients not turned up for follow-up regularly
6. Hematological parameters:

(1) WBC< 4000/ cumm **(2)** PC< 15000/ cumm **(3)**Sr-Creatinin >1.5 mg/ cumm

1. Palliative resection of stomach cancer
2. Histologies other than adenocarcinoma

Pre-treatment evaluation:

1. Complete history and physical examination including supraclavicular lymphadenopathy, P/V (for any adnaxel masses), P/R (for deposits in POD)
2. Routine hematological, Radiological investigations and Histopathological examinations were done.

Protocol Design:

Resected stage I-IV (MO)
Adenocarcinoma of the stomach
I cycle chemotherapy with 5 FU/ LV
Regime followed – Inj. 5FU- 425/ m^2 D1- D5
↓ Inj. LV – 20 mg/ m^2 D1-D5
After 4 weeks
↓
Radiation to stomach bed
↓
5 FU 400 mg/ m^2 D1-D4 of RT
LV 20 mg/ m^2 D1-D4 of RT
↓
5 FU 400 mg/ m^2 D23-D25 of RT
LV 20 mg/ m^2 D23-D25 of RT
↓
After 4 weeks
↓
2 more cycles of chemotherapy with doses given as in 1st cycle, 1 month apart.

External Radiotherapy details:

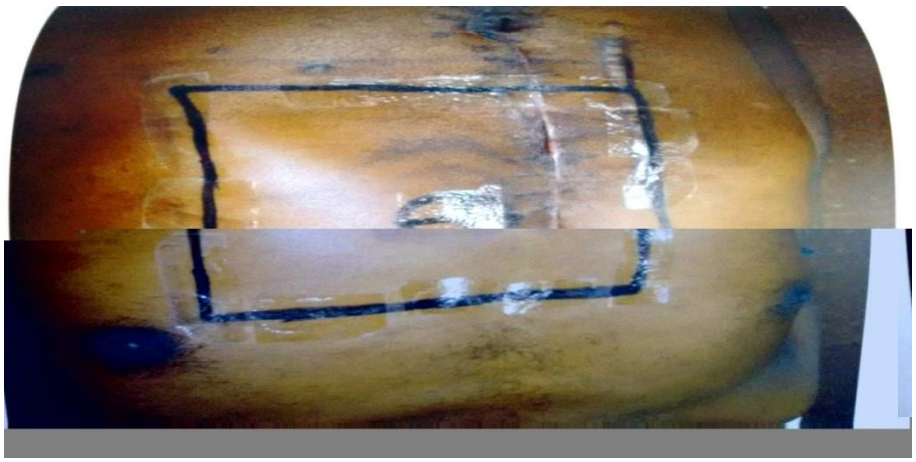
1. Patient in supine position with arms by the side
2. At least 3 hr fasting before planning of radiotherapy and treatment
3. Planned under simulation for all patients
4. Treated by AP-PA parallel opposing abdominal fields with Co-60 Teletherapy machine.

5. Field borders – Depending upon tumor location with 4-5 cm margin around the tumor, determined by post-op histopathology report, post-op barium meal fluoroscopy and pos-op CT Scan.
6. Field borders we have used in general.

1. Superior : Upper border of T10 vertebral body
2. Inferior : Middle of L3 vertebral body
3. Left : 2/3 – 3/4 of left hemidiaphragm
4. Right : 3-4 cm lateral to vertebral bodies.

1. Dose : 45 Gy in 5 weeks, 1.8 Gy/ fraction,5 fractions/ week.

IV. Field Borders On Patient Skin:



Chemotherapy details:

Cycle	Drug	Dose	Day of Administration
1	Inj.5 FU Inj. Ca.LV.	425 mg/ m^2 20 mg/ m^2	D1-D5 D1-D5
2	Inj.5 Fu Inj. Ca.L.V.	400 mg/ m^2 20 mg/ m^2	D1- D4 of RT D1-D4 of RT
3	Inj.5 Fu Inj. Ca.L.V.	400 mg/ m^2 20 mg/ m^2	D23-D25 of RT D23-D25 of RT
4	Inj.5 Fu Inj. Ca.L.V.	425 mg/ m^2 20 mg/ m^2	D1-D5 D1-D5
5	Inj.5 Fu Inj. Ca.L.V.	425 mg/ m^2 20 mg/ m^2	D1-D5 D1-D5

Follow-up :

2. After completion of the treatment, regular follow up was done
3. Every 8 weeks for 6 months & Every 12 weeks for 2 years.
4.

Observations

5. A prospective study of 20 patients with adenocarcinoma of the stomach. Post-OP, following strict selection criteria as outlined previously was done.
6. The patients were treated with adjuvant concurrent chemo-radiation as per the protocol mentioned previously.
7. Informed consent was taken after explaining in detail the treatment benefits & risks.
8. Emphasis was laid on documenting the toxicity of the treatment & nutritional status of the patients during treatment.

Age Distribution

Age group	No. of patients
21-30	2
31-40	4
41-50	5
51-60	6
61-70	3

Sex Distribution: Male patients 15, Female patients 5.

Tumor Location

Location	No. of patients
Proximal	2
Body	4
Antrum	14

T- Stage:

T- Stage	No. of patients
T2	10
T3	8
T4	2

N- Stage :

N- Stage	No. of patients
N0	4
N1	11
N2	4
N3	1

Stage :

Stage	No. of patients
IB	3
II	6
IIIA	6
IIIB	2
IV	3

Grade: The patients selected were belong to Grade I were 3, Grade II were 12 and Grade III were 5.

LN- Dessection:

LN-Dissection	No.of patients
D1	9
D2	11

V. Results

Based on the observations above mentioned, the relapses were observed in patients with stage 3 and 4, poorly differentiated adenocarcinoma. In 5 patients who experienced relapse 2 patients had D1-LN dissection and 3 patients had D2-LN dissection.

These results were compared with 20 patients of carcinoma stomach who underwent curative resection and kept on follow up from our institute with similar tumor patient characteristics as study group, 10/20 patients (50%) relapsed locoregionally and 2/20 (10%) relapsed distantly. All the patients who relapsed during follow up period had D2 lymphnode dissection mostly were stage III and IV.

VI. Discussion

Gastric cancer is the 4th most common malignancy and 2nd leading cause of cancer related deaths in the world. The incidence of stomach cancer worldwide treatment remains the challenge for Oncologists and the prognosis remains poor. The only proven curative treatment for gastric cancer is surgical resection of all gross and microscopic disease[8], nevertheless studies have shown that surgery alone is less than satisfactory with the 5 years survival rate is as low as 10-20%[9-12] except in Japan where 5 year survival is 40-45%[6].

Because both local & systemic relapses are common after resection of high risk gastric cancers (beyond serosa, node positive or both), adjuvant treatment is indicated for these patients.

Extent of surgery: Randomized trials of D1 vs D2 dissection.

		5 year survival %		Operative Mortality %	
Series	No. of patients	D1	D2	D1	D2
Dutch	711	45	47	4	10
MRC	400	35	33	6.5	13

Patterns of relapse:

The sites of treatment failure after surgical treatment were mainly loco-regional in the tumor bed. 38-85% of the patients relapsed locally and lymphnode involvement the relapse rate was as high as 85%.

Adjuvant chemotherapy: The role of chemotherapy in the adjuvant post operative treatment of resected high risk gastric cancer remains uncertain.

Randomized phase-III trails.Adjuvant post-operative chemotherapy vs Surgery only				
Series	Regimen	No. of patients	Interval	OS %
Neri et al	5FU, Epirubicin, LV surgery alone	69 68	5 years	30 13
Bajetta et al	EAP, 5 FU + LV Surgery alone	137 137	5 years	52 48
Nashimoto et al	5 FU, MMC, Ara-C Surgery alone	127 123	5 years	91 86
Bouche et al	5 FU, Cisplatin Surgery alone	127 133	5 years	46 41

Adjuvant Irradiation: Irradiation has only been minimally evaluated as the sole adjuvant treatment following complete surgical resection in randomized phase-III trails. Adjuvant EBRT reduced local-regional failures when compared with the surgery alone arm in British adjuvant trial, but no survival benefits were found[10].
Surgery ± adjuvant therapy for resected gastric or gastroesophageal cancer.

Phase 3 trials

1. British stomach group (3 years)

	No. of patients	Survival %	LR-Relapse
Surgery alone	145	20	27
Post OP chemo	138	19	19
Post OP EBRT	153	12	10

2. Japan – Surgery ± IOERT

	No. of patients	3 yr Survival %	LR-Relapse
Stage-1	43/24	93 vs 87	--
Stage-2	11/20	62 vs 84	--
Stage-3	38/30	37 vs 62	--
Stage-4	18/27	0 vs 15	--

Moertel and colleagues randomized post-operative patients with advanced gastric cancer to receive 40 Gy of RT with 5 FU as a Radio-sensitizer and demonstrated improved survival associated with the combined modality therapy.

The present study attempts to duplicate the INT 0116 study with little modification of the protocol, more suitable for our set of population. We have delivered conventional radiation to gastric bed 45 Gy with 5 FU and leucovorin in first 4 days and last 3 days of radiotherapy, followed by 2 more cycles of adjuvant chemotherapy with 5 FU, leucovorin. The results of our study indicate the concurrent chemo-radiotherapy reduced loco-regional recurrence rates and improved loco-regional control rates 73.6% vs 50% with surgery alone group with acceptable toxicity.

At our institute where D2 dissection of gastric cancer is practiced routinely adjuvant chemo-radiation has shown promising results with reduced loco-regional recurrence rates (26.3% vs 50%) with chemo-radiotherapy and median DFS is 13 month vs 8 months with surgery alone.

VII. Conclusion

Adjuvant treatment with fluoro-pyrimidines plus leucovorin and radiotherapy has shown definite benefits for all patients with high risk gastric cancer who underwent curative surgery.

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