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NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY VS SURGERY ALONE IN SQUAMOUS CELL CARCINOMA OESOPHAGUS: PROSPECTIVE STUDY

Oncology

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ABSTRACT

Oesophageal cancer is the third most common gastrointestinal malignancy and is among the 10 most prevalent cancers worldwide [1]. As with all other tumors, the outcome for patients with oesophageal cancer is strongly associated with the stage at initial diagnosis. Surgical resection is currently the best curative treatment for patients without distant metastases or locally advanced tumor growth. An excellent 5-year survival rate in the range of 57%–78% has been reported in patients with early oesophageal cancer [2]. In this study we have tried to evaluate the role of neoadjuvant chemotherapy in squamous cell carcinoma of oesophagus. Although the number of patients studied here was small & the results were from only a single institution, this study throws light on some important findings about the efficacy of neoadjuvant chemotherapy for locally advanced squamous cell carcinoma of oesophagus.

METHODOLOGY: 50 patients visiting oncology opd fulfilling inclusion criteria were included in study .prospective study done

CONCLUSION: Induction chemotherapy induces a high response rate that may facilitate definitive surgery in a borderline cases

KEYWORDS

Neoadjuvant chemptherapy, esophagus cancer

INTRODUCTION:

Oesophageal cancer is the third most common gastrointestinal malignancy and is among the 10 most prevalent cancers worldwide [1]. As with all other tumors, the outcome for patients with oesophageal cancer is strongly associated with the stage at initial diagnosis. Surgical resection is currently the best curative treatment for patients without distant metastases or locally advanced tumor growth. An excellent 5-year survival rate in the range of 57%–78% has been reported in patients with early oesophageal cancer [2]. However, patients with locally advanced disease have a poor Prognosis despite aggressive attempts at resection, and patients with distant metastatic disease are considered to have an incurable disease[3]. Consequently, accurate preoperative staging and assessment of response to neoadjuvant therapy are crucial in determining the most suitable therapy and avoiding inappropriate attempts at curative surgery. Although computed tomography (CT) has been the mainstay for staging oesophageal cancer, the increasing use of endoscopic ultrasonography (EUS) and positron emission tomography (PET) with 2-[fluorine 18]fluoro-2-deoxy-d-glucose (FDG) has improved the staging algorithm for newly diagnosed oesophageal cancer. Currently, the combined use of CT, endoscopic US, and PET is advocated to determine whether a patient should be treated with surgery, chemotherapy, or a combination of chemotherapy and radiation therapy. As with many malignancies, the staging criteria for oesophageal cancer include depth of local invasion, regional lymph node involvement, and distant metastases. The aforementioned imaging modalities have different strengths and weaknesses with respect to each of these criteria. Therefore, accurate preoperative assessment of oesophageal cancer requires knowledge of the advantages and disadvantages of each modality, as well as an understanding of how the disease manifests and progresses, the oesophageal anatomy and tumor spread patterns of oesophageal cancer, the staging systems used, and the multidisciplinary treatment approaches available. In this thesis I have tried to evaluate the role of neoadjuvant chemotherapy in squamous cell carcinoma of oesophagus. Although the number of patients studied here was small & the results were from only a single institution, this study throws light on some important findings about the efficacy of neoadjuvant chemotherapy

MATERIAL AND METHOD:

Study site: Surgical Oncology Department

Gujarat Cancer and Research Institute attached to B.J. Medical College, Ahmedabad. (A UICC approved Regional Cancer Centre)

Study population: Untreated biopsy proven borderline operable, non metastatic SCC of mid and lower esophagus (T3 - T4a).

Study Design: Prospective, Observational study (all the decisions related to type of treatment and any type of interventions needed were taken by tumor board)

Sample size : 50 Patients
Time frame: Nov 2014 to Nov 2015

Patients in group A (n=25) were those who were referred for neoadjuvant chemotherapy (NACT) with an intention to operate at a later date from November 2014 to November 2015.

Group B also had 25 patients who were operated upfront from November 2014 to November 2015.

All patients underwent thorough clinical examination by joint committee of surgical, medical & radiation oncologist from routine blood investigations all the patients had chest X ray, Upper GI endoscopy with biopsy, CT scan of thorax and upper abdomen, sonography of abdomen and pelvis, bronchoscopy done as the minimum required investigations. PET scan was was done in indicated patients.

All patients referred for NACT were borderline operable locally advanced cancers .

Inclusion Criteria:

1. Operable and borderline operable cases
2. Multiple nodal disease (subcarinal, paratracheal, celiac)
3. Disease segment more than 7 cm on endoscopy.
4. Age 20 to 60 years.
5. Patient must be willing for all three treatment modalities i.e. surgery, chemotherapy and radiotherapy.
6. ECOG performance status must be less than or equal to 2.
7. WBC Count > 4000/mm3 and platelet count > 1,00,000/mm3, normal serum creatinine
8. Adequate nutritional, cardiac & pulmonary status.

Exclusion Criteria:

1. Metastasis,Previously treated patients with recurrence or second primary.
2. Patients with inadequate nutritional, cardiac, pulmonary status.
3. Immunosupression and collagen vascular diseases.
4. Pregnancy.
5. Past history of RT for any reason
6. Patients not fit for chemotherapy.

Consent:-

Proper written informed valid consent is obtained from each patient

Due to institutional constraints pre operative endoscopic ultrasound was not done

NACT Protocol:
Paclitaxel + Carboplatin:- Paclitaxel: 175mg/m2 + Carboplatin: 5AUC To be repeated every 21 days

Standard premedication was used. However, this regimen was given on outpatient basis in the daycare.

Response evaluation was done clinically after every cycle i.e. after 21 days. However repeat CT scan was done after 2-3 cycles.

Response to Chemotherapy on CT scan was considered when
1 Regression of nodal disease
2 Decrease in the volume of the disease(25% or more)

Repeat endoscopy was done in all the patients to evaluate regression of disease and involvement of esophageal wall . Most of the patients were given 2-3 cycles of chemotherapy. Treatment response was assessed clinically, radiologically & endoscopically. Inoperability was defined as involvement of trachea, left main bronchus & inferior pulmonary vein.

All patiend underwent Surgery performed was Standard Esophagectomy however the approach varied according to the surgeon or unit preference. Different approaches were as follows:
Apart from the epidemiological details two groups were studied on the
- response to chemotherapy
- R0 resections,
- postoperative complications
- recurrence .

All the patients were staged according to the 7th edition AJCC cancer staging manual[2].

All the patients who had post NACT R0 resection were referred for any adjuvant radiotherapy. All patients who had upfront surgery were referred for radiotherapy

Concurrent CT+RT were given to all the patients with adverse prognostic factors such as perineural invasion, lymphatic invasion, extranodal spread and R1 resection.

Follow Up:
Patients were followed monthly for three months and 3 monthly thereafter. Survival was calculated from the day of surgery to the death of the patient or last patient contact. The time of recurrence was also calculated from the day of surgery.

Management After Recurrence
Those who metastasis received palliative CT or pure palliative care as per ECOG performance status.

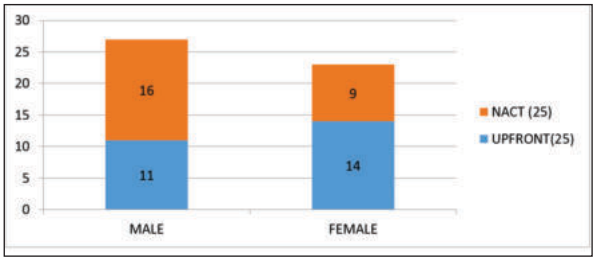
OBSERVATIONS AND RESULTS:
In this study 50 patients were enrolled after fulfilling the inclusion criteria.Group A are 25 patient received NACT and Group B 25 patient who underwent upfront surgeryFollowing table shows various parameters of the two groups:

Table 2: Comparison between two groups

	Group A (NACT)	Group B (Surgery)
Total Patients	25	25
Gender Ratio (M:F)	2:1	1:1
Mean Age in years	50.7	52.05
Patient underwent Surgery	25	25
Differentiation (WD/MD/PD)	WD = 02 MD = 18 PD = 05	WD = 05 MD = 20 PD = 0
Surgery (THE open: 3 stage:Ivor Lewis)	THE = 13 Three stage (Thoracoscopic mobilization)= 7 Open Three stage = 4 Ivor Lewis = 0	THE = 13 Three stage with (Thoracoscopic mobilization) = 4 Open Three stage = 5 Ivor Lewis = 3
Anastamosis (Hand Sewn: Stapler)	18: 7	20:5
No. Of Nodes positivity	N0 = 16 N+ = 09	N0 = 13 N+ = 12
Incomplete Resection	R2 = 00 R1 = 01	R2 = 01 R1 = 02
Adverse Prognostic Factors (ECE/PNI/LVI)	ECE = 1 PNI = 2 LVI = 0	ECE = 06 PNI = 02 LVI = 01
Early Complications	Pneumonia: 03 Leak: 02 Other:1	Pneumonia: 05 Leak: 03 Other:2
Late Events	Metastasis: 03 Mortality: 01	Metastasis: 05 Mortality :02
Mean Follow Up	18months	16months

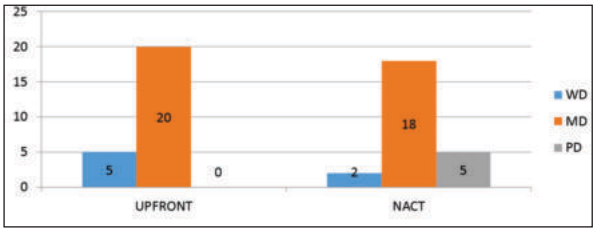
Observation
Sex Distribution-
As per sexual distribution males were more in NACT gp signifying aggressive disease pattern in males.

sex	Upfront surgery	NACT
MALE	11(44%)	16 (64%)
FEMAE	14(56%)	9 (36%)



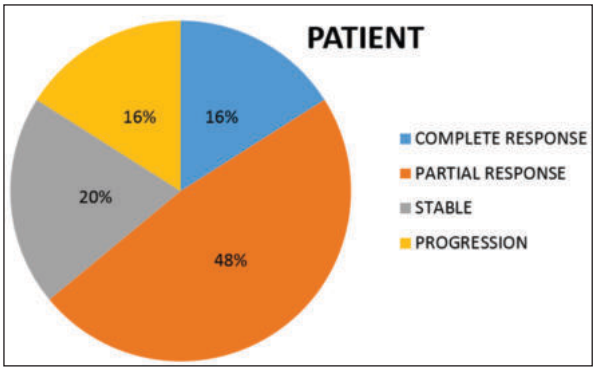
Degree Of Differentiation-
Moderately differentiated tumors were maximum in both the groups

	W.D.	M.D.	P.D.
UPFRONT	5 (20%)	20 (80%)	0
NACT	2 (8%)	18 (72%)	5(20%)



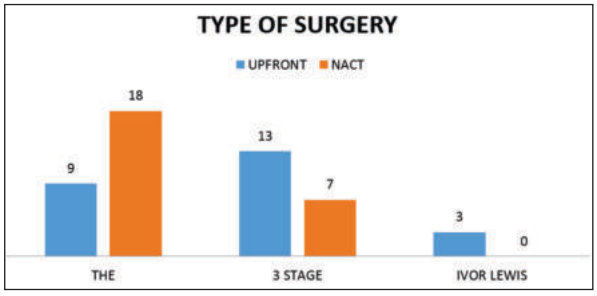
Response To Neoadjuvant Chemotherapy-
48% of patients had partial response (>30% reduction) after NACT, where as 16% of the patients had progression of disease.

RESPONSE TO NACT	NO. OF PATIENTS
COMPLETE RESPONSE	4 (16%)
PARTIAL RESPONSE	12 (48%)
STABLE DISEASE	5 (20%)
PROGRESSION	4 (16%)



Type Of Surgery-

NAME	UPFRONT	NACT
THE	9 (36%)	18(72%)
3 STAGE	13 (52%)	7(28%)
IVOR LEWIS	3 (12%)	0



Duration Of Surgery-

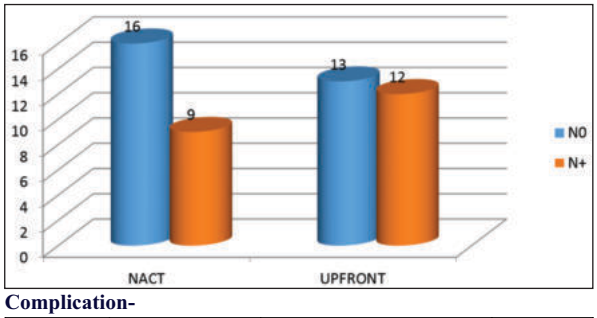
Average duration of surgery is slightly more in upfront group

	AVERAGE DURATION
NACT	270 minutes
UPFRONT	300 minutes

Nodal Positivity-

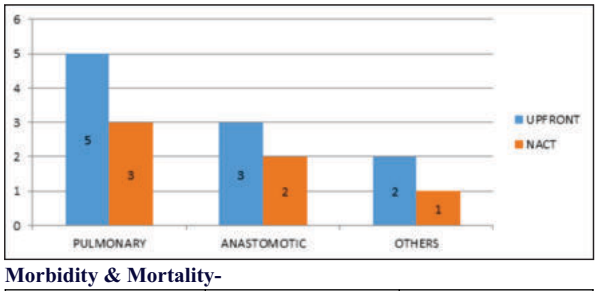
Nodal retrieval increases after NACT but nodal positivity decreased after it as in other cancers.

	N0	N+
NACT	16	9
UPFRONT	13	12



Complication-

	PULMONARY	ANASTOMOTIC LEAK	OTHER
UPFRONT	5(20%)	3 (12%)	2 (8%)
NACT	3 (12%)	2 (8%)	1 (4%)



Morbidity & Mortality-

	METASTASIS	MORTALITY
UPFRONT	6 (24%)	2 (8%)
NACT	3 (12%)	1 (4%)

DISCUSSION:

There have been two landmark trials so far on the issue of NACT in oesophagus one is the Medical Research Council trial [12] and second is the Intergroup trial [13]. However our study is not fairly comparable to these two trials as these were multicentre randomised trials with fixed chemotherapy protocols and longer duration of study forming category 1 evidence. Ours is a prospective observational study with Neoadjuvant chemotherapy regimen, incomplete pre operative staging and shorter follow up forming a category 3 evidence.

Table 4: Differences Between Two Trials And Our Study Comparison:

Differences in basic design of Intergroup trial, MRC trial and our Study		
Intergroup	MRC	Our Study
Adenocarcinoma + Squamous cell Carcinoma	Adenocarcinoma + Squamous cell Carcinoma	Squamous cell Carcinoma only
Middle Third + Lower Third	Middle Third + Lower Third	Middle Third + lower third
Transhiatal or transthoracic approach	Transhiatal or transthoracic approach	Thranshiatal or thoracoscopic approach or open
No node count mentioned to complete staging	No node count mentioned to complete staging	Node positivity and negativity taken into consideration

Table 5: Comparison between Intergroup, MRC & Our Study.

	INTERGROUP TRIAL		MRC TRIAL		OUR STUDY	
	SURG	NACT	SURG	NACT	SURG	NACT
NUMBER	106	981	124	123	25	25
AGE (Years)	62	62	62	63	52.05	50.7
MALE/FEMALE	3.8:1	5.53:1	2.8:1	3.2:1	1:1	2:1
R1 Resections	15%	4%	18%	10%	8%	4%
R2 Resections	11%	10%	13%	09%	4%	0%
Mortality	6%	6%	10%	10%	8%	4%
Leak	-	-	6%	7%	12.5%	15%

Response to NACT:

- 48% of patients had partial response (>30% reduction) after NACT
- 16% of the patients had progression of disease
- 20% of patient had stable disease
- 16% of patients had progression of disease

Increase in R0 resection rate in NACT Group.

Complication are less in NACT group compared to surgery group.

COMPLICATION	NACT	SURGERY
PULNONARY	12%	20%
ANASTOMOTIC LEAK	08%	12%
OTHER	04%	08%

Node Positivity:

One more point of interest, similar to what is seen with neoadjuvant therapy in any other cancer is the decrease in number of nodal positivity in harvested nodes with NACT.

	N0	N+
NACT	16	9
SURGERY	13	12

Metastasis:

Neoadjuvant group (12%) had less metastasis compared to surgery group(24%).

Median Follow Up:

Survival:

Survival has not been compared as our study has very short follow up which cannot be compared with these trials.

Limitations of this study:

1) The study was done in limited time frame.
2) The population size was small.
3) Follow up was till only limited time

It has been suggested that in the advent of newer chemotherapy molecules & regimens and more aggressive drug combinations might result in survival benefit after NACT schedule. This study convincingly demonstrated the feasibility of neoadjuvant chemotherapy with acceptable results. However elaborate studies are necessary from surgical, medical and radiation oncologist community before this induction approach could legitimately be incorporated into standard care.

1. Conclusion: SCC of esophagus is found more in men with median age is 50.7 yrs with dysphagia to solid and liquids as the most common presenting symptoms and most patients have history of tobacco consumption.
2. Surgical excision is the mainstay of treatment of esophageal. The aim of the surgery is to completely excise tumor with adequate margin .
3. Induction chemotherapy induces a high response rate that may facilitate definitive surgery in a borderline cases
4. In our study Neoadjuvant therapy had partial response rate of 48% and complete response of 16%
5. Induction chemotherapy was well tolerated in all patients and does not appear to affect subsequent definitive managements with either surgery or radiotherapy.

6. A clinical (if not pathological) complete response can be used as a good prognostic marker in follow up.

Following conclusions were noted considering aims and objectives.

- R1 & R2 resections – There were one R1 + R2 resections in group A and three in group B which is statistically insignificant.
- Post operative complications - There were six postoperative complications in group A & ten in group B.
- Recurrence – There were three recurrences in group A & six in group B.
- Follow up – Mean follow up in group A was 18 mth & group B was 16 mths.

This is a study of small number of patients and the duration of the study is about 2 years, hence it has its own limitations. Therefore, a larger study is required to comprehensively analyze various parameters related to the study to derive more concrete results.

Amongst all the parameters described and in our study neoadjuvant chemotherapy have any added advantage over upfront surgery arm in the terms of

- completeness of resection
- postoperative complications
- recurrence
- median follow up.

Whatever be the treatment modality used carcinoma of oesophagus continues to give a survival of approximately 2 years in patients with good subset of disease parameters.

Large scale multicentre randomized, controlled trials and meta-analysis are necessary to evaluate the efficacy of neoadjuvant CT in locally advanced SCC of esophagus as this approach may be worth for further exploration.

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