

## Original Research Article

# A prospective study on the role of neoadjuvant chemoradiotherapy on surgical outcome in resectable oesophageal carcinoma

Hrishikesh Deka\*, Bhabesh Kumar Das, Rajiv Paul, Supriyo Majumdar

Department of Surgical Oncology, State Cancer Institute GMCH, Assam, India

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### \*Correspondence:

Dr. Hrishikesh Deka,

E-mail: Dr.hrishikeshdeka@gmail.com

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## ABSTRACT

**Background:** Initial results of the chemo-radiotherapy for oesophageal cancer followed by surgery study (CROSS) comparing neoadjuvant chemoradiotherapy (NACRT) plus surgery versus surgery alone in patients with squamous cell carcinoma and adenocarcinoma of the oesophagus or oesophagogastric junction showed a significant increase in 5-year overall survival in favour of the NACRT plus surgery group after a median of 45 months' follow-up. In this study we will interpret the short-term results of NACRT on resectable, locally advanced oesophageal carcinoma.

**Methods:** Patients with clinically resectable, locally advanced cancer of the oesophagus or oesophagogastric junction (clinical stage T1N1M0 or T2-3N0-1M0, according to the AJCC, 8<sup>th</sup> edition) were assigned to receive weekly administration of four cycles of NACRT (intravenous carboplatin [AUC 2 mg/mL per min] and intravenous paclitaxel [50 mg/m<sup>2</sup> of body-surface area] for 23 days) with concurrent radiotherapy (41.4 Gy, given in 23 fractions of 1.8 Gy on 5 days per week) followed by McKeown's oesophagectomy from 01 January, 2020 to 31 May, 2021.

**Results:** It was observed in our study that 38.46% patients had achieved a CPR after the administration of NACRT as per the CROSS-trial protocol which is comparable to PCR achieved in CROSS trial (29%). All the patients underwent an R0 resection during surgery (100%) which is comparable to CROSS trial (92%).<sup>12</sup>

**Conclusions:** In our study which had collected data over a period of 17 months we learnt that the administration of NACRT in locally advanced oesophageal cancer was effective in reducing the tumor burden and achieving a satisfactory CPR of 38.46%.

**Keywords:** Esophagectomy, NACRT, CROSS protocol, Resectability

## INTRODUCTION

Esophageal cancer is the eighth most commonly diagnosed cancer and the sixth most common cause of cancer-related deaths worldwide.<sup>1</sup> The predominant histological types of esophageal cancer are adenocarcinoma and squamous cell carcinoma.<sup>2</sup> Adenocarcinoma of the distal esophagus predominates in the West, whereas squamous cell carcinoma, which tends to localize in the middle thoracic esophagus, predominates in the East. In Western societies,

esophageal squamous cell carcinoma (ESCC) is associated with low socioeconomic status, a history of smoking and drinking, liver dysfunction, and pulmonary comorbidities.<sup>3</sup>

Although the prognosis for patients with either type of esophageal cancer is poor, the outlook is worse for ESCC patients than for those with adenocarcinoma, according to some studies.<sup>4,5</sup> However, a surveillance, epidemiology, and end-results (SEER) study of 4753 cases archived in a database revealed no difference between the two types.<sup>6</sup>

Traditionally, both adenocarcinomas and squamous cell tumors have been treated by surgical resection; however, high frequencies of systemic and local tumor recurrence have urged investigations into multimodality therapies that combine surgery with radiotherapy (RT), chemotherapy (CT), and chemoradiotherapy (CRT).

It is a highly lethal disease, causing more than 400,000 deaths per year.<sup>7</sup>

Despite adequate preoperative staging, 25% of patients treated with primary surgery have microscopically positive resection margins (R1), and the 5-year survival rate rarely exceeds 40%.<sup>8</sup>

The role of NACRT has been debated for several decades. In most randomized trials, no survival benefit could be shown, and the trials were criticized for inadequate trial design, samples that were too small, and poor outcomes in the surgery-alone group. Meta-analyses suggest a survival benefit from NACRT, albeit frequently at the cost of increased postoperative morbidity and mortality.<sup>9,10</sup>

In a previously reported phase 2 trial of NACRT consisting of weekly administration of carboplatin and paclitaxel with concurrent radiotherapy, the regimen was associated with a low rate of serious toxic effects, and a complete resection with no tumor within 1 mm of the resection margins (R0) was achieved in all patients who underwent resection.<sup>11</sup> These results encouraged to initiate a multicenter, randomized, controlled, phase 3 study comparing NACRT followed by surgery with surgery alone in patients with potentially curable esophageal or esophagogastric-junction carcinoma which is known as the CROSS trial.<sup>12</sup>

In this study we will interpret the short-term results of neoadjuvant chemoradiation on resectable, locally advanced oesophageal carcinoma.

### ***Aims and objectives***

The aim and objectives were to assess the effectiveness of NACRT in making a locally advanced oesophageal tumor operable, to assess the intra-operative difficulties faced the following NACRT and to assess the effectiveness of NACRT in the post-operative histopathological report.

### ***Staging***

All patients underwent pre-treatment staging. This included a history taking; physical examination; pulmonary-function tests, routine hematologic and biochemical tests; upper gastrointestinal endoscopy with histologic biopsy; computed tomography of the neck, chest, and upper abdomen; endoscopic ultrasonography was not available at our institute. For the final analysis,

the available endoscopic reports were the centrally reviewed.

## **METHODS**

In this prospective study that took place in our institute, State cancer institute, Assam, patients with clinically resectable, locally advanced squamous cell carcinoma of the oesophagus or oesophagogastric junction (clinical stage T1N1M0 or T2-3N0-1M0, according to the AJCC, 8<sup>th</sup> edition) were assigned to receive weekly administration of four cycles of NACRT (intravenous carboplatin [AUC 2 mg/mL per min] and intravenous paclitaxel [50 mg/m<sup>2</sup> of body-surface area]) with concurrent radiotherapy (41.4 Gy, given in 23 fractions of 1.8 Gy on 5 days per week) followed by McKeown's oesophagectomy from 01<sup>st</sup> January, 2020 to 31<sup>st</sup> May, 2021.

### ***Inclusion criteria***

Patients with clinically resectable, locally advanced squamous cell carcinoma of the oesophagus or oesophagogastric junction (clinical stage T1N1M0 or T2-3N0-1M0, according to the American joint committee on cancer (AJCC) tumor-node-metastasis (TNM) classification, 8<sup>TH</sup> edition) were included in the study.

### ***Exclusion criteria***

Patients with adenocarcinoma of the esophagus, oesophageal carcinoma with distant metastasis, patients not fit for surgery at initial presentation and patients who have received NACT or definitive CRT with residual disease were excluded from the study.

Only patients with tumors of clinical stage T1N1 or T2-3N0-1 and no clinical evidence of metastatic spread (M0), according to the AJCC tumor-node-metastasis (TNM) classification, were enrolled. Eligible patients were 18 to 75 years of age, had a world health organization (WHO) performance status score of 2 or lower (on a scale of 0 to 5, with 0 indicating fully active, 1 unable to carry out heavy physical work, and 2 up and about more than half the day but unable to work), and had lost 10% or less of body weight. Patients also had to have adequate hematologic, renal, hepatic, and pulmonary function, as well as no history of previous radiotherapy or chemotherapy.

### ***Chemotherapy***

On days 1, 8, 15, and 22, carboplatin targeted at an area under the curve of 2 mg per milliliter per minute and paclitaxel at a dose of 50 mg per square meter of body-surface area were administered intravenously. All patients were intravenously premedicated with dexamethasone, clemastine, and ranitidine as well as standard antiemetic agents. The patients were closely monitored for toxic effects of chemotherapy with the use

of the national cancer institute's common terminology criteria for adverse events, version 3.0.

**Radiotherapy**

A total radiation dose of 41.4 Gy was given in 23 fractions of 1.8 Gy each, with 5 fractions administered per week, starting on the first day of the first chemotherapy cycle. All patients were treated by means of external-beam radiation.

**Surgery**

All patients underwent McKeown’s 2-field oesophagectomy as soon as possible after completion of chemoradiotherapy (preferably, within 4 to 6 weeks). Gastric-tube reconstruction with a cervical anastomosis was the preferred technique for restoring the continuity of the digestive tract.

**Pathological analysis**

Reports on pathological examination had to describe the tumor type and extension, lymph nodes, and resection margins. In the absence of macroscopic tumor, any abnormal-appearing tissue was paraffin-embedded in total in order to make an adequate assessment for the presence of residual tumor and the effects of therapy.

Tumor regression after neoadjuvant therapy was assessed on the basis of modified Ryan scheme which gives a score as such: 0 (complete response): no viable cancer cells, 1 (near complete response): single cells or rare small groups of cancer cells, 2 (partial response): residual cancer with evident tumor regression but more than single cells or rare small groups of cancer cells and 3 (poor or no response): extensive residual cancer with no evident tumor regression.

If a vital tumor was present at 1 mm or less from the proximal, distal, or circumferential resection margin, it was considered to be microscopically positive (R1).

An ethics committee approval was taken at the beginning of this study.

**RESULTS**

**Gender**

A total of 26 patients were included in the study of which 21 were males and 5 were females.

**Table 1: Gender.**

Gender	Number
Male	21
Female	5
Total	26

Average age of the patients was 51.07 years.

**Family history of cancer**

Four patients had a positive family history of cancer of which one patient had a family history of oesophageal carcinoma in his grandfather.

**Tobacco use**

All the patients had a positive history of tobacco consumption either in the form of chewing tobacco or smoking or both.

**Previous cancer history**

One patient had a past history of multiple myeloma for which he was treated and was cured 3 years back.

**Duration of symptoms**

The average duration of symptoms at presentation was 3.53 months.

**Dysphagia grade**

The average dysphagia grade at presentation was 2.

**Comorbidities**

Three patients were suffering from hypertension; 2 patients were suffering from diabetes mellitus and 1 patient had both hypertension and diabetes mellitus.

**Table 2: Comorbidities.**

Comorbidity	Number of patients
Hypertension	3
Diabetes mellitus	2
HTN + DM	1

**Performance status**

All patients had a performance status Eastern co-operative oncology group (ECOG) score of 1 except 3 who had a ECOG score of 2. Incidentally of the three patients with ECOG two as well as two suffered mortalities.

**Table 3: ECOG score.**

ECOG score	Number of patients
0	0
1	23
2	3
3	0
4	0
5	0

### Location of tumor

Twelve patients had tumor in the mid esophagus; twelve patients had tumor in the lower esophagus and two patients had tumor involving both mid and lower esophagus.

**Table 4: Location of tumor.**

Location of tumor	Number of patients
Mid oesophagus	12
Lower oesophagus	12
Mid + lower oesophagus	2

### Response on CT scan

Three patients had no significant regression of disease; 1 patient had mild response to NACRT; 4 patients had moderate response and 16 patients had good response to NACRT.

**Table 5: Response assessment on CECT.**

Response assessment	Number of patients
No response	3
Mild response	1
Moderate response	4
Good response	16

### Response in dysphagia

Twenty-four patients had significant improvement in dysphagia; 1 patient had no change in dysphagia grade (grade was 1 before and after NACRT) and 1 patient had an increase in dysphagia from grade 2 to grade 4.

**Table 6: Response in dysphagia.**

Response in dysphagia	Number of patients
significant improvement	24
no change	1
increase in dysphagia	1

### McKeown's oesophagectomy

Fourteen patients underwent open thoracotomy and 12 patients underwent video-assisted thoracoscopic surgery (VATS) thoracotomy.

**Table 7: Type of thoracotomy approach.**

Type of approach	Number of patients
Open thoracotomy	14
VATS	12

### Blood loss

Average blood loss was 248 ml.

### Duration of surgery

Average operative time was 6.57 hours. Operative time was more during our initial operating days which was around 9-10 hours and with more experience in this procedure the operative time has significantly come down to around 5-6 hours.

### ICU stays

Average ICU stay was 3.34 days. It was observed that ICU stay was more for an open thoracotomy approach. Post-operative pain was significantly more following an open thoracotomy approach. Ventilator support was needed in 7 patients.

### Operative findings

#### Pleural adhesions

In 5 patients no pleural adhesions were seen, in 12 patients' mild pleural adhesions were seen, 4 patients had moderate pleural adhesions and 5 patients had dense pleural adhesions which increased the operative time during adhesiolysis.

**Table 8: Pleural adhesions.**

Pleural adhesions	Number of patients
None	5
Mild	12
Moderate	4
Dense	5

#### Perilesional fibrosis

Eleven patients had mild perilesional fibrosis; 4 patients had dense perilesional fibrosis and in 11 patients no perilesional fibrosis was seen.

**Table 9: Peri-lesional fibrosis.**

Peri-lesional fibrosis	Number of patients
None	11
Mild	11
Dense	4

#### Intraoperative injury

One patient had intraoperative lung injury which was repaired primarily. It was observed that this patient also had dense pleural adhesions.

#### Post-operative period

##### Post operative complications

Two patients had anastomosis leaks which was managed conservatively. One patient was having haemoptysis

which was managed conservatively. Two patients had pleural effusion. one patient suffered from hypovolemic shock and ultimately suffered mortality. one patient was taken for re-exploration on POD one for intrathoracic bleed and it was controlled. The source was found to be from an intercostal vessel in the thoracic wall wound. Incidentally it was the patient in whom intraoperative lung injury had occurred. Three mortalities have occurred in the post-operative period.

**Table 10: Postoperative complications.**

Post-operative complications	Number of patients
Anastomosis leaks	2
Haemoptysis	1
Pleural effusion	2
Hypovolemic shock	1
ICDT bleed	1
Mortality	3

Average blood transfusions required was 2-unit whole blood.

Average hospital stay duration was 16.23 days.

**Pathological report**

*Response to NACRT on HPE report*

The 10 (38.46%) patients had complete pathological response; 3 (11.5%) patients had MRS 1; 2 (7.69%) patients had MRS 2; 5 (19.23%) patients had MRS 3.

**Table 11: Response to NACRT on HPE.**

Response to NACRT	Number of patients
CPR	10
MRS 1	3
MRS 2	2
MRS 3	5

It was observed in our study that 38.46% patients had achieved a CPR after the administration of NACRT as per the CROSS-trial protocol. A) Average nodes harvested was 14.26, B) 4 patients had pN1 after HPE, C) LVSI was positive in 2 patients and PNI was positive in 3 patients and D) Circumferential margin was positive in 1 patient; rest all patients had margins negative.

**DISCUSSION**

It was observed in our study of the 26 patient’s majority were males (80.76%) with an average age of 51.07 years. All the patients had a positive history of tobacco consumption, one patient had a positive family history of oesophageal carcinoma in his grandfather who had succumbed to the disease. One patient had a previous history of multiple myeloma for which he was treated and

was cured 3 years back. Incidentally this patient suffered mortality in the immediate post-operative period.

The average duration of symptoms at presentation was 3.53 months indicating there is a scope for raising public awareness for early detection of the disease. The average dysphagia grade was 2 at presentation indicating patients waited till dysphagia increased to consumption of semisolids only before seeking medical attention.

The 46.15% patients had tumour in the mid oesophagus; 46.15% patients had tumour in the lower oesophagus and 7.69% patients had tumour involving both mid and lower oesophagus.

On assessing response on CECT imaging 4 weeks after finishing NACRT, 61.54% patients had good response to neoadjuvant therapy, 15.38% patients had moderate response, 3.84% patients had mild response and 11.54% patients showed no response to neoadjuvant treatment on imaging studies.

The 92.30% patients had significant improvement in dysphagia post NACRT, but 1 patient had an increase in dysphagia grade from 2 to 4 post NACRT and in 1 patient there was no change in grade of dysphagia.

Of the 26 patients that underwent McKeown’s esophagectomy with gastric pull-up; 53.85% patients underwent an open thoracotomy approach and 46.15% patients underwent VATS thoracotomy. With our increasing experience with this procedure more patients are benefitting from a VATS approach while an open thoracotomy approach is only reserved for cases where one lung ventilation could not be achieved with satisfaction or there is gross perilesional fibrosis and an R0 resection would be difficult to achieve. A VATS approach has resulted in less postoperative pain and shorter duration of ICU stay. Operative time was more with a VATS approach initially which has come down with our increasing use of this procedure. Over time with increasing experience, we are thriving towards a laparoscopic approach to the abdominal part of the procedure.

Intraoperatively-80.76% patients had pleural adhesions post NACRT and of them 19.23% patients had dense pleural adhesions which increased the operative time during adhesiolysis. One patient who had dense pleural adhesions had an intraoperative lung injury which was repaired primarily.

The 57.69% patients had peri-lesional fibrosis and of them 15.38% patients had dense fibrosis. It was observed that blood loss was more in patients with dense fibrosis and also operative time was increased. But we could tackle the disease using a VATS approach and it didn’t have to be converted to an open approach.



In the postoperative period, 2 patients had anastomosis leaks which was managed conservatively. One patient was having hemoptysis which was managed conservatively. Two patients had pleural effusion. One patient suffered from hypovolemic shock and ultimately suffered mortality. One patient was taken for re-exploration on POD 1 for intrathoracic bleed and it was controlled. The source was found to be intercostal vessel in the thoracic wall wound. Incidentally it was the patient in whom intraoperative lung injury had occurred. Three mortalities have occurred in the post-operative period. Average blood transfusions required was 2-unit whole blood. Average hospital stay duration was 16.23 days. Postoperative morbidity has been 26.92%.

Four mortalities occurred in the postoperative period. 1 patient had hypovolemic shock, 1 patient did not recover from anaesthesia who had a ECOG score of 2, 1 patient who had haemoptysis and 1 patient had a sudden myocardial infarction after first 8 hours of surgery. 1 patient had expired at home. He became COVID-19 positive in the immediate post-operative period, recovered and was discharged. On follow-up correspondence it was learnt that he expired at home a month after surgery. Overall mortality in our study has been 19.23% of which 2 patients had a cancer unrelated event. Therefore, cancer specific mortality has been 11.5%.

During the follow-up period; 2 patients had developed stricture at the anastomosis site which was managed with serial dilatation. A total of 3 patients had anastomotic leak which healed conservatively. One patient had left vocal palsy which was diagnosed pre-operatively as the patient had hoarseness of voice and it was not a complication of the treatment. 1 patient had developed incisional hernia at the abdominal laparotomy site.

Tumour regression after neoadjuvant therapy was assessed on the basis of modified Ryan scheme which gives a score as such: 0 (complete response): no viable cancer cells, 1 (near complete response): single cells or rare small groups of cancer cells, 2 (partial response): residual cancer with evident tumour regression but more than single cells or rare small groups of cancer cells and 3 (poor or no response): extensive residual cancer with no evident tumour regression

In the post-operative histopathological examination report, 38.46% patients had complete pathological response, 11.5% patients had MRS 1; 7.69% patients had MRS 2 and 19.23% patients had MRS 3.

It was observed in our study that 38.46% patients had achieved a CPR after the administration of NACRT as per the CROSS-trial protocol which is comparable to PCR achieved in CROSS trial (29%).<sup>12</sup> All the patients underwent an R0 resection during surgery (100%) which is comparable to CROSS trial (92%).<sup>12</sup>

R0 resection has varied widely in different trials. In trials comparing surgery to neoadjuvant chemoradiation, R0 resection ranged from 81% in the Bosset et al study to 100% in the Lee et al study in the NACRT group.<sup>13,14</sup> In their surgical group, R0 resection ranged from 69% in the CROSS trial to 95% in the study by Lee et al.<sup>12,14</sup>

None of the patients have received adjuvant treatment after surgery. All the patients are on regular follow-up as per NCCN guidelines and no recurrence has been reported as of date.

On retrospective analysis of CECT response to post-operative HPE report; 7 patients with good response on imaging had a CPR; 3 patients with good response had an MRS of 1; 1 patient with good response had an MRS 2 and 2 patients with good response had MRS 3.

Four patients with moderate response had CPR; 1 patient with moderate response had MRS 1 and 1 patient with moderate response had MRS 3.

One patient with mild response had MRS 2 and 1 patient with mild response had MRS 3.

One patient who showed no response on imaging had an MRS of 1.

Such disparity in response evaluation by CECT imaging and post-operative HPE report indicated CECT imaging modality is not very effective in response evaluation after receiving neoadjuvant treatment.

## CONCLUSION

In our study which had collected data over a period of 17 months we learnt that the administration of NACRT in locally advanced oesophageal cancer was effective in reducing the tumor burden and achieving a satisfactory CPR of 38.46%. The intraoperative difficulties found were tackled with our increasing experience in this field and as we grow in our expertise in this domain, we are being able to extend the benefits of a minimally invasive procedure to our patients.

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## REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55:74-108.
2. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med.* 2003;349:2241-52.
3. Brown LM, Hoover R, Silverman D, Baris D, Hayes R, Swanson GM et al. Excess incidence of squamous cell esophageal cancer among US Black men: role of

- social class and other risk factors. *Am J Epidemiol.* 2001;153:114-22.
4. Siewert JR, Stein HJ, Feith M, Bruecher BL, Bartels H, Fink U. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world. *Ann Surg.* 2001;234:360-7.
  5. Bonavina L, Incarbone R, Saino G, Clesi P, Peracchia A. Clinical outcome and survival after esophagectomy for carcinoma in elderly patients. *Dis Esophagus.* 2003;16:90-3.
  6. Chang DT, Chapman C, Shen J, Su Z, Koong AC. Treatment of esophageal cancer based on histology: a surveillance epidemiology and end results analysis. *Am J Clin Oncol.* 2009;32:405-10.
  7. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000: the global picture. *Eur J Cancer.* 2001;37(8):S4-66.
  8. Kelsen DP, Ginsberg R, Pajak TF. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med.* 1998;339:1979-84.
  9. Malthaner R, Fenlon D. Preoperative chemotherapy for resectable thoracic esophageal cancer. *Cochrane Database Syst Rev.* 2001;1:CD001556.
  10. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol.* 2001;19:305-13.
  11. Van Meerten E, Muller K, Tilanus HW. Neoadjuvant concurrent chemoradiation with weekly paclitaxel and carboplatin for patients with oesophageal cancer: a phase II study. *Br J Cancer.* 2006;94:1389-94.
  12. van Hagen P, Hulshof MC, van Lanschot JJ. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med.* 2012;366:2074-84.
  13. Bosset JF, Gignoux M, Triboulet JP. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med.* 1997;337:161-7.
  14. Lee JL, Park SI, Kim SB. A single institutional phase III trial of preoperative chemotherapy with hyperfractional radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma. *Ann Oncol.* 2004;15:947-54.

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