ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Surgical outcomes of neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy in patients of locally advanced carcinoma of esophagus: A prospective cross-sectional comparative study

Rohit Kumar Jha[1], Shalini Kumari[2], Sumedha Gargy[3], Rajen A Tankshali[4], Kiran C Kothari[5]

[1]Assistant Professor, [3]Senior Resident Department of Surgical Oncology, Rajendra Institute of Medical Sciences, Ranchi, [2]Senior Resident, Department of ENT and HNS, Shaheed Nirmal Mahto Medical College, Dhanbad, Jharkhand, [4,5]Retired Professor, Department of Surgical Oncology, The Gujarat Cancer and Research Institute, Ahmedabad, Gujarat, India

Submission: 22-09-2023 Revision: 31-12-2023 Publication: 01-02-2024

ABSTRACT

Background: Neoadjuvant chemoradiotherapy + radiotherapy (NACT + RT) or neoadjuvant chemotherapy (NACT) has been shown to improve survival in locally advanced esophageal carcinoma (EC). Comparative evaluation of NACT + RT versus NACT is ambiguous. **Aims and Objectives:** The current study was designed to evaluate the outcomes of NACT + RT versus NACT in locally advanced EC. **Materials and Methods:** In this prospective cross-sectional study, patients with operable, non-metastatic squamous cell carcinoma, and adenocarcinoma of the mid and lower esophagus (T3–T4a) were treated with NACT (paclitaxel 175 mg/m^2 plus carboplatin 5 Area under curve (AUC) every 3 weeks) or NACT + RT (NACT with 45 Gy in 25 fractions over 5 weeks). Response, R0 resections, post-operative complications, and recurrence were comparatively evaluated. **Results:** Of 40 enrolled patients, 20 received NACT and 20 received NACT + RT. In the NACT arm, 50% of patients had a partial response and 20% had disease progression. In the NACT + RT arm, 10% of patients had disease progression whereas 25% of patients had complete pathological response. Transhiatal esophagectomy was performed in 60% of patients in the NACT arm, whereas in the NACT + RT arm, 80% of patients had three-stage esophagectomy. The average surgery duration was numerically greater for the NACT + RT arm; blood loss was also greater. Pulmonary complications and anastomotic leak rate were higher in NACT + RT arm whereas other complications such as hoarseness of voice, and wound dehiscence were higher in the NACT arm. **Conclusion:** NACT + RT had better partial and complete response rates and low recurrence rates versus NACT. Post-operative complications were higher in the NACT + RT, especially pulmonary complications and anastomotic leak. Further, large-scale studies are warranted to confirm the efficacy of NACT versus NACT + RT in EC.

Key words: Esophageal carcinoma; Neoadjuvant; Chemoradiotherapy; Chemotherapy; Paclitaxel; Carboplatin

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v15i2.58705

E-ISSN: 2091-0576

P-ISSN: 2467-9100

Copyright (c) 2024 Asian Journal of Medical Sciences

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

INTRODUCTION

Esophageal carcinoma (EC) is a common tumor with approximately 604,000 newly diagnosed cases and 544,000 deaths in 2020.[1] The prognosis of EC is poor, with an estimated 5-year survival rate of 20%.[1,2] In eligible EC patients, radical surgery stands as a cornerstone intervention.[1] Neoadjuvant chemoradiotherapy +

Address for Correspondence:
Dr. Rohit Kumar Jha, Assistant Professor, Department of Surgical Oncology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India. **Mobile:** +91-9852440549. **E-mail:** rohitjhaonco@gmail.com

radiotherapy (NACT+RT) or neoadjuvant chemotherapy (NACT) has been shown to improve survival for locally advanced EC.[3,4] NACT aims to improve operability by shrinking the tumor, downstaging the disease and treating occult metastatic disease.[5] A multicentre study conducted by the Medical Research Council (OEO2), showed a 9% improvement in 2-year survival in patients given two cycles of NACT compared to those who were not. Five-year survival with surgery alone was 17%, compared with 23% with NACT.[6] Moreover, NACT+RT has also shown significant survival benefits followed by esophagectomy.[7,8]

Gradually, neoadjuvant therapy combined with esophagectomy has become the standard of care for locally advanced EC.[9,10] However, it is not clear whether adding radiotherapy to NACT is superior to NACT in treating locally advanced EC patients. Very few randomized controlled trials have directly compared NACT with NACT+RT in EC.[11-14] Studies in esophageal adenocarcinoma have shown slightly favorable survival benefits toward NACT+RT but without statistical significance.[12,13] Similar results were also reported in one trial studying esophageal squamous cell carcinoma (SCC) patients[14] and another trial with mixed EC tumor types.[11] Comparative evaluation of NACT+RT versus NACT is ambiguous, with none of the studies reaching statistical significance in survival outcomes. Hence, the choice of optimal neoadjuvant treatment remains unclear.

Aims and objectives

This prospective cross-sectional study was conducted to evaluate the surgical outcomes of NACT+RT versus NACT in locally advanced carcinoma of esophagus in terms of tumor down-staging, postoperative complications, and overall survival.

MATERIALS AND METHODS

Study design

This was a prospective, observational study conducted at the Surgical Oncology Department, Gujarat Cancer and Research Institute, B.J. Medical College, Ahmedabad, Gujarat, India. The study was conducted after approval from the Institutional Ethics Committee. All patients provided written informed consent. Patients with untreated biopsy-proven borderline operable, non-metastatic SCC, and adenocarcinoma of the mid and lower esophagus (T3–T4a) were enrolled.

Inclusion criteria

The study inclusion criteria were male and female patients aged 20–60 years having a borderline operable disease, multiple nodal diseases (subcarinal, paratracheal, and celiac), a disease segment of <7 cm on endoscopy, an eastern cooperative oncology arm (ECOG) performance status of ≤2, white blood cell count >4000/mm^3, platelet count >1,00,000/mm^3 with normal serum creatinine and adequate nutritional, cardiac, and pulmonary status.

Exclusion criteria

The exclusion criteria were a metastatic disease, previously treated patients with recurrence or second primary patients with inadequate nutritional, cardiac, and pulmonary status, patients with immunosuppression and collagen vascular diseases, pregnancy, history of RT for any reason and patients who are not fit for chemotherapy. Patients were categorized into two arms: Arm A was referred for NACT whereas arm B was referred for NACT+RT. Later patients in both arms underwent esophagectomy.

Pre-treatment examination

All patients underwent thorough clinical examination by a joint committee of surgical, medical, and radiation oncologists. All the patients had routine blood investigations, chest X-ray, upper gastrointestinal endoscopy with biopsy, computed tomography (CT) scan of the thorax and upper abdomen, sonography of the abdomen and pelvis, and bronchoscopy. A positron emission tomography scan was done in indicated patients. Staging was classified according to the 6th Union for International Cancer Control (UICC)-tumor (T), nodes (N), and metastases (M) UICC-TNM classification.

NACT

Paclitaxel plus carboplatin was used in the NACT arm. The regimen consisted of paclitaxel (175 mg/m^2) plus carboplatin (5 AUC) repeated every 21 days. Standard pre-medication was used. Response evaluation was carried out clinically after every cycle, that is, after 21 days. Repeat computed tomography (CT) scan was done after 2–3 cycles.

NACT + RT

For pre-operative radiotherapy, a CT-guided three-dimensional marking of the esophageal field (lesion+5 cm craniocaudal+8 cm radial) was done in all cases. A total dose of 45 Gy was delivered in 25 fractions (five fractions per week) over 5 weeks, starting on the 1st day of chemotherapy. Carboplatin 5 AUC was given weekly for 5 or 6 weeks along with RT. Standard pre-medication was used. A repeat CT scan was done for response evaluation after 3 weeks of completion of NACT+RT. Response to NACT and NACT+RT on CT scan was considered when there was regression of nodal disease and reduction in the volume of the disease (25% or more). Response assessment was done based on the World Health Organization and Response Evaluation Criteria in Solid Tumors criteria.

Endoscopy was repeatedly done in all the patients to evaluate the regression of disease and involvement of the esophageal wall. Treatment response was assessed clinically, radiologically, and endoscopically. Inoperability was defined as the involvement of the trachea, left main bronchus, and inferior pulmonary vein.

Surgery and pathological analysis

Standard esophagectomy was the surgery performed. The surgery approach varied according to the surgeon or unit preference. The surgery consisted of total thoraco-laparoscopic esophagectomy, open three-stage esophagectomy, thoracoscopic esophageal mobilization with laparotomy and cervical stage, transhiatal esophagectomy, and Ivor Lewis procedure depending on the tumor localization and patient characteristics. In all the cases, stomach pull-up was done with anastomosis in the neck except in cases where the Ivor Lewis approach was done wherein the anastomosis was intra-thoracic. Anastomoses were either hand-sewn or stapled.

Both arms were studied to determine the response to NACT and NACT+RT, R0 resections, post-operative complications, and recurrence. All patients were staged according to the 7th edition of the American Joint Committee on Cancer staging manual[15] and adjuvant treatment was planned as per the National Comprehensive Cancer Network guidelines.[16]

Follow-up

After surgery, all the patients were followed every month for 3 months and every 3 months thereafter. Whenever a relapse was suspected, radiologic, endoscopic, or histologic confirmation was required for diagnosis of the recurrence. Those with metastasis received palliative CT or pure palliative care as per their ECOG performance status.

Statistical analysis

The results are presented as frequency and percentages. The surgery details are presented as average values. All calculations were performed with the Statistical Package for the Social Sciences software version 21.0.

RESULTS

A total of 40 patients were enrolled in the study. Before surgery, arm A patients (n=20) received NACT whereas arm B patients (n=20) received NACT+RT. Patients and tumor characteristics are presented in Table 1. The mean age was comparable in both arms. The majority of the patients were males in both arms. The majority of the patients had disease in the lower region of the esophagus in both arms. In the NACT+RT arm, most (95%) of the patients had SCC whereas in the NACT arm, there was equal distribution of SCC and adenocarcinoma.

Table 1: Patients and tumor characteristics

Characteristics	Arm A (NACT) n=20	Arm B (NACT+RT) n=20
Age in years, mean	51.6	46.05
Gender, n (%)		
Male	17 (85)	12 (60)
Female	3 (15)	8 (40)
Site of disease, n (%)		
Mid	2 (10)	1 (5)
Low	13 (65)	17 (85)
Gastroesophageal junction	5 (25)	2 (10)
Histology, n (%)		
Squamous cell carcinoma	10 (50)	19 (95)
Adenocarcinoma	10 (50)	1 (5)
Differentiation, n (%)		
Well-differentiated	2 (10)	1 (5)
Moderately differentiated	13 (65)	17 (85)
Poorly differentiated	5 (25)	2 (10)

NACT: Neoadjuvant chemoradiotherapy or neoadjuvant chemotherapy, RT: Radiotherapy

Response to neoadjuvant therapy

In the NACT arm, 50% of the patients had a partial response and 20% had disease progression. In the NACT+RT arm, only 10% of patients had disease progression whereas 25% of patients had a complete pathological response (pCR). The graphical representation of data is given in Figure 1.

Surgery analysis

Transhiatal esophagectomy was done in 60% of patients in the NACT arm, whereas in the NACT+RT arm, 80% of patients had three-stage esophagectomy (Figure 2). It signifies that the majority of the patient who received NACT+RT had their disease in the middle third of the esophagus. Table 2 depicts surgery and histological details. The average surgery duration was numerically greater for the NACT+RT arm; blood loss was also greater in this arm.

Post-operative morbidity and mortality

Five (25%) patients in the NACT arm developed recurrence (local and systemic) compared to only three patients (15%) in the NACT+RT arm. Two (10%) patients died in the post-operative period in the NACT+RT arm. No significant difference was noticed in the intensive care unit and hospital stay among the arms. Pulmonary complications and anastomotic leak rate were higher in patients who received NACT+RT, whereas other complications such as hoarseness of voice and wound dehiscence were higher in the NACT arm. Table 3 summarizes post-operative characteristics.

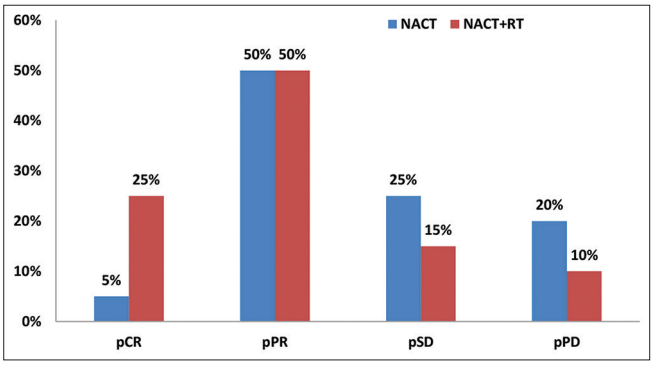

Figure 1: Response after neoadjuvant therapy. pCR: Pathological complete response, pPR: Pathological partial response, pSD: Pathological stable disease, pPD: pathological progressive disease

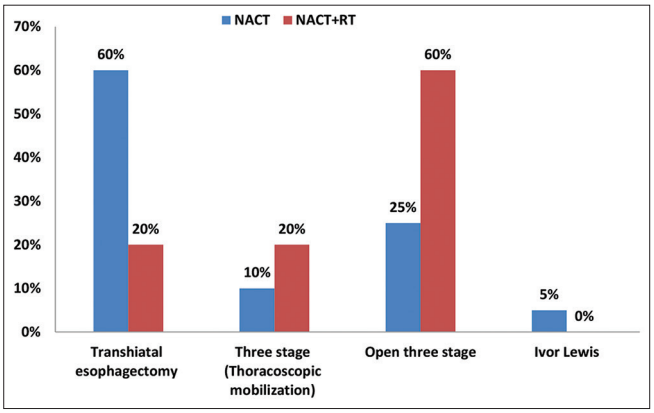

Figure 2: Surgery details–distribution of esophagectomy types in treatment arms. This figure illustrates the distribution of esophagectomy types among patients in the neoadjuvant chemotherapy (NACT) and neoadjuvant chemotherapy+radiotherapy (NACT+RT) arms. In the NACT arm, 60% of patients underwent transhiatal esophagectomy, whereas in the NACT+RT arm, a higher proportion (80%) of patients opted for three-stage esophagectomy

DISCUSSION

The prognosis of surgically treated EC has progressively improved with time, not only due to precise pre-operative staging, post-operative management, and surgical techniques but also due to the incremental inclusion of patients with EC in neoadjuvant treatment protocols.[17-19] The present study was a prospective cross-sectional comparative study to determine the surgical outcomes of NACT+RT versus NACT in patients of locally advanced EC.

pCR is associated with favorable prognosis in patients with EC who receive neoadjuvant treatment, and NACT+RT improves the rate of pCR compared with that of NACT.[20,21] Our study showed that the pCR rate was 25% in the NACT+RT arm versus 5% in the NACT arm. A total of 50% of patients in both arms had partial response (>30% reduction) after neoadjuvant treatment, whereas 20% of the patients had progression of disease after NACT compared to only 10% after NACT+RT.

Table 2: Surgery and histological details

Characteristics	Arm A (NACT) n=20	Arm B (NACT+RT) n=20
Average surgery duration (min)	299.5	308
Average blood loss (mL)	339.5	415
Average node retrieval	12.2	10.65
Nodal positivity	11	4
Incomplete resection	Nil	Nil
Adverse prognostic factors, n (%)		
Extracapsular extension	6 (30)	2 (10)
Perineural involvement	2 (10)	1 (5)
Lymphovascular invasion	9 (45)	0

NACT: Neoadjuvant chemoradiotherapy or neoadjuvant chemotherapy, RT: Radiotherapy

Table 3: Post-operative characteristics

Characteristics	Arm A (NACT) n=20	Arm B (NACT+RT) n=20
Average intensive care unit stay (days)	3.8	4.5
Average hospital stay (days)	14.5	15.3
Metastasis, n (%)	5 (25)	3 (15)
Mortality, n (%)	1 (5)	2 (10)
Pathological complete response, n (%)	1 (5)	5 (25)
Pulmonary complications, n (%)	3 (15)	5 (25)
Anastomotic leak, n (%)	1 (5)	3 (15)
Other (hoarseness of voice and wound dehiscence), n (%)	5 (25)	2 (10)

NACT: Neoadjuvant chemoradiotherapy or neoadjuvant chemotherapy, RT: Radiotherapy

Neoadjuvant CT may adversely affect the immune system, and influence wound healing as well as cause morbidity following an infeciton.[22] The concurrent chemoradiotherapy may lead to higher intra-postoperative incidences because of radiotherapy-induced edema, inflammation, and fibrosis.[23] Gronnier et al. reported that post-operative anastomotic leakage rates in NACT+RT versus surgery alone were 8.8% versus 10.6% (P=0.220), and 90-day post-operative morbidity rates were 33.4% versus 32.1% (P=0.564).[24] A randomized clinical trial also revealed no significant difference in the incidence of complications between patients in NACT and NACT+RT arms. However, the nature of the complications was severe in the NACT+RT arm.[25] In our study, pulmonary complication (25% vs. 15 %) and anastomotic leak (15% vs. 5%) were higher in the NACT+RT arm, whereas other complications such as hoarseness of voice and wound dehiscence were higher in NACT arm.

An interesting finding of the study was a reduced number of average nodal retrieval (12.3 vs. 10.65) and nodal

positivity (11 vs. 4) in the harvested nodes with NACT+RT when compared to NACT. In addition, the duration of surgery was longer in NACT-RT arm as compared to NACT arm, which may be due to the impact of radiation resulting in tissue edema and fibrosis. However, NACT+RT arm had a low metastasis rate (15%) compared to NACT arm (25%). The mortality rate was similar in both arms. Median follow-up was 18 months in NACT+RT arm compared to 16 months in NACT arm. Both local and systemic recurrence rates were lower in NACT+RT arm. Hence, it can be inferred that although surgery becomes easier after NACT, and immediate complications are less because of long-term scenarios NACT+RT is a better option. However, elaborate studies are necessary from the surgical medical and radiation oncologist community before this approach can legitimately be incorporated into standard care.

Limitation of the study

While yielding promising results of our study, several limitations have come to light, warranting an open acknowledgment of the challenges that have shaped our findings. Although a prospective study, the sample size was of modest proportions, potentially constraining the generalizability of our findings. The heterogeneity observed in the surgical interventions among our patient cohort introduces an element of imbalance, which has the potential to compromise the robustness of our explanatory capacity. Furthermore, the relatively short follow-up duration within the NACT arm itself introduces a caveat, as the precision of our outcome measurements could be influenced by this temporal constraint.

CONCLUSION

NACT and chemoradiotherapy, which are well-tolerated, induce a high response rate that may facilitate definitive surgery in borderline EC patients. NACT had better partial and complete response rates and low recurrence rates when compared to NACT. However, the post-operative complications were higher in the NACT, especially pulmonary complications and anastomotic leak. Large-scale multicenter randomized, controlled trials are necessary to evaluate the efficacy of NACT + RT versus NACT in locally advanced EC.

ACKNOWLEDGMENT

The authors are thankful to Dr. Lav Patel (Intas Pharmaceutical Ltd, Gujarat, India) for critically reviewing the manuscript and for fruitful suggestions. Authors also acknowledge Dr. Mehul R. Chorawala and Ms. Sakshi Srivastava, Intas Pharmaceutical Ltd, Gujarat, India, for medical writing assistance and additional editorial communication. The authors are also grateful to the study patients for their participation in this study.

DATA AVAILABILITY

The datasets generated during the study are available from the corresponding author upon reasonable request.

REFERENCES

1. 1. Lagergren J, Smyth E, Cunningham D and Lagergren P. Oesophageal cancer. Lancet. 2017;390(10110):2383-2396.
https://doi.org/10.1016/s0140-6736(17)31462-9
2. Thrift AP. Global burden and epidemiology of Barrett oesophagus and oesophageal cancer. Nat Rev Gastroenterol Hepatol. 2021;18(6):432-443.
https://doi.org/10.1038/s41575-021-00419-3
3. Van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-2084.
https://doi.org/10.1056/nejmoa1112088
4. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: A randomised controlled trial. Lancet. 2002;359(9319):1727-1733.
https://doi.org/10.1016/s0140-6736(02)08651-8
5. Cox SJ, O'Cathail SM, Coles B, Crosby T and Mukherjee S. Update on neoadjuvant regimens for patients with operable oesophageal/gastrooesophageal junction adenocarcinomas and squamous cell carcinomas. Curr Oncol Rep. 2017;19(1):7.
https://doi.org/10.1007/s11912-017-0559-8
6. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
https://doi.org/10.1056/nejmoa055531
7. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-1098.
https://doi.org/10.1016/s1470-2045(15)00040-6
8. Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z, et al. Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus (NEOCRTEC5010): A phase III multicenter, randomized, open-label clinical trial. J Clin Oncol. 2018;36(27):2796-2803.
https://doi.org/10.1200/jco.2018.79.1483
9. Kitagawa Y, Uno T, Oyama T, Kato K, Kato H, Kawakubo H, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: Part 2. Esophagus. 2019;16(1):25-43.
https://doi.org/10.1007/s10388-018-0642-8
10. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2019;17(7):855-883.

https://doi.org/10.6004/jnccn.2019.0033

11. Von Döbeln GA, Klevebro F, Jacobsen AB, Johannessen HO, Nielsen NH, Johnsen G, et al. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or gastroesophageal junction: Long-term results of a randomized clinical trial. Dis Esophagus. 2019;32(2):1-11.
https://doi.org/10.1093/dote/doy078
12. Stahl M, Walz MK, Riera-Knorrenschild J, Stuschke M, Sandermann A, Bitzer M, et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. Eur J Cancer. 2017;81:183-190.
https://doi.org/10.1016/j.ejca.2017.04.027
13. Burmeister BH, Thomas JM, Burmeister EA, Walpole ET, Harvey JA, Thomson DB, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer. 2011;47(3):354-360.
https://doi.org/10.1016/j.ejca.2010.09.009
14. Nygaard K, Hagen S, Hansen HS, Hatlevoll R, Hultborn R, Jakobsen A, et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: A randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. World J Surg. 1992;16(6):1104-1109; discussion 1110.
https://doi.org/10.1007/bf02067069
15. Singletary SE and Connolly JL. Breast cancer staging: Working with the sixth edition of the AJCC cancer staging manual. CA Cancer J Clin. 2006;56(1):37-47; quiz 50-51.
https://doi.org/10.3322/canjclin.56.1.37
16. Strong VE, D'Amico TA, Kleinberg L and Ajani J. Impact of the 7th edition AJCC staging classification on the NCCN clinical practice guidelines in oncology for gastric and esophageal cancers. J Natl Compr Canc Netw. 2013;11(1):60-66.
https://doi.org/10.6004/jnccn.2013.0009
17. Pennathur A, Farkas A, Krasinskas AM, Ferson PF, Gooding WE, Gibson MK, et al. Esophagectomy for T1 esophageal cancer: Outcomes in 100 patients and implications for endoscopic therapy. Ann Thorac Surg. 2009;87(4):1048-1054; discussion 1054-1045.
https://doi.org/10.1016/j.athoracsur.2008.12.060
18. Talsma AK, Damhuis RA, Steyerberg EW, Rosman C, van Lanschot JJ and Wijnhoven BP. Determinants of improved survival after oesophagectomy for cancer. Br J Surg. 2015;102(6):668-675.
https://doi.org/10.1002/bjs.9792
19. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: An FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(16):1715-1721.
https://doi.org/10.1200/jco.2010.33.0597
20. Berger AC, Farma J, Scott WJ, Freedman G, Weiner L, Cheng JD, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. J Clin Oncol. 2005;23(19):4330-4337.
https://doi.org/10.1200/jco.2005.05.017
21. Luc G, Vendrely V, Terrebonne E, Chiche L and Collet D. Neoadjuvant chemoradiotherapy improves histological results compared with perioperative chemotherapy in locally advanced esophageal adenocarcinoma. Ann Surg Oncol. 2015;22(2):604-609.
https://doi.org/10.1245/s10434-014-4005-y
22. Hao D, Li X, Yang Y, Zhang Y, Wu X, Chen Y, et al. Neoadjuvant chemoradiotherapy versus chemotherapy and surgery for patients with locally advanced esophageal squamous cell carcinoma. Transl Cancer Res. 2017;6(2):346-353.
https://doi.org/10.21037/tcr.2017.03.34
23. Hoeppner J, Zirlik K, Brunner T, Bronsert P, Kulemann B, Sick O, et al. Multimodal treatment of locally advanced esophageal adenocarcinoma: Which regimen should we choose? Outcome analysis of perioperative chemotherapy versus neoadjuvant chemoradiation in 105 patients. J Surg Oncol. 2014;109(3):287-293.
https://doi.org/10.1002/jso.23498
24. Gronnier C, Tréchot B, Duhamel A, Mabrut JY, Bail JP, Carrere N, et al. Impact of neoadjuvant chemoradiotherapy on postoperative outcomes after esophageal cancer resection: Results of a European multicenter study. Ann Surg. 2014;260(5):764-770; discussion 770-761.
https://doi.org/10.1097/sla.0000000000000955
25. Klevebro F, Johnsen G, Johnson E, Viste A, Myrnäs T, Szabo E, et al. Morbidity and mortality after surgery for cancer of the oesophagus and gastro-oesophageal junction: A randomized clinical trial of neoadjuvant chemotherapy vs. neoadjuvant chemoradiation. Eur J Surg Oncol. 2015;41(7):920-926.
https://doi.org/10.1016/j.ejso.2015.03.226

Authors Contribution:
RKJ- Definition of intellectual content, literature survey, prepared the first draft of a manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation, and submission of the article; Coordination and Manuscript revision **SK**- Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **SG**- Design of study, statistical analysis, and interpretation; **RAT, KCK**- Review manuscript, literature survey, and preparation of figures.

Work attributed to:
(1) Rajendra Institute of Medical Sciences Ranchi, Jharkhand, India; (2) Gujarat Cancer and Research Institute, B. J. Medical College, Ahmedabad, Gujarat, India.

Orcid ID:
Rohit Kumar Jha - https://orcid.org/0009-0003-1650-449X
Shalini Kumari - https://orcid.org/0009-0002-9435-6069
Sumedha Gargy - https://orcid.org/0000-0001-5960-5600
Kiran C Kothari - https://orcid.org/0000-0003-2930-5142

Source of Support: Nil, **Conflicts of Interest:** None declared.