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A Prospective Study to Assess the Toxicity and Response of Preoperative Chemoradiotherapy in Oesophageal or Oesophagogastric Junction Cancer

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Abstract **Original Research Article**

Background: Carcinoma of the esophagus is an aggressive disease. Neoadjuvant chemoradiotherapy achieves the highest complete pathologic response rates, R0 resection rates, and improves 3-5 years survival rates. ***Methods:*** Patients with resectable carcinoma oesophagus were included in this prospective study. 22 patients were enrolled. All eligible patients were given radiation for a total radiation dose of 41.4Gy in 23 fractions of 1.8Gy each with five fraction administered per week. Weekly chemotherapy given with carboplatin (AUC 2mg/mm/mt) and paclitaxel (50mg/m2 of BSA). The patients were monitored weekly during the treatment for toxicities. These patients were evaluated with CECT after four to six weeks, and sent for surgery. Histopathological reports of these patients which included lymph node status, pathological response and resection margins were noted. ***Results:*** A total of 22 patients were enrolled. Neutropenia was the most common hematological toxicity and 4.5% had grade 2 neutropenia.There was no Grade 3 or 4 hematological toxicity. Most common GI toxicity seen was esophagitis and anorexia. 1 patient developed grade 3 esophagitis. 22% patients had grade 2 anorexia.17 patients underwent surgery and all of them had negative resected margins, 5 out of these 17 patients had pathological complete response. ***Conclusion:*** Preoperative chemoradiotherapy with weekly paclitaxel and carboplatin have good clinical response in terms of negative resection margin and pathological complete response with accepted level of toxicity. Prospective trials in larger series of patients are needed with long follow up.

Keywords: Oesophageal, neoadjuvant, chemoradiation, toxicity.

INTRODUCTION

Oesophageal cancer constitutes a major health problem. It is the ninth most common cancer worldwide [1]. Fewer than 60% of patients with locoregional cancer can undergo a curative resection. Nearly 70%-80% of the resected specimens have metastases in the regional lymph nodes. Thus, clinicians are often dealing with advanced-stage carcinoma in newly diagnosed patients [2].

Multiple clinical trials have addressed the preferred treatment sequence in managing locally advanced oesophageal cancer, but no standard therapy had been established. While oesophagectomy is the cornerstone treatment of localized oesophageal carcinoma, the systemic nature of the disease attributes to the failure of surgery alone. Despite changes in the treatment approach over the past two decades and even following complete resection, most patients will eventually relapse and die as a result of their disease.

The incidence of oesophageal cancer depends upon the regions of the world. Highest incidence occurs in areas such as northern Iran, southern Russia, and northern China. This area forms a very high incidence 'oesophageal cancer belt' [3]. Squamous cell carcinoma accounts for 95% of the pathology of oesophageal cancers worldwide, but adenocarcinomas are becoming an increasing, common entity in the western world.

In India, most parts have moderately high incidence rate for carcinoma oesophagus [3]. It is the third leading cause of death in males and fourth leading cause in females [4].

For loco regional disease, surgery has been the mainstay of therapy with 5-year survival rates ranging from 10%-40% and distant metastasis being the most common mode of treatment failure [5]. Radiation therapy alone has been evaluated for local control and,

in one large series 3-year survival was only 6% [6]. Chemotherapy for locally advanced oesophageal cancer has a response rate of 45% to 75% in numerous studies but relapse rates are high and long-term survival rates are very low [7].

The role of multi-modality treatment as a way to achieve higher long-term survival rates has been debated for many years. Neither preoperative radiation therapy nor chemotherapy alone in the neoadjuvant settings have been proven beneficial based on the trials performed.

Combined modality treatment is among the standard treatment for oesophageal cancers, especially in case of resectable oesophageal cancers. A multi-institutional phase III study (CROSS trial) in 2012, evaluated the benefit of neoadjuvant therapy using carboplatin, paclitaxel and 41.4Gy radiation *versus* surgery alone [8]. Only one fourth of the patients had squamous histology. Pathological complete response was seen in 47 of 161 patients (29%) after resection. Postoperative complication rate were similar in both treatment groups, and in-hospital mortality rate was 4% in both. Median overall survival seen was 49.4 months in the chemoradiation surgery group versus 24 months in the surgery group. Overall survival was seen to be significantly better in the chemoradiation group [HR 0.657 (0.495-0.871; P=0.003)]. An updated analysis(9) of this group of patients had shown a lower local recurrence rate and lower risk of peritoneal carcinomatosis after neoadjuvant chemoradiation and that squamous cell carcinoma was an independent prognostic variable in the surgery alone group.

Preoperative combination therapy offers several advantages, but neoadjuvant chemoradiotherapy achieves the highest complete pathologic response rates (29%), R0 resection rates (92%), and improves 3-5 years survival rates in patients with locally advanced oesophageal cancer.

OBJECTIVES

1. To assess the pathological response rates of the preoperative chemoradiotherapy in patients with oesophageal or oesophagogastric junction cancer.
2. To assess the acute toxicity profile during preoperative chemoradiotherapy in patients with oesophageal or oesophagogastric junction cancer.

We present the following article/case in accordance with the STROBE reporting checklist.

METHODS

The aim of this study is to find out the treatment response in terms of pathological complete response and achievement of R0 resection (microscopically negative margins) and to find out the toxicity profile of preoperative concurrent chemoradiation therapy in resectable esophageal and gastroesophageal cancers.

This is a prospective observational study conducted at Department of Radiotherapy, Govt. Medical College, and Kottayam during the period of one year from June 1st 2016 to May 31st 2017. Study population included patients with primary resectable oesophageal or gastroesophageal junction cancer eligible for neoadjuvant chemoradiotherapy with curative intent as per standard treatment protocol.

Sample size - Based on previous similar study by P. Van Hagen et al, calculated sample size would be 83 according to the formula

Sample size –

$$\frac{(\boldsymbol{Z}\alpha)^{\boldsymbol{2}}\boldsymbol{pq}}{\boldsymbol{d^2}}$$

Where, p= 0.92 q= 1-p d=5%
Zα= 1.96 for α at 5% level of significance

During 2014, 50 patients with carcinoma oesophagus or gastro oesophageal junction cancer attended the radiotherapy department of Kottayam medical college. For my study, I included all the patients fulfilling the inclusion criteria, attending the department. The number of patients included in the study is 22.

INCLUSION CRITERIA

1. Adult patients (age more than 18years and less than 75 yrs, both sexes)
2. Histologically confirmed squamous cell carcinoma, adenocarcinoma or large cell undifferentiated carcinoma of oesophagus or oesophagogastric junction
3. Clinical stage T1N1 or T2-3N0-1
4. Performance status ECOG (Eastern Cooperative Oncology Group) 0-2
5. Patients must have signed an approved informed consent.

EXCLUSION CRITERIA

1. Type III gastroesophageal junction tumors.
2. Tumor extending to within 5cms below the upper oesophageal sphincter.
3. History of previous cancer or previous radiotherapy or chemotherapy.
4. Distant metastasis
5. Serious illness or medical conditions that precludes the safe administration of the trial treatment including surgery-as in ongoing or active infection, cardiac arrhythmias, unstable angina pectoris , congestive heart failure, psychiatric illness/social situations that would limit compliance with the study requirements.

Study procedure

A detailed history and clinical examination of all the patients were done. Routine blood investigations done and results were recorded. Investigations appropriate for assessing the extend of primary tumour done which included oesophagogastroduodenoscopy and biopsy, CECT chest and abdomen, and chest X ray. All eligible patients were treated with external beam radiation on cobalt theratron 780C machine, for a total radiation dose of 41.4Gy in 23 fractions of 1.8Gy each with five fractions administered per week.

Concurrent chemotherapy was given on days 1,8,15,22 and 29 with carboplatin (targeted at an area under the curve of 2mg/mm/mt) and paclitaxel (50mg/m^2 of BSA). These patients were monitored weekly during the treatment for toxicities, which were graded according to National cancer institute common terminology criteria for adverse effect version 4.0 (CTCAE).

These patients were further evaluated with CECT after four to six weeks, disease status and operability assessed and operable patients were sent for surgery. Histopathological reports of these patients were collected and the tumor extension, lymph node status, pathological response and resection margins were noted.

Data management and analysis

Data analysis was done with the help of Excel 2010 and SPSS 20 statistical software. All patients were included under intention to treat analysis. Toxicity grades and pathological response rates were entered in Excel 2010 worksheet for each variable. The highest toxicity during any cycle was considered as toxicity grade of that patient. Analysis was done using SPSS for the toxicity profile and pathological response rates. Quantitative variables summarised as mean, categorical variables measured as proportions. P value set at <0.05.

Ethical considerations

Only relevant statistical data was taken from each patient and individual details of the patient will not be revealed under any circumstances. All patients included in the study had to understand and agree to the consent form and acknowledge it in presence of a witness. The patients did not have to bear any extra cost due to inclusion in the study. The patient had the right to withdraw from the study at any time.

RESULTS

In this study 22 patients were accrued who satisfied the criteria for patient selection from January 2016 to December 2017

Age: The age group ranged from 40 to 80 years. Majority patients belonged to the age group 60 to 70. 1 patient belonged to the age group 70 to 75.

Gender: Males predominated in the study population. There were 20 males and 2 females [795].

Performance status: Only 2 patients were of performance status 2. All other had performance status of 0 or 1.

Distribution of smokers and nonsmokers: 19 patients (86%)in the study population were smokers. Only 3 patients were nonsmokers.

Tumor pathology: 2 patients (9.09%) had adenocarcinoma. 20 patients (90.91%)had Squamous cell carcinoma. 19 patients (70.5%) had moderately differentiated tumours.1 patient(4.55%) had well differentiated and 2 patients (9.09%) had poorly differentiated tumors

Tumour site: 13 patients (59.1%) had mid thoracic and 9 patients (40.9%) had lower thoracic disease.

Tumour (T) STAGE: 16 patients (72.7%) had T2 tumours.6 patients (27.3%) had T3 tumours.

Nodal characteristics: 13 patients (59.1%) were node negative. 9 patients (40.9%) were node positive.

Clinical stage: 4patients (18.18%) belonged to stage 1B, 7patients (31.82%) belonged to stage 2A, 8patients (36.36%) to stage 2B, 3patients (13.64%) belonged to stage 3A

Assessment of Toxicities

Incidence of toxicities increased as the treatment continued. But there were no grade three or grade four toxicities. The data on toxicities are displayed in Table no. 1

Table-1: Toxicity assessment during the course of chemoradiation according to national cancer institute common terminology for adverse effect version4.0

SL.NO	TOXICITY	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
1	ANEMIA	15 (68.2%)	7 (31.7)%	--	--	--
2	LEUCOPENIA	5(22.3%)	15 (68.2%)	2(9%)		
3	NAUSEA	5 (22.3%)	16(72.7%)	--	--	--
4	VOMITING	4(18.2%)	14(63.63%)	4(18.2%)	--	--
5	CONSTIPATION	14(63.63%)	8(36.36%)	--	--	--
6	DIARRHOEA	21(95.4%)	1(4.5%)	--	--	--
7	OESOPHAGITIS	--	--	18(85.7%)	4(18.2%)	--
8	ANOREXIA	3(13.6%)	14(63.63%)	5(22.3%)	--	--
9	FATIGUE	3(13.6%)	0	19(86.36%)	--	--
10	PERIPHERAL NEUROPATHY	15(68.2%)	--	7(31.8%)	--	--
11	ALOPECIA	8(36.36%)	--	14(63.63%)	--	--

Post chemoradiation response as assessed by CECT

One patient had worsening of general condition because of toxicity and it was planned to put her on palliative care. Among others response was seen in 19 patients. 2 patients (9.09%) had progression of disease. One patient had progression with development of tracheoesophageal fistula. His general condition worsened and he could not undergo surgery. Other patient developed lung metastasis and was put on palliative treatment.

Operability

Among the patients, 2 patients were not willing for surgery. Hence there were only 17 patients who were operable.

Type of surgery

10 patients underwent two stage oesophagectomy. and 7 patients underwent 3 stage oesophagectomy.

Surgical outcomes

2 patients (11.76%) had post op complications. Among these, one had anastomotic leak and sepsis, and patient expired on post op day 14. Other patient had sepsis which developed post operatively, patient recovered completely.

Resected margin status

All patients who underwent surgery had R0 resected margins.

Pathological response

Response was assessed using tumor regression score suggested by the CAP Cancer Protocol for Oesophageal Carcinoma. Pathological complete response was seen in 5 patients (22.73%). All others had moderate response. Data on pathological response displayed in Table 2.

Table-2: Pathological respose as per ttumor regression score suggested by the cap cancer protocol for oesophageal cancers

Pathological response	Number of patients
NOT APPLICABLE	5 (22.73%)
COMPLETE PATHOLOGICAL RESPONSE	5 (22.73%)
MODERATE RESPONSE	12 (54.5%)
TOTAL	22

DISCUSSION

This study is a single arm prospective trial of neoadjuvant chemoradiotherapy in patients with oesophageal and GO junction cancer .It was aimed at assessing the response to treatment response and toxicities of these patients with this treatment regimen. The chemo radiation therapy regimen was based on a previous international landmark trial in carcinoma oesophagus (CROSS trial) published in 2012 May in NEJM and a previous phase 2 trial [8, 10]. The dosages and schedules of radiation and chemotherapy followed in this study are the same as in CROSS trial which is the current standard of care in such patients. These trials have shown that neoadjuvant chemoradiation schedules result in better pathological response rates (29.4%), R0 resection (100%) and this is likely to improve survival rates in patients with resectable oesophageal and oesophagogastric tumours.

In this study, out of a total of 22 patients, there were 20 males (90.9%) and 2 females (9.09%). This may be a reflection of the increasing incidence of carcinoma oesophagus in males. In our study 95% of the males are smoker. So this may be possibly due to increased incidence of alcoholism and smoking in Indian males (2). It is well known that carcinoma of the oesophagus is a disease predominantly seen in the elderly (4). In this study also the majority of patients

were between 60 and 70 years of age (54.5%). Mean age was 65 years. 50% of the patients were having ECOG PS-0 .This was important for patient compliance as the patients needed to tolerate the treatment protocol which included chemoradiation and surgery.

13 patients had disease in the mid – thoracic region (59.1%) and 9 patients (40.9%) had disease in the lower thoracic oesophagus. In the CROSS trial only 14 % of patients had disease in the mid thoracic while 58% had disease in the lower thoracic oesophagus .The higher incidence of lesions higher up in the oesophagus than in the Western population could be attributed to the differences in aetiology of this malignancy in India. In our study, 86% of the patients were smokers. So, smoking still forms the major causative factor in Carcinoma oesophagus in India while it is on the decline in the Western world.

Only 2 patients had disease extending to the GE junction and both were type 1 GE junction tumours .Surgery was not possible in cases of cervical oesophageal and upper thoracic oesophagus malignancies as adequate surgical margins of 3 to 5 cm may be difficult to obtain in these cases. The CROSS trial also included only 2% patients in the chemoradiotherapy arm in the upper cervical oesophagus but it had 22% patients with tumours in the GE junction, which may again be attributed to increased incidence of lower GE malignancies in Western poupualtion.

The number of squamous cell carcinomas in this study was higher than adenocarcinomas in this study and this ratio was much higher than that of most international trials. This may be again attributed to the aetiology of the disease but has prognostic significance also. The recent 5year update of the CROSS trial published by Shapiro *et al*. [11], there is a statistically significant difference in patients with squamous cell carcinoma (median overall survival = 81.6 vs 21.1 months, HR = 0.48, P= .008) and among those with adenocarcinoma (median overall survival = 43.2 vs 27.1 months, HR = 0.73, P = .038). This shows the continued advantage of chemoradiation therapy is more in patients with squamous cell carcinoma which includes the bulk of our patients.

72 % of patients had T2 disease and only 27.3% patients' had T3 lesions .Only 9 patients were node positive at the time of starting treatment. Of the 19 patients with squamous cell carcinoma 3 patients had stage IB, 6 had stage 2B and 3 had stage 3A .Of the 2 patients with adenocarcinoma 1 patient was stage 2A and the other was 2B .Median length of the tumour was 5.1 cm.

The inclusion criteria of this study assured that only patients with T2 or T3 lesions would be included in the study. But the distribution of patients is different than most other international studies in that this study had more T2 than T3 lesions while most foreign studies have more of T3 lesions .This may be because the patients with T3 lesions may have had a longer history of dysphagia which may have worsened their performance status and excluded them from the study .The need for community oriented education had a proper referral system especially in rural population must be stressed here which would allow for earlier detection of patients thus ensuring radical treatment.

There was no significant treatment breaks .Patients were able to tolerate the treatment except one female patient who had grade 2 neutropenia and had to stop the radiation treatment for 3 days. Her advanced age, that is 74yrs may be the reason for her decreased tolerance to the treatment. Further her general condition worsened and she was put on palliative care. This is in par with the CROSS trial it appears that with proper education most patients will be able to complete the treatment schedule without significant breaks in treatment.

Toxicities were assessed during treatment. Incidence of anaemia increased as the treatment continued. There was only grade 1anaemia seen in 31.8% of patients. No grade 2 or more anaemia seen. As the treatment continued, leucopenia was seen developing after 3 weeks. 2 patients (9.09%) developed grade 2 leucopenia, 15 patients (68.18%) had grade 1 leucopenia. No grade 3 or grade 4 toxicity seen. Grade 2 neutropenia was seen in only 1 patient (4.55%) and she needed treatment break. Grade I neutropenia was seen in 13 patients (59%). There was no grade 3 or grade 4 toxicity. In cross trial only 60% patient had leucopenia, and 9% patients had neutropenia.

In our study most of the patients had grade 2 oesophagitis (72.73%). Grade 3 event was seen in 6 patients (27.27%). No grade 4 events seen. And no treatment breaks were needed. This is much higher than the reference study. Other GI Toxicities, nausea, vomiting, anorexia and fatigue is also comparatively higher than reference study. These differences may be the reflection of difference in the Indian population, which needs to be evaluated in further studies.

After 6 weeks the patients were assessed for response to treatment with a repeat CECT evaluation .Response was seen in terms of decrease in the thickness and length of the disease and response was present in 20 patients (90.1%) and 2 patients had progression of the disease 1 patient had progression with development of trachea-oesophageal fistula which was diagnosed by CECT evaluation. The general condition of this patient worsened and the patient could not undergo surgery. Another patient had progression with lung metastasis and is on palliative chemotherapy.

2 patients were not willing for surgery after chemoradiation and had to be changed to palliative chemotherapy .They are being monitored and are largely asymptomatic at the time of completion of the study. Out of the 17 patients who underwent surgery, 10 patients had 2 stage oesophagectomy while 7 patients underwent 3 stage oesophagectomy .Median number of lymph nodes dissected was 7. Only 2 patients had significant surgical complications in the form of infection and delayed wound healing. One patient had post-operative anastomotic leak and sepsis and the patient expired on post op day 14.

All patients who underwent surgery had R0 resection with gross and microscopically negative margins. As in all regimens of preoperative chemoradiation, proper communication and teamwork between the radiation oncologist and the surgeon is of utmost importance in the timing of surgery and radiation. This study had the advantage that all patients underwent surgical resection under the guidance of a single surgeon and an expert team well experienced in oesophageal surgeries. This is reflected in the fact that all patients had a complete resection of the tumor. Another important aspect is that the surgery should be complete and the surgeon should be well used to the procedure. This is important in order to decrease the complications associated with the surgery and to get an R0 resection. As this was a single arm study, it could not evaluate the absolute effect of preoperative chemoradiation on the surgical resection margins, but in the CROSS trial, 92% patients had R0 resection in the chemoradiation arm and 69% in the surgery alone arm. As expected, few patients had operative complications after the chemoradiation, but the CROSS trial data proves that despite the operative complications, there was an advantage in the disease free survival and overall survival as seen in the intention to treat analysis.

5 out of the 17 operated patients had pathological complete response. Rest of the patients had moderate response .There were no patients who didn't get any pathological response to the treatment. 20 to 30% is the PCR rates seen in most international phase 2 and 3 trials of chemoradiation in upper GI malignancies. As in other sites, PCR can be taken as a surrogate marker associated with an improvement in survival and this has been established in various studies. This study proves that the results of the large studies like the CROSS trial are reproducible and promise better survival rates to patients.

The review of Meta analyses by Bas P. L. Wijnhoven *et al*. [12] which reviewed all the Meta analyses of neoadjuvant chemoradiation in carcinoma oesophagus found that the number needed to treat to obtain an advantage with neoadjuvant therapy in carcinoma oesophagus was only ten. This stresses the importance of neoadjuvant treatment and impels that in treating 22 patients we have improved the outcome of 2 patients is important in a disease like carcinoma oesophagus.

This study has many limitations. One of the major limitations was the small number of patients. The major problem was that most of the patients belonged to elderly age group with multiple comorbidities. Their general condition would not be permitting for a radical surgery and preoperative chemoradiotherapy. Many patients presented in advanced stage so that a curative treatment could not be offered. Another limitation is because of the unavailability of endoscopic ultrasound and MRI in our institution, and most of the patients could not afford the procedure being done outside. So our tumor staging was based on CECT evaluation, which is not as sensitive as MRI or EUS.

CONCLUSION

Neoadjuvant concurrent chemoradiation is the standard of care for patients with resectable oesophageal carcinoma, and associated with higher rates of pathological complete response, with acceptable levels of toxicity profile in selected patients and this may have survival advantage. But proper patient selection is important. This treatment can be offered on an outpatient basis and this will be useful in a busy Radiotherapy department. Longer duration of follow up is needed to clearly assess the loco regional control of the disease, long term toxicities and survival of these patients. Prospective trials in larger series of patients with long term follow up are needed.

FOOTNOTE

Reporting checklist

The authors have completed the STROBE reporting checklist,

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The local institutional review board of the Government Medical College Kottayam approved the use of the database maintained by the Department of Radiation Oncology for research purposes (No 10/2016). The study was conducted in accordance with the Declaration of Helsinki (as revised in Edinburgh 2000).

REFERENCES

1. Kamangar, F., Dores, G. M., & Anderson, W. F. (2006). Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different

geographic regions of the world. *Journal of clinical oncology*, *24*(14), 2137-2150.

2. Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., Murray, T., & Thun, M. J. (2008). Cancer statistics, 2008. *CA: a cancer journal for clinicians*, *58*(2), 71-96.
3. Parkin, D. M., & Muir, C. S. (1992). Cancer Incidence in Five Continents. Comparability and quality of data. *IARC scientific publications*, (120), 45-173.
4. Annual report. (2012). National Cancer Registry Program New Delhi; Indian Council of Medical Research, 2014.
5. Kelsen, D. P., Ginsberg, R., Pajak, T. F., Sheahan, D. G., Gunderson, L., Mortimer, J., & Roth, J. A. (1998). Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *New England Journal of Medicine*, *339*(27), 1979-1984.
6. Earlam, R., & Cunha-Melo, J. R. (1980). Oesophageal squamous cell carcinoma: I. A critical review of surgery. *Journal of British Surgery*, *67*(6), 381-390.
7. Malthaner, R. A., Wong, R. K., Rumble, R. B., Zuraw, L., & Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. (2004). Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. *BMC medicine*, *2*(1), 35.
8. van Hagen, P., Hulshof, M. C. C. M., Van Lanschot, J. J. B., Steyerberg, E. W., Henegouwen, M. V. B., Wijnhoven, B. P. L., ... & van der Gaast, A. (2012). Preoperative chemoradiotherapy for esophageal or junctional cancer. *New England Journal of Medicine*, *366*(22), 2074-2084.
9. Oppedijk, V., van der Gaast, A., van Lanschot, J. J., van Hagen, P., van Os, R., van Rij, C. M., ... & Hulshof, M. C. (2014). Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *Journal of Clinical Oncology*, *32*(5), 385-391.
10. van Meerten, E., Muller, K., Tilanus, H. W., Siersema, P. D., Eijkenboom, W. M. H., van Dekken, H., ... & van der Gaast, A. (2006). Neoadjuvant concurrent chemoradiation with weekly paclitaxel and carboplatin for patients with oesophageal cancer: a phase II study. *British journal of cancer*, *94*(10), 1389-1394.
11. O'Sullivan, K. E., Hurley, E. T., & Hurley, J. P. (2015). Understanding complete pathologic response in oesophageal cancer: implications for management and survival. *Gastroenterology research and practice*, *2015*.
12. Wijnhoven, B. P., van Lanschot, J. J., Tilanus, H. W., Steyerberg, E. W., & van der Gaast, A. (2009). Neoadjuvant chemoradiotherapy for esophageal cancer: a review of meta-analyses. *World journal of surgery*, *33*(12), 2606-2614.