Phase II trial of induction chemotherapy followed by chemoradiation with carboplatin and paclitaxel before minimally invasive surgery for locally advanced carcinoma of the esophagus and esophago-gastric junction (QUIMERA)

Sabino FD, Siqueira MB, Guedes MTS, Carneiro MP, Pelosi AD, de Oliveira IM, Carrada C, Guimarães MAC, Resiner RG, da Silva RGD, Pinto LFR
Instituto Nacional de Câncer

INTRODUCTION

In Brazil, most patients with newly diagnosed carcinoma of the esophagus and esophago-gastric junction (EGJ) presents with locally advanced disease. Because of high rates of distant and local failure, there has been interest in multimodality therapy, involving chemotherapy, radiotherapy and surgery. Since the publication of the CROSS trial in 2012, a dutch randomized multicenter phase III trial, neoadjuvant chemoradiation became the standard of care in many countries and also in our instituition. Nonetheless, the optimal neoadjuvant approach is still matter of debate and the contribution of induction chemotherapy (IC) before preoperative chemorradiation is not known. The IC may allow for upfront systemic therapy to better adress the risk of distant disease and potentially contibute to cytoreduce the primary tumor, enhancing local control. Based on this considerations, we started a single center phase II trial to investigate the efficacy, feasibility and safety of preoperative IC followed by chemoradiation and minimally invasive surgery in patients with carcinoma of the esophagus and the EGJ. Our hypothesis is that the IC can increase the rate of pathologic complete response (PCR) and thus prolong survival.

METHODS

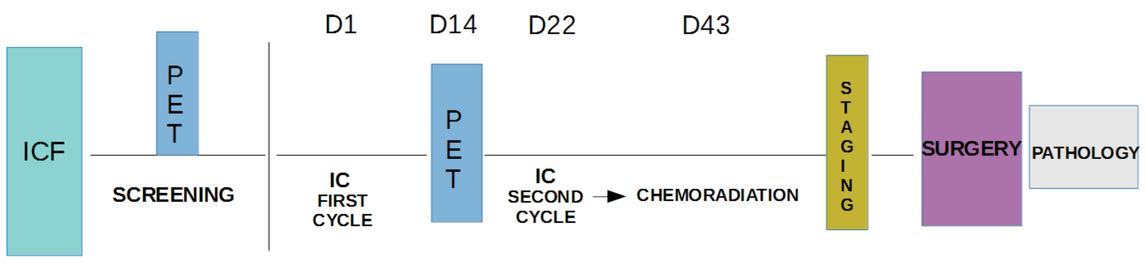
Inclusion criteria and evaluation

Patients with histologically confirmed squamous cell or adenocarcinoma of the thoracic esophagus or GEJ (Siewert type I or II), aged 18-75 years, with a PS 0-2, clinical stage cT1b-3 cN0-2, will be eligible. Pretreatment staging will consist of medical history, physical examination, upper endoscopy with biopsy, broncoscopy, computed tomography (CT) scans of the neck, chest and abdomen and positron emission tomography (PET-CT).

Treatment plan

Preoperative treatment will consist of two cycles of IC with carboplatin (175 mg/m2) and paclitaxel (AUC=5) on days 1 and 22, followed by radiotherapy of 45 Gys (25 x 1.8 Gys) and concurrent chemotherapy comprising carboplatin (AUC=2) and paclitaxel (50 mg/m2) weekely for five weeks. On day 14, patients will have another PET-CT to evaluate the early metabolic response. Four weeks after the ending of the neoadjuvant regimen, the patients will be re-staged with CT, endoscopy and PET-CT. To proceed to surgery, patients will be required to have no newly detected stage M1 disease and/or inoperable T4 disease. The surgery will be scheduled 8-12 weeks after the completion of chemoradiation. A minimally invasive thoraco-abdomino-cervical approach will be performed. A complete two-field lymphadenectomy is mandatory and the reconstruction will be done preferably by a gastric conduit. All surgical procedures will be done the same surgeon.

Study design



Criteria for response

Histopathological response will be based on the findings after esophagectomy and classified according to the Mandard classification of tumor regression grade (TRG). TRG 1 is defined as complete regression or no residual cancer; TRG 2 as presence of rare residual cancer cells and TRG >2 as increased number of residual cancer cells.

Statistics and Sample Size

Our primary endpoint is the evaluation of the PCR rate. A PCR rate (i.e.TRG1) of 30% will be considered promising for further study, and a rate of 15% will be considered insufficient. Hence, the sample size calculated for this study with the Fleming method was 37 cases.

PARCIAL RESULTS

From March 2017 to July 2018, 42 patients signed the informed consent form and were enroled. Of these, 26 were excluded because of M1 disease and 16 started the protocol. So far, 9 patients underwent surgery and 3 completed the neoadjuvant regimen and are waiting for the surgical procedure. During the IC, 2 patients had dysphagia grade 3. During the chemoradiation, one patient had gastrointestinal bleeding grade 3, one had diarrhea grade 3, two had dysphagia grade 3, one had lymphopenia grade 3. The mean time interval between neoajuvant treatment and surgery was 10 weeks. R0 resection was achieved in all cases and all patients survived for more than 30 days after surgery. Four patients (3 squamous cell carcinoma and one adenocarcinoma) showed complete (TRG 1) and 3 (all adenocarcinomas) poor pathological remission (TRG>2).

TABLE 1 – Patient and Tumor Characteristics

Age (years)	58.5 (43 – 71)
Male	6
Female	3
Tobacco use	9
Alcohol use	5
Histology	
SCC	5
AC	4
Tumor Location	
Upper third	0
Middle third	2
Lower third and EGJ	7
Serum Albumin (mean)	4.0 g/dl (3.2-4.4)
Clinical stage	
IA	0
IB	0
IIA	0
IIB	2
IIIA	4
IIIB	3
IIIC	0
IV	0
Time to surgery (mean)	11 weeks (9-13)
Histopathological response rate	
TRG 1 (PCR)	4
TRG 2	0
TRG 3-5	3

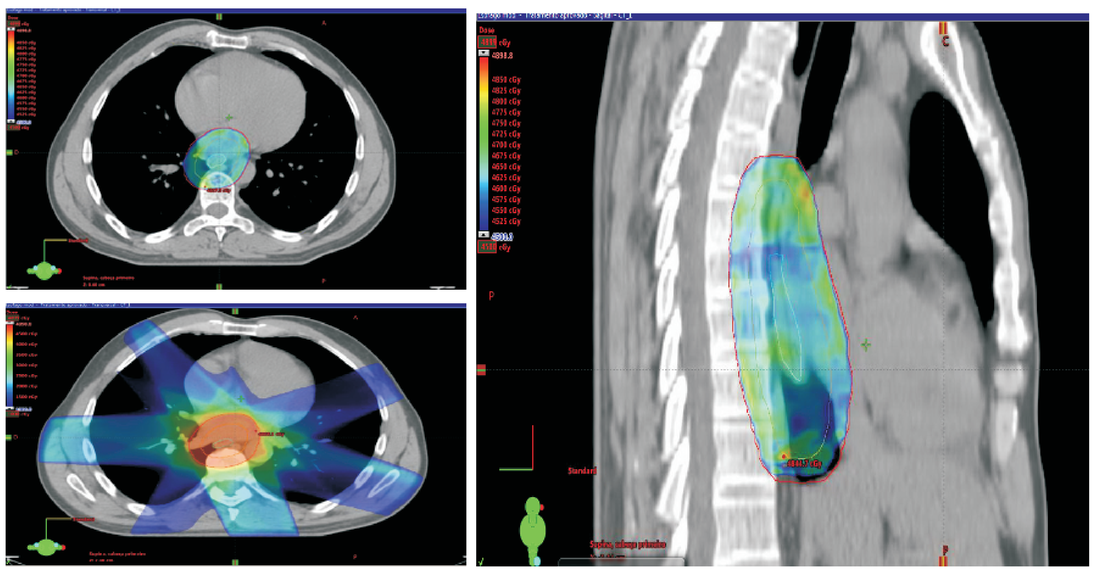


Figure 1. Radiotherapy planning (IMRT technique) for a middle thoracic esophageal tumor

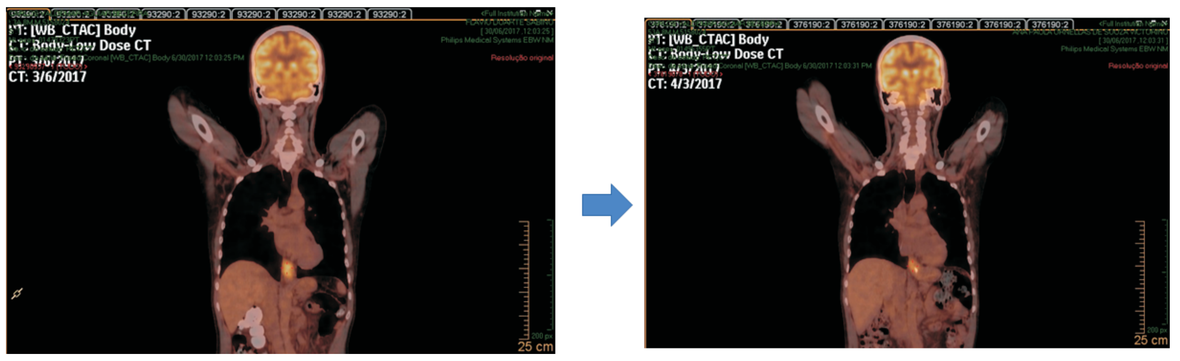


Figure 2. PET scan showing reduction of metabolic tumor activity 14 days after the first cycle of induction chemotherapy

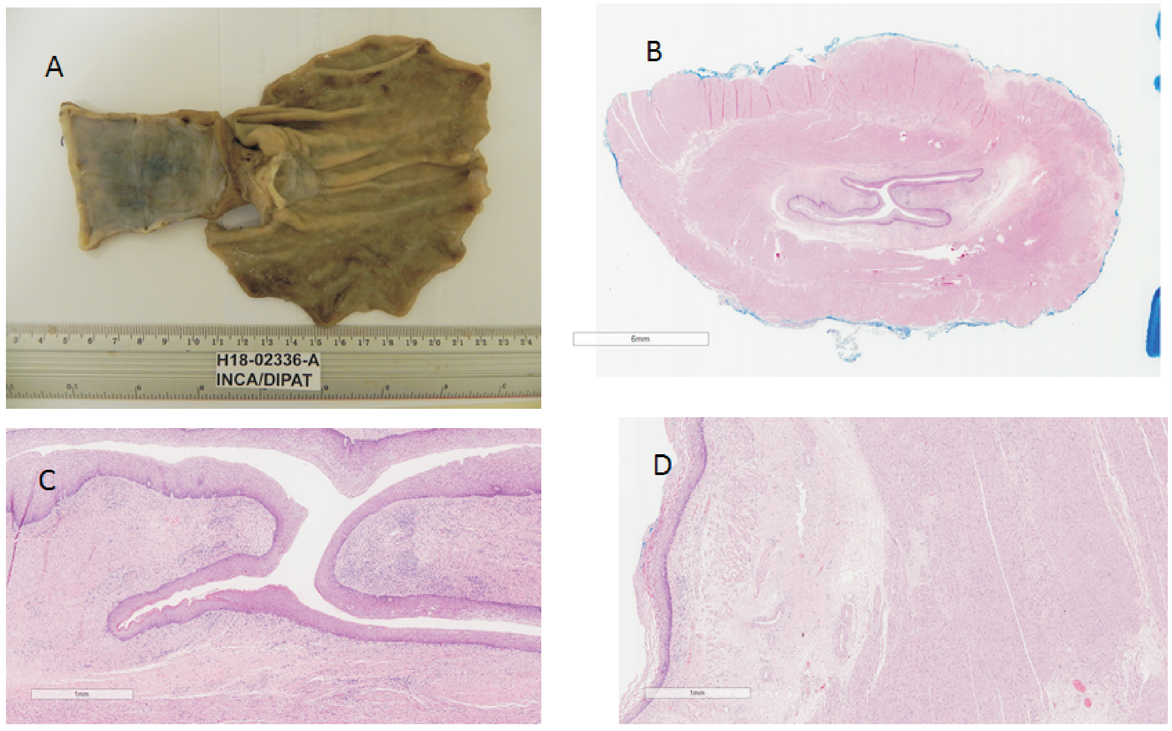


Figure 3. A Surgical specimen; B- Photomicrography of a transversal slice of the esophagus showing no residual tumor; C and D- Photomicrographys showing reepithelization of the squamous epithelium associated with submucosal fibrosis and chronic inflamatory infiltrate

CONCLUSION

Our initial results are encouraging and suggests that IC followed by chemoradiation is a safe, feasible, active and well-tolerated regimen and that it may increase the PCR, especially for squamous cell carcinoma.

REFERENCES

- Ajani JA, Xiao L, Roth JA, Hofstetter WL, Walsh G, Komaki R, Liao Z, Rice DC, Vaporciyan AA, Maru DM, Lee JH, Bhutani MS, Eid A, Yao JC, Phan AP, Halpin A, Suzuki A, Taketa T, Thall PF, Swisher SG. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. Ann Oncol. 2013 Nov;24(11):2844-9.
- Gerber N, Ilson DH, Wu AJ, Janjigian YY, Kelsen DP, Zheng J, Zhang Z, Bains MS, Rizk N, Rusch VW, Goodman KA. Outcomes of induction chemotherapy followed by chemoradiation using intensity-modulated radiation therapy for esophageal adenocarcinoma. Dis Esophagus. 2014 Apr;27(3):235-41.
- Eisterer W, DE Vries A, Kendler D, Spechtenhauser B, Königsrainer A, Nehoda H, Virgolini I, Lukas P, Bechter O, Wöll E, Ofner D. Triple induction chemotherapy and chemoradiotherapy for locally advanced esophageal cancer. A phase II study. Anticancer Res. 2011 Dec;31(12):4407-12.
- Ruhstaller T, Widmer L, Schuller JC, et al. Multicenter phase II trial of preoperative induction chemotherapy followed by chemoradiation with docetaxel and cisplatin for locally advanced esophageal carcinoma (SAKK 75/02). Annals of Oncol. 2009 May;20(9):1522-1528.
- Ajani JA, Correa AM, Walsh GL, Komaki R, Lee JH, Vaporciyan AA, Rice DC, Yao JC, Maru DM, Hofstetter WL, Phan AT, Swisher SG. Trimodality therapy without a platinum compound for localized carcinoma of the esophagus and gastroesophageal junction. Cancer. 2010 Apr 1;116(7):1656-63.
- Van Hagen P, Hulshof MC, van Lanschot JJ, *et al.* Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012 May 31;366(22):2074-84.

Projeto Gráfico: Setor de Edição e Informação Técnico-Científica / INCA

MINISTÉRIO DA SAÚDE