

# Local effectiveness and complications of neoadjuvant therapy in esophageal squamous cell carcinoma: radiotherapy versus chemoradiotherapy

## *Eficácia local e complicações da terapêutica neoadjuvante no carcinoma epidermóide do esôfago: radioterapia versus radioterapia associada à quimioterapia*

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### A B S T R A C T

**Objective:** To evaluate tumor responses to neoadjuvant therapy, according to the histopathological findings of surgical specimens of patients operated and treated for squamous cell carcinoma of the middle third and distal esophagus. **Methods:** We conducted a retrospective nonrandomized study including 97 patients distributed as follows: Group I - 81 (83.5%) underwent neoadjuvant radiation therapy, and group II - 16 (16.5%) underwent neoadjuvant radiotherapy and chemotherapy. A third group of 26 patients undergoing esophagectomy alone was used for comparison of postoperative complications. The characteristics of each patient (age, gender and race), tumor site, staging, and histological evaluation of treatment modalities were reviewed and analyzed. Tumor response to neoadjuvant therapy was evaluated by histopathology of the specimen. **Results:** There was no statistically significant differences regarding race, gender, age, staging and postoperative complications in patients in the three groups. Patients undergoing radiotherapy and neoadjuvant chemotherapy showed more satisfactory tumor reduction, with improved local efficacy when compared to the group only submitted to neoadjuvant radiotherapy. **Conclusion:** The study suggests that radiotherapy combined with chemotherapy was more efficient in reducing tumor site when compared to the group treated with radiotherapy. In addition, neoadjuvant therapy did not increase the postoperative complications when compared to patients undergoing surgery alone.

**Key words:** Esophageal neoplasms. Carcinoma, squamous cell. Therapeutics. Chemotherapy, adjuvant. Radiotherapy, adjuvant.

### INTRODUCTION

Esophageal cancer is the eighth most frequent type of cancer in the population worldwide, with estimated 10,550 new cases in Brazil for the year 2008<sup>1</sup>. Despite the recent year's progress in the surgical treatment of carcinoma of the esophagus, long-term survival of these patients remains disappointing even after complete resection. Only a minority of patients obtains a complete macroscopic and microscopic resection of the primary tumor, including their sites of lymphatic drainage (R0 resection, as defined by the Union for International Cancer Control – UICC). At diagnosis, about two thirds of patients present with already locally advanced tumors that have grown beyond the esophageal

wall or tumors invading the adventitia (T3) and adjacent structures (T4)<sup>2</sup>.

Radiation therapy in esophageal cancer has been used for many years with good results, either as the definitive treatment (radiotherapy) or as neoadjuvant treatment to improve locoregional control of disease, an attempt to preserve the organs of resection: the larynx in cases of cancer of the cervical esophagus or the stomach in cases of commitment of the distal esophagus<sup>3</sup>. Consequently, multidisciplinary therapeutic strategies employing adjuvant (postoperative treatment after complete resection) and/or neoadjuvant (preoperative) principles have received increasing attention by the scientific community.

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Neoadjuvant therapy should be completed three to four weeks before surgery and has advantages such as improved ease of complete tumor resection after tumor reduction ("down-size") and, eventually, regression final stage ("down-stage").

Although no therapeutic strategy has been considered definitely superior, a survival benefit was suggested in the subgroup of patients who showed no viable tumor cells on pathological examination of surgically resected esophagi after neoadjuvant therapy<sup>4-7</sup>.

Our objective was to evaluate, through a retrospective, nonrandomized study, tumor responses to neoadjuvant therapy according to the histopathological findings of surgical specimens of patients operated and treated for squamous cell carcinoma of the esophagus.

## METHODS

A review of the database was performed to identify all patients diagnosed with squamous cell carcinoma of the esophagus who had undergone esophagectomy in the period from 1979 to 2006. This research was approved by the Research Ethics Committee of the Faculty of Medical Sciences, UNICAMP (No. 677/2006)

The characteristics of each patient (age, gender and race), tumor site, staging, histologic evaluation, treatment modalities and follow-up were reviewed and analyzed.

Inclusion criteria were: I) patients with esophageal cancer who underwent esophagectomy; II) squamous cell carcinoma diagnosed at histopathological exam; III) tumor location in the middle and lower thirds of the esophagus. Patients with records not found or incomplete data were excluded.

We used the nonparametric Mann-Whitney test to compare continuous variables of the two groups. When comparing three or more groups we used analysis of variance (ANOVA) with rank transformation, due to lack of normality of the data, to reduce asymmetry and variability. When the difference was significant, we performed a multiple comparison test (Tukey test) to identify the differences. The association between categorical variables was assessed by the chi-square ( $\chi^2$ ). When the expected values were less than 5, we used the Fisher exact test. The level of significance was 5%, i.e.,  $p < 0.05$ . The programs used were: The Statistical Analysis System (SAS) (SAS Institute Inc, 1999-2000, Cary, NC, USA) and SPSS (SPSS Inc, 1989-1999, Chicago, IL, USA).

The pathological staging was performed according to the criteria of the TNM classification, recommended by UICC<sup>8</sup>. The age of patients corresponded to the calculated age at the time of surgery.

Patients included in the study summed 97 cases, distributed as follows: Group I - 81 (83.5%), submitted to

neoadjuvant radiation therapy, and group II - 16 (16.5%), submitted to neoadjuvant radiotherapy and chemotherapy. A third group of 26 patients undergoing esophagectomy alone was used for the comparison of postoperative complications.

The most performed type of surgical resection was transmediastinal subtotal esophagectomy (80% of cases) as the technique described by Pinotti<sup>9</sup>. The remaining patients underwent esophagectomy with thoracotomy according to the technique as McKeown<sup>10</sup>. The preferred reconstruction of the digestive tract was with the gastric tube and cervical esophagogastric anastomosis (95% of cases).

Radiotherapy (RTX) was the application of teletherapy with a mean dose of 3762.71 cGy (standard deviation 792.62 cGy) in group I (radiation) and a mean dose of 4212.5 cGy (standard deviation 602.07 cGy) in group II (radiotherapy and chemotherapy), with no statistically significant differences ( $p > 0.05$ ) for the total dose and interval between radiotherapy and surgery between the two groups.

The chemotherapy (Qtx) used consisted of neoadjuvant cisplatin (one to two cycles of 75mg/m<sup>2</sup> D1 to D4) with or without 5-fluorouracil (continuous infusion 1000mg/m<sup>2</sup> in D1).

Tumor response to neoadjuvant therapy was evaluated by histopathological studies of the surgical specimens<sup>11,12</sup>, defining three possible findings to the local effectiveness of neoadjuvant therapy: I) absence of tumor response, i.e., there was no evidence of tumor decreased; II) partial response to neoadjuvant therapy, when residual tumor cells were found at microscopy of the specimen; III) complete response to neoadjuvant therapy, when absence of tumor cells was observed in the surgical specimen and lymph nodes at the optical microscope, but without the use of immunohistochemical studies.

## RESULTS

There was no statistically significant differences regarding race, gender and age of patients in the study groups ( $p > 0.05$ ) (Table 1).

There was no statistically significant difference in the staging of the two groups (Fisher test,  $p = 0.2013 - p > 0.05$ ) (Table 2).

The location of tumors in the esophagus was: I) in the groups with surgical treatment alone and neoadjuvant Qtx + RTX was 50% of the tumors were located in the middle third of the esophagus and 50% of the cases in the distal third; II) in the RTX neoadjuvant group 79% of cases were tumors in the middle third and 21% of tumors in the distal third. Statistical analysis ( $\chi^2$ ) showed  $p = 0.0043$  ( $p < 0.05$ ), therefore, there was a statistically significant difference for the location in the middle third in the group undergoing neoadjuvant RTX.

Tumor response observed in the different groups are shown in table 3.

Statistical analysis of tumor response (Fisher's test) showed a statistically significant difference between the two groups ( $p = 0.0011$ ), with improved local efficacy in neoadjuvant Qtx + RTX group.

Postoperative complications and deaths are listed in table 4. Statistical analysis of complications as follows: a) intraoperative bleeding complications (Fisher's test):  $p = 0.5072$  ( $p > 0.05$ ); b) fistula/stenosis complications ( $\chi^2$ ):  $p = 0.0978$  ( $p > 0.05$ ); c) chest tube complications ( $\chi^2$ ):  $p = 0.0411$  ( $p < 0.05$ ); d) pneumonia (Fisher's test):  $p = 0.4414$  ( $p > 0.05$ ); and e) postoperative death (Fisher's test):  $p = 1.000$  ( $p > 0.05$ ). Therefore, there were no significant differences in postoperative complications between the groups, except for the drainage of the chest, where there was a lower prevalence among esophagectomy alone.

## DISCUSSION

The surgical treatment of resectable esophageal cancer results in survival rates over five years from 5 to

30%, with longer survival in patients with early disease. This therapeutic modality is associated with an operative mortality rate of less than 10%<sup>13,14</sup>. In order to improve survival and relieve dysphagia, strategies using the combination of radiotherapy and radiotherapy with chemotherapy have aroused the interest of the scientific community. Phase III studies compared treatment with neoadjuvant chemotherapy to radiotherapy with surgery alone in patients with esophageal cancer<sup>13-17</sup>.

A prospective randomized multicenter study in which cisplatin was associated with radiotherapy (37Gy in fractions of 3.7 Gy) followed by surgery compared with surgery alone in patients with squamous cell carcinoma of the esophagus showed no improvement in overall survival. Moreover, postoperative mortality presented higher (12% vs 4%) in the combined therapy group<sup>14</sup>. In a subsequent study, patients were randomized (75% with adenocarcinoma) to 5-FU, cisplatin, vinblastine, and radiotherapy (1.5 Gy twice daily for a total of 45 Gy) associated with resection and compared with esophagectomy alone<sup>16</sup>. After eight years of follow-up, no significant difference between surgery and the combination of treatments in median survival (17.6 months vs. 16.9 months), survival rates (16% vs. 30% after three years), or

**Table 1** - Color, gender and age (years) in the groups analyzed.

Prevalence: color, gender and age		Neoadjuvant Rtx		Neoadjuvant Rtx + Qtx	
Color	White	64	79.0 %	14	87.5 %
	Mulatto	10	12.3 %	1	6.25 %
	Black	7	8.7 %	1	6.25 %
Sex	Male	71	87.6 %	14	87.5 %
	Female	10	12.4 %	2	12.5 %
Age (years)	Average	53.7		57.4	
	Standard Deviation	8.2		8.8	

**Table 2** - Staging of the groups analyzed.

Stage	Neoadjuvant Rtx		Neoadjuvant Rtx + Qtx	
0	13	16.04 %	5	31.25 %
I	7	8.64 %	3	18.75 %
IIA	34	41.98 %	4	25 %
IIB	16	19.76 %	2	12.5 %
III	11	13.58 %	2	12.5 %

**Table 3** - Tumor Response in groups treated with neoadjuvant therapy.

Tumor Response	Neoadjuvant Rtx (81)		Neoadjuvant Rtx + Qtx (16)	
Absent	54	66.67 %	6	37.5 %
Partial	15	18.52 %	4	25 %
Complete	12	14.81 %	6	37.5 %

**Table 4 -** Prevalence of surgical morbidity and mortality among the groups studied.

Complications	Surgery Alone(26)		Neoadjuvant Rtx (81)		Neoadjuvant Rtx + Qtx (16)	
Intraoperative Haemorrhage	0	0 %	4	4.93 %	1	6.25 %
Thorax drainage	14	53.84 %	64	79 %	12	75 %
Bronchopneumonia	3	11.53 %	18	22.22 %	4	25 %
Anastomotic Fistula/stenosis	12	46.15 %	32	39.5 %	11	6.25 %
Postoperative Deaths	3	11.54 %	10	12.35 %	1	6.25 %

free survival recurrence (16% vs. 28% at three years) were observed.

The Intergroup study (CALGB-9781)<sup>17</sup>, planned to recruit 475 patients with adenocarcinoma or squamous cell carcinoma to treatment with preoperative chemoradiotherapy (5-FU, cisplatin and 50.4 Gy) followed by esophagectomy or surgery alone, was closed due to low recruitment and the included results of 56 patients, with a median follow up of six years, were published. The median survival was 4.48 years for trimodal therapy versus 1.79 years for surgery alone ( $p = 0.002$ ), with a rate of five-year survival of 39% (95% CI, 21% -57%) for the trimodal therapy versus 16% (95% CI, 5% -33%) for surgery alone. It should be noted that in the CALGB-9781 only 23% of patients had squamous cell carcinoma.

In recent years, several authors have shown the advantages of neoadjuvant treatment with chemotherapy and radiotherapy followed by esophagectomy in the approach of squamous cell carcinoma of the esophagus. The advantages mentioned are improved preoperative dysphagia (allowing the patient to eat better and have better weight gain and nutritional status for surgery), tumor shrinkage, ease of resection, concomitant lymph node treatment and better overall survival. They emphasize that chemotherapy should be performed concomitantly with radiotherapy, and the dosage of radiation should be around 30 to 40 Gy, i.e., lower than the maximum dose allowed per patient<sup>18-21</sup>.

The results of this study suggests that the group submitted to neoadjuvant chemotherapy and radiation therapy combination had more satisfactory tumor reduction when compared to the group submitted only to neoadjuvant radiotherapy<sup>22,23</sup>. Neoadjuvant Radiation therapy and/or chemotherapy was well tolerated by patients, not causing an increase in postoperative complications.

The results presented here are similar to those of the CALGB 9781<sup>17</sup>, demonstrating that patients with squamous cell carcinoma of the esophagus, when subjected to trimodal treatment, present complete or near complete response rate of in 62.5% of patients, while patients submitted to surgery followed by radiotherapy present 33.3%.

Although surgical treatment alone remains the first choice of many surgeons in the approach to squamous cell carcinoma of the esophagus, the results obtained in this study with neoadjuvant therapy suggest significant benefits for patients, within the philosophy of "multimodal" treatment, and similar to results obtained by other groups<sup>14,15,17,18-21,24</sup>.

In conclusion, this study suggests that the use of neoadjuvant therapy with chemotherapy and radiation targeting at improved local effectiveness and better complete resection rates, and possibly a reduction in clinical staging in the preoperative period, brought benefits to patients.

## R E S U M O

**Objetivo:** avaliar por meio de um estudo retrospectivo não randomizado as respostas tumorais à terapêutica neoadjuvante, conforme os achados histopatológicos das peças cirúrgicas dos pacientes operados e tratados por carcinoma espinocelular do terço médio e distal do esôfago. **Métodos:** Foram incluídos no estudo 97 pacientes assim distribuídos: grupo I – 81 (83,5%) submetidos à radioterapia neoadjuvante; e grupo II – 16 (16,5%) submetidos à radioterapia e quimioterapia neoadjuvantes. Um terceiro grupo de 26 pacientes submetidos à esofagectomia exclusiva foi utilizado na comparação das complicações pós-operatórias. As características de cada paciente (idade, sexo e raça), o local do tumor, o estadiamento, e a avaliação histológica das modalidades de tratamento foram revisadas e analisadas. A resposta tumoral à terapêutica neoadjuvante foi avaliada com estudos histopatológicos da peça cirúrgica. **Resultados:** Não houve diferenças estatísticas significativas quanto à cor, sexo, idade, estadiamento e complicações pós-operatórias nos pacientes dos três grupos analisados. Os pacientes submetidos à radioterapia e quimioterapia neoadjuvante apresentaram redução tumoral mais satisfatória, com melhor eficácia local, quando comparado ao grupo submetido apenas a radioterapia neoadjuvante. **Conclusão:** o estudo sugere que a radioterapia associada à quimioterapia apresentou maior eficácia local na redução tumoral em comparação com o grupo tratado com radioterapia; além disso, a terapêutica neoadjuvante não elevou as complicações pós-operatórias em comparação aos pacientes submetidos à cirurgia exclusiva.

**Descritores:** Neoplasias esofágicas. Carcinoma de células escamosas. Terapêutica. Quimioterapia adjuvante. Radioterapia adjuvante.

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