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NEOADJUVANT CHEMORADIOTHERAPY AND SURGERY COMPARED WITH SURGERY ALONE IN SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS

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ABSTRACT - ***Context*** - Despite progress in recent years in methods of diagnosis and surgical treatment of esophageal cancer, there is still controversy about the benefits from neoadjuvant chemoradiotherapy. ***Objective*** - To analise the survival of patients submitted to esophagectomy for squamous cell carcinoma of the esophagus with or without neoadjuvant chemoradiotherapy. ***Method*** - A retrospective, non-randomized study conducted using the medical charts of patients operated for squamous cell carcinoma of the esophagus at the School of Medical Sciences, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil between 1979 and 2006. The Kaplan-Meier analysis was used to calculate survival curves and the log-rank test to compare data in each group. The significance level was settled as 5%. ***Results*** - A total of 123 patients were evaluated in this study, divided into three groups: I - 26 (21.2%) patients submitted to esophagectomy alone; II - 81 (65.8%) patients submitted to neoadjuvant radiotherapy plus esophagectomy and III - 16 (13%) patients submitted to neoadjuvant chemoradiotherapy plus esophagectomy. A statistically significant survival was recorded between the groups (log rank = 6.007; *P = 0.05*), survival being greatest in the group submitted to neoadjuvant chemoradiotherapy, followed by the group submitted to neoadjuvant radiotherapy compared to the group submitted to esophagectomy alone as the initial treatment of choice. ***Conclusion*** - Radiotherapy and chemotherapy neoadjuvants in patients with squamous cell carcinoma of the esophagus offers benefits and increases survival.

HEADINGS – Esophageal neoplasms. Carcinoma, squamous cell. Esophagectomy. Chemotherapy, adjuvant. Radiotherapy, adjuvant.

INTRODUCTION

Despite the progress made in recent years in diagnostic methods and surgical treatment of esophageal cancer, the long term survival rate, even following radical resection, remains disappointing. Complete macro and microscopic resection of the primary tumor including its lymph nodes is achieved in only a minority of patients. In around 2/3 of patients, the tumor has already advanced locally and extended beyond the wall of the esophagus by the time it is diagnosed, i.e. the tumor has already invaded the adventitia (T3) and adjacent structures (T4)[1, 8, 11, 14, 28].

Consequently, multidisciplinary therapeutic strategies using neoadjuvant and/or adjuvant principles have increasingly attracted the attention of the scientific community[7, 13, 15, 18, 21, 29].

The main etiologies of squamous cell carcinoma (SCC) are smoking and alcohol consumption, consumption of hot food and drinks, preserved vegetables (nitrous compounds), infectious agents (human papilloma virus), socioeconomic factors (malnutrition), celiac sprue, Plummer-Vinson syndrome, micronutrient deficiencies (riboflavin, vitamins A, C and E, zinc and molybdenum), palmar tylosis (a rare autosomal dominant disease), previous radiotherapy, previously treated neoplasias of the head/neck, idiopathic achalasia, chagasic megaesophagus and previous caustic stenosis[4, 5, 6, 7, 18, 20]. On the other hand, adenocarcinoma in the distal third of the esophagus is closely associated with intestinal metaplasia of the Barrett's esophagus and therefore related to chronic gastroesophageal reflux[5].

In Brazil for the year 2012, were expected 7,770 new cases of esophageal cancer in men and 2,650 in women. These values correspond to an estimated risk of eight new cases in men and three in women per 100,000 habitants and rendering this form of cancer the 8th most common type in the Brazilian population. Moreover, the incidence is higher in the south and southeast of the country[4, 6].

The objective of this non-randomized, retrospective study was to evaluate the differences in survival of

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patients operated for SCC of the esophagus with or without the addition of neoadjuvant therapy.

METHOD

The protocol of this study was approved by the Ethics Committee of the Internal Review Board of the School of Medical Sciences at the University of Campinas (UNICAMP) and included patients operated for squamous cell carcinoma of the esophagus between 1979 and 2006.

The criteria for inclusion were: 1) patients adults without age limit and with esophageal cancer submitted to surgical resection; 2) histological diagnosis of squamous cell carcinoma; and 3) neoadjuvant radiotherapy and/or chemotherapy. Patients whose charts could not be located and those with incomplete data were excluded from the study.

A total of 123 patients divided in groups were included in the study: I - 26 (21%) patients submitted to esophagectomy alone (ages = 22 males and 4 females; ethnicities: 21 whites and 5 blacks); II – 81 (65.8%) patients submitted to neoadjuvant radiotherapy (ages: 71 males and 10 females; ethnicities: 64 whites and 17 blacks); and III - 16 (13%) patients submitted to neoadjuvant radiotherapy and chemotherapy (ages: 14 males and 2 females; ethnicities: 15 whites and 1 black). The mean age (SD = standard deviation) of the three groups were respectively: 53.8 years (SD = 11.7), 53.7 years (SD = 8.2) and 57.4 years (SD = 8.8).

Pathological staging was performed according to the 6th edition of the UICC-AJCC TNM classification for esophageal cancer[23].

The Fisher's exact test was used to calculate differences of the groups, staging and postoperative complications. The chi-square test (χ^2) was used to calculate the differences of the site of tumors, tumor recurrence and complications. The Kaplan-Meier analysis was used to calculate survival curves and the log-rank test to compare data in each group the significance level was settled as 5% ($P<0.05$).

RESULTS

There were no statistically significant differences between the three groups with respect to gender, age or ethnicity (Fischer's test $P = 0.3507$).

The surgical technique performed in the three groups consisted of transmediastinal subtotal esophagectomy followed by esophagogastroplasty using an isoperistaltic gastric tube placed in the mediastinum, while cervical esophagogastric anastomosis was used to reconstruct the digestive passage in accordance with the technique described by Pinotti[19] and Sugimachi et al.[22].

The mean dose of radiation therapy in group II was 3,762.71 cGy (SD = 792.62) and 4,212.5 cGy in group III. There were no significant differences between the two groups with respect either to the total dose used or the interval between radiotherapy and surgery.

The neoadjuvant chemotherapy employed the cisplatin (one to two cycles of 75 mg/m^2 for 4 days (D1-D4) associated or not with 5-fluorouracil (1000 mg/m^2) administered as a continuous infusion on D1.

The most common location of the tumor was: 1) middle third in 50% of the cases and in the distal third of the esophagus in 50% in the groups I and II; 2) middle third of the esophagus in 79% of the cases and in the distal third in 21% in group III. Therefore in the group III the tumor was located in the middle third of the esophagus in a significantly greater number of cases compared to the other two groups (χ^2; $P = 0.0043$, $P<0.05$).

No statistically significant difference was found between the groups with respect to staging (Fisher's exact test; $P = 0.2013$), postoperative complications (Fisher's exact test; $P = 0.0635$) or the prevalence of tumor recurrence (χ^2, $P = 0.3960$) (Table 1).

The distribution of perioperative complications and deaths are shown in Table 2. There were no statistically significant differences in complication rates between groups

TABLE 1. Staging of tumors (6th edition of the UICC-AJCC TNM classification) according to the treatment employed in the three groups studied

Stage	Surgery alone		Neoadjuvant radiotherapy		Neoadjuvant radiotherapy + chemotherapy	
	n	%	n	%	n	%
0	0	0	13	16.04	5	31.25
I	6	23.07	7	8.64	3	18.75
IIA	11	42.3	34	41.98	4	25
IIB	3	11.55	16	19.76	2	12.5
III	6	23.08	11	13.58	2	12.5
IV	0	0	0	0	0	0

TABLE 2. Surgical morbidity / mortality compared with the treatments employed in the groups studied

Complications	Surgery alone		Neoadjuvant radiotherapy		Neoadjuvant radiotherapy + chemotherapy	
	n	%	n	%	n	%
Intraoperative hemorrhage	0	0	4	4.93	1	6.25
Chest 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
Perioperative deaths	3	11.54	10	12.35	1	6.25

with the exception of chest drainage, the incidence of which was significantly lower in the group of patients submitted to surgery alone. Statistical analysis of the complications among three groups described above showed a) intraoperative hemorrhage: $P = 0.5072$ (Fisher's exact test); b) fistula/stenosis: $P = 0.0978$ (χ^2); c) chest drainage: $P = 0.0411$ (χ^2); d) bronchopneumonia: $P = 0.4414$ (Fisher's exact test) and perioperative death: $P = 1.000$ (Fisher's exact test).

The survival for the groups, calculated using the Kaplan-Meier analysis, is shown in Figure 1 with the exception of the patients who died within 30 days of surgery, who were excluded from this calculation. Therefore was observed a statistically significant difference between the groups (log rank = 6.007; $P = 0.05$), and survival was greater in the group submitted to neoadjuvant chemoradiotherapy (group III), followed by the group submitted to neoadjuvant radiotherapy (group II) compared to the group submitted to esophagectomy alone (group I) as the initial treatment of choice. The follow-up and survival time, the number of deaths and survivals, and the statistically significant differences (standard error, 95% confidence interval and *P*-values) between the groups are shown in Table 3.

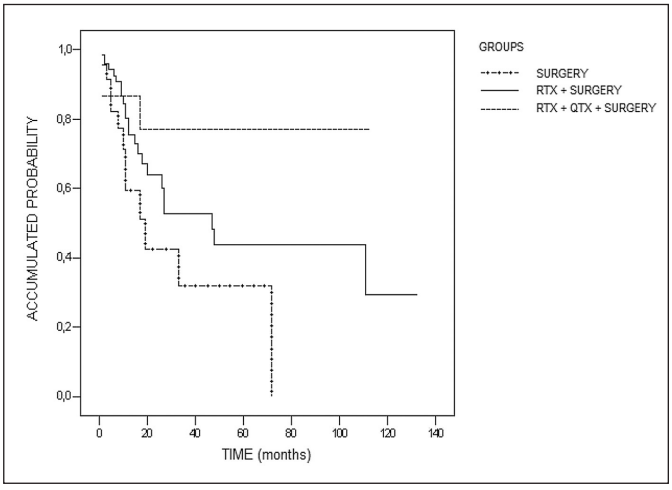

FIGURE 1. Survival curve for the groups of patients submitted to surgery alone, radiotherapy + surgery and radiotherapy + chemotherapy + surgery (Kaplan-Meier analysis)

DISCUSSION

The prognosis of patients with squamous cell carcinoma of the esophagus remains poor despite advances made over recent years in the diagnosis and treatment of this neoplasia. Many authors have discussed and recommended neoadjuvant therapy emphasizing the need to implement this therapeutic option and the advantages obtained with this treatment. The benefits are: 1) improvement in the clinical condition of the patient prior to surgery, since tumor size is reduced, facilitating food intake, even solid food; 2) reduction in tumor size, improving the possibility of complete resection and eliminating systemic micrometastases; 3) devitalization of tumor cells, thereby minimizing the risk of intraoperative metastasis; 4) administration of more aggressive doses of cisplatin combined with other drugs; 5) to improve the possibility of complete resection of the lesion, and prolong both overall and disease-free survival[13, 15, 18, 21, 24, 27, 28].

In a randomized study carried out in France, Le Prise et al.[12] evaluated the benefits of neoadjuvant chemoradiotherapy (two cycles of 5-fluouracil and cisplatin concomitantly with 20 Gy of radiotherapy) compared to a control group in which only surgery was performed. These investigators concluded that neoadjuvant therapy failed to result in any significant difference in intraoperative mortality or in the survival time of patients with squamous cell carcinoma of the esophagus.

Bosset et al.[3] in a randomized, multicenter study performed in Europe, compared neoadjuvant chemoradiotherapy followed by surgery (combined therapy) with surgical treatment alone in stage I or II SCC of the esophagus. These investigators concluded that no improvement occurred in overall survival, however, disease-free survival increased.

Urba et al.[25] conducted a randomized study in the United States in 100 patients operated for esophageal cancer comparing surgery alone (group I) with neoadjuvant chemoradiotherapy (group II), and concluded that there was no statistically significant difference in survival.

In a randomized, prospective study carried out in Italy, Ancona et al.[2] analysed two groups of patients (41 patients in each group) with resectable squamous cell carcinoma of the esophagus submitted to surgery alone (group A) with patients submitted to neoadjuvant chemotherapy (group B),

TABLE 3. The follow-up and survival time, the number of deaths and survivals and statistic analysis in the three groups studied

	Surgery	Surgery + radiotherapy	Surgery + radiotherapy + chemotherapy
No. of patients	23	71	15
No. of late deaths	12	23	3
Percentage of deaths	52.2	32.4	20.0
Mean time of follow-up (months)	32.43	65.75	87.28
Standard error	7.81	9.43	12.21
95% confidence interval	17.12-47.74	47.26-84.23	63.34–111.22
***P*-value**	**Surgery versus surgery + radiotherapy**		0.05
	Surgery versus surgery + radiotherapy + chemotherapy		0.04
	Surgery + radiotherapy versus Surgery + radiotherapy + chemotherapy		0.27

evaluating overall survival and the impact of the patient's response to chemotherapy on survival. These investigators reported that there was a statistically significant improvement in survival only in patients who achieved complete pathological response to chemotherapy ($P = 0.01$).

Urschel et al.[26] carried out a meta-analysis of nine randomized, controlled studies involving 1,116 patients with SCC of the esophagus in which they compared surgical treatment alone with neoadjuvant chemoradiotherapy followed by surgery and reported a 3-year improvement in survival and a reduction in locoregional tumor recurrence. The study showed a tendency towards an increase in mortality in the neoadjuvant chemoradiotherapy group, without statistical significance.

Fiorica et al.[9] conducted a meta-analysis of six controlled, randomized studies and concluded that in patients with resectable esophageal cancer, neoadjuvant chemoradiotherapy followed by radical surgery significantly reduces third-year mortality rates compared to surgical treatment alone. Nevertheless, these authors concluded that neoadjuvant chemoradiotherapy resulted in an increase in postoperative mortality.

Greer et al.[10] performed a meta-analysis in which six randomized studies were evaluated (neoadjuvant chemoradiotherapy followed by surgery versus surgery alone) and concluded that neoadjuvant chemoradiotherapy is associated with increased overall survival that is not statistically significant.

Malthaner et al.[16] conducted a meta-analysis evaluating 34 randomized studies and 6 meta-analyses involving 13 different combinations of neoadjuvant and/or adjuvant therapy in resectable esophageal cancer. They concluded that surgical treatment alone (i.e. with no neoadjuvant or adjuvant therapy) should be recommended as standard treatment for cases of resectable thoracic esophageal cancer. The Table 4 summarizes the mentioned studies.

TABLE 4. Literature review on neoadjuvant therapy in SCC of the esophagus

Author	Type of study	Number of patients	Mean survival (months)	*P*-value
Le Prise et al.1994[12]	Randomized	41 (chemo) vs 45 (surgery)	11 11	0.56
Bosset et al.1994[3]	Randomized	143 (chemo) vs 139 (surgery)	18.6 18.6	0.78
Ancona et al.2001[2]	Randomized	47 (chemo) vs 47 (surgery)	25 24	0.01 (only complete pathological response)
Urba et al.2001[25]	Randomized	50 (chemo) vs 50 (surgery)	17.6 16.9	0.15
El Nakadi et al.2001[8]	Non-randomized	38 (surgery) vs 61 (radio + chemo)	Unavailable 21	0.19
Urschel et al.2002[26]	Meta-analysis of nine randomized studies	1116 (total) surgery vs (radio + chemo)	Odds ratio: 0.79 (1st year) 0.77 (2nd year) 0.66 (3rd year)	0.016 (3rd year)
Makary et al.2003[14]	Non-randomized	76 (surgery) vs 40 (radio + chemo)	17.2 vs 35.7	0.01
Liao et al.2004[13]	Non-randomized	72 (surgical) vs 60 (radio + chemo)	12 vs. 62	<0.05
Malaisrie et al.2004[15]	Non-randomized	65 (surgical) vs 31 (radio + chemo)	28.7 vs 24.1	0.14
Fiorica et al.2004[9]	Meta analysis of six randomized studies	390 (surgery) vs 388 (radio + chemo)	Odds ratio: 0.53 (3rd year)	0.03 (3rd year)
Greer et al.2005[10]	Meta-analysis (6 randomized studies)	364 (surgery) vs 374 (radio + chemo)	Odds ratio: 0.86	0.74
Zhang et al.2005[29]	Non-randomized	59 (surgery) vs 56 (radio + chemo)	19.3% (4 years) vs 33.3% (4 years)	<0.05
Morgan et al.2007[18]	Non-randomized	117 (chemo) vs 88 (radio + chemo)	24 vs 43	0.03
Andreollo et al.2012	Non-randomized	23 (surgery) vs 71 (radio) vs 16 (radio + chemo)	32.4 65.4 87.2	0.05

Van Hagen et al.[27] including patients with resectable esophageal tumors treated by surgery alone or weekly administration of carboplatin and paclitaxel for 5 weeks and concurrent radiotherapy, followed by surgery, demonstrated that the overall survival was significantly better in the chemoradiotherapy-surgery group. They concluded that preoperative chemoradiotherapy improved survival among patients with potentially curable esophageal or esophagogastric-junction cancer.

In the present study, the majority of the patients were at stages IIA and IIB[23], although there were cases of stage 0 in the neoadjuvant therapy groups and stage I in all three groups. Postoperative complications and the prevalence of tumor recurrence were unrelated to the staging of the disease. Statistical analysis showed significant difference in survival between the three groups (log rank = 6.007; $P = 0.05$), survival being greatest in the group submitted to neoadjuvant chemoradiotherapy, followed by the group submitted to neoadjuvant radiotherapy in comparison with the group submitted to esophagectomy alone. Moreover, neoadjuvant therapy did not result in any increase in intra- or postoperative morbidity or mortality rates.

In conclusion, statistically significant differences were found in the survival of patients in the groups analysed, confirming the benefits of neoadjuvant therapy. It is important to emphasize that this is a retrospective nonrandomized study, the number of cases submitted to neoadjuvant chemoradiotherapy is not as great and therefore the results may have vies despite the follow-up period of 5 years and the statistical analyses. Nevertheless, further prospective, randomized studies in future should be carried out to confirm these new therapeutic strategies for squamous cell carcinoma of the esophagus.

Andreollo NA, Tercioti Jr. V, Lopes LR, Coelho-Neto JS. Radioterapia e quimioterapia neoadjuvantes e cirurgia comparado com a cirurgia no tratamento do carcinoma epidermoide do esôfago. Arq Gastroenterol. 2013,50(2):101-6.

RESUMO - ***Contexto*** - Apesar dos progressos realizados nos últimos anos em métodos de diagnóstico e tratamento cirúrgico do câncer de esôfago, ainda há controvérsias sobre os benefícios reais da quimioradioterapia neoadjuvante. ***Objetivo*** - Avaliar o tempo de sobrevida em pacientes operados de carcinoma de células escamosas do esôfago com ou sem quimioradioterapia neoadjuvante. ***Método*** - Estudo retrospectivo, não randomizado, realizado com os prontuários dos pacientes submetidos a esofagectomia por carcinoma de células escamosas do esôfago na Faculdade de Ciências Médicas da Universidade de Campinas (UNICAMP), Campinas, São Paulo, Brasil, entre 1979 e 2006. Na análise estatística, o estimador de Kaplan-Meier foi utilizado para calcular as curvas de sobrevivência e do teste log-rank para comparar a sobrevivência em cada grupo. O nível de significância foi estabelecido em 5%. ***Resultados*** - O total de 123 pacientes foi avaliado neste estudo, dividido em três grupos: I - 26 (21,2%) pacientes submetidos a esofagectomia, II - 81 (65,8%) pacientes submetidos a radioterapia neoadjuvante seguido de esofagectomia e III - 16 (13%) submetidos a quimioradioterapia neoadjuvante seguido de esofagectomia. Diferença estatisticamente significativa na sobrevida foi registrado entre os grupos (log rank = 6,007, $P = 0,05$), tendo maior sobrevida o grupo submetido a quimioradioterapia neoadjuvante, seguida pelo grupo submetido a radioterapia neoadjuvante em comparação com o grupo submetido a esofagectomia apenas como o tratamento inicial de escolha. ***Conclusão*** - A radioterapia e a quimioterapia neoadjuvantes em pacientes com carcinoma de células escamosas do esôfago oferecem benefícios e aumenta a sobrevida.

DESCRITORES – Neoplasias esofágicas. Carcinoma de células escamosas. Esofagectomia. Quimioterapia adjuvante. Radioterapia adjuvante.

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