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ARTIGO ORIGINAL/ORIGINAL ARTICLE

Quimio-radioterapia sequencial no carcinoma pulmonar não de pequenas células: estudo retrospectivo de 100 doentes

Sequential chemo-radiation in non-small cell lung cancer: a retrospective study of 100 patients

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RESUMO

A combinação da quimioterapia e da radioterapia revelou-se a terapêutica corrente no carcinoma pulmonar não de pequenas células irressecável, após a aplicação da radioterapia isolada, durante vários anos, ter revelado sobrevidas

ABSTRACT

Combined chemotherapy and radiotherapy has shown to be the correct treatment of unresectable non-small cell lung cancer, aier many years of poor survival figures with standard radiotherapy alone. It has also been demonstrated

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pobres. Constatou-se que o benefício da quimioterapia se deveu aos esquemas com cisplatina.

Os autores apresentam os resultados de um estudo retrospectivo de 100 doentes com carcinoma pulmonar não de pequenas células, estádio III, tratados com um esquema sequencial de quimioterapia e radioterapia, em que avaliam as sobrevidas média e global, os tempos livres até à progressão local e à progressão à distância, constatando que os seus resultados são muito semelhantes aos publicados na literatura.

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Palavras-chave: Carcinoma pulmonar não de pequenas células; quimioterapia e radioterapia sequencial.

that the benefit of chemotherapy is mainly achieved if cisplatin-based schedules are used. The authors present a retrospective study of 100 cases of stage III non-small cell lung cancer treated with a sequential approach of chemotherapy and radiotherapy and evaluate median and overall survival, local progression-free survival and distant progression-free survival.

The results of our series are quite similar to those published in literature.

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Key-words: non-small cell lung cancer; sequential chemo-radiation

INTRODUCTION

Non-small cell lung cancer (NSCLC), accounts for about 80% of all lung cancers and surgery is the curative treatment[33], with 5 year survival rates of 55%, 30% and 18% in stages I, II and III, respectively[13]. Unfortunately, surgery is only possible in 15% to 25% of cases, due to loco-regional invasion or disseminated disease at the diagnosis, or medically inoperable patients or surgery refusal[3,8,41]. In locally advanced tumours, those with small and ipsilateral mediastinal lymph nodes — minimal N2 — are a therapeutic challenge, because they may benefit with neo-adjuvant treatment[3,32]. Randomized studies published in 1994 have confirmed that benefit[25,26] and the studies from *Memorial Sloan-Kettering Cancer Center*[22] and from *Southwest Oncology Group*[1] have demonstrated resection rates of 65% and 73%, respectively, after chemotherapy (CT) and radiotherapy (RT). All other stage IIIA and all stage IIIB cases are classically considered unresectable[18,24] and, since many years, RT alone has been the standard therapy[19]. Although the results were extremely disappointing, with median survival less than one year and 5 year survival rates of 0% to 9%[6,10,15,17,32], it was the only chance of cure for a very small number of patients.

From the end of 80 decade and beginning of 90 decade, some authors have shown that the ideal approach in unresectable NSCLC is combining CT and RT, in patients with good performance status and minimal weight loss [2,4,5,8,11,12,16,17,21,23.28.29,35,39]. In most series. this combination demonstrated a survival gain of 2 to 4 months and two times more survivors at 2 and 3 years with CT schedules containing cisplatin[18],if combined with RT , when compared with RT alone[20]. The randomized study from *CALGB,* published in 1990[11] and up-dated in 1996[12] with 155 patients presents a median survival gain from 9.7 months to 13.8 months and a 3 year survival from 11% to 23%. Other randomized study from *Institut Gustave Roussy*[21], with 353 patients, shows a median survival gain from 10 months to

TABLE I
CT shedule

MVP	**Mitomycin 8 mg/m²** **Vindesine 3 mg/m²** **Cisplatin 80 mg/m²**	**each 28 days**	**NIP**	**Vinorelbine 30 mg/m² D_1, D_8** **Ifosfamide 3 mg/m² D_1** **Cisplatin 80 mg/m² D_1**	**each 21 days**
MIP	**Mitomycin 6 mg/m²** **Ifosfamide 3 mg/m²** **Cisplatin 80 mg/m²**	**each 21 days**	**GP**	**Gemcitabine 1000 mg/m² D_1, D_8, D_{15}** **Cisplatin 100 mg/m² D_1**	**each 28 days**

TABLE II
Patients and treatment features

CASES	Nº = %
SEX	
Male	90
Female	10
HISTOLOGY	
Squamous cell	46
Adenocarcinoma	34
Mixed Tumours	3
Unclassified NSCLC	16
Large cell	1
STAGE	
IIIA	24
IIIB	76
CT SCHEDULE	
MVP	23
MIP	58
NIP	14
GP	5
CT CYCLES	
3	60
4	40
RT DOSE	
60 Gy	92
<60 Gy	8

12 months and a 3 year survival from 5% to 11%. Both an Italian group[8] and a Spanish group[34], with 66 and 45 patients, respectively, have shown encouraging results with combined CT-RT.

However, timing of both modalities is still controversial, taking in consideration the final endpoint of a longer survival without increasing the toxicity. With the purpose of clearing this point, some publications have tried to demonstrate the superiority of concurrent CT-RT, with encouraging results[7,9,14,31,36,37,38.40].

MATERIAL AND METHODS

From January 1992 until December 1998, one hundred patients with stage III NSCLC and Karnofsky index ≥ 70, have been treated with 3 or 4 cycles of CT followed by RT with 60 Gy/6 weeks. Median age is 64.5 years (range 38-77 years), 90 patients are male and 10 are female. According to histologic type, 46% are squamous cell carcinomas. 34% adenocarcinomas. 3% mixed adenosquamous tumours, 1% large cell carcinoma and 16% unclassified NSCLC. According to stage, 24% are in stage IIIA and 76% in stage IIIB. In 23% of the patients, CT schedule includes mitomycin, vindesine and cisplatin (MVP), in 58% vindesine is changed to ifosfamide (MIP), in 14% vinorelbine is included in the schedule combined with ifosfamide and cisplatin (NIP) and in 5% gemcitabine is associated to cisplatin (GP). Complete CT schedule is presented in Table I. 60% of the patients have been submitted to 3 CT courses and 40% to 4

courses. Concerning RT, 8% of the patients did not complete 60Gy, due to disease progression or poor general condition. The patients and treatments features are summarized in Table II.

Kaplan-Meier method has been used for survival curves and log rank for significance tests.

RESULTS

Median survival is 17 months. There is not any statistically significant difference according to histology: 17 months in squamous cell carcinomas and 14 months in adenocarcinomas, with p= 0.6 (Fig. 1); there is not any statistic difference too between stages: 23 months in stage IIIA and 16 months in stage IIIB, with p= 0.16 (Fig.2); also according to CT schedule and number of courses, there is not any difference: 18 months with MVP 17 months with MIP, 15 months with NIP and 10 months with GP, with p= 0.79 (Fig. 3), 16 months with 3 courses and 17 months with 4 courses with p = 0.88 (Fig. 4); despite the very small number of patients treated with < 60 Gy, there is almost statistically significant difference between RT dosis: 17 months with 60 Gy and 9 months with < 60 Gy, with p= 0.069 (Fig. 5).

Overall survival at 1, 2 and 3 years and survival probability at 5 years is 69.2%, 36%, 23.3% and 11.6%, respectively (Fig. 6). Median time to local progression is 15 months. Local progression-free survival at 1, 2 and 3 years is 65.9%. 28.7% and 26.7%, respectively (Fig. 7).

Median time to distant progression is 17 months. Distant progression-free survival at 1,2 and 3 years is 58.8%, 38.2% and 34.2%, respectively (Fig. 8). The most frequent first site of dissemination is brain in 37% of the cases, followed by bone (33.3%), lung (16.6%) and liver (13%).

Five patients developed second neoplasic diseases: thyroid, pancreas, prostate, myelodisplasia and rectum.

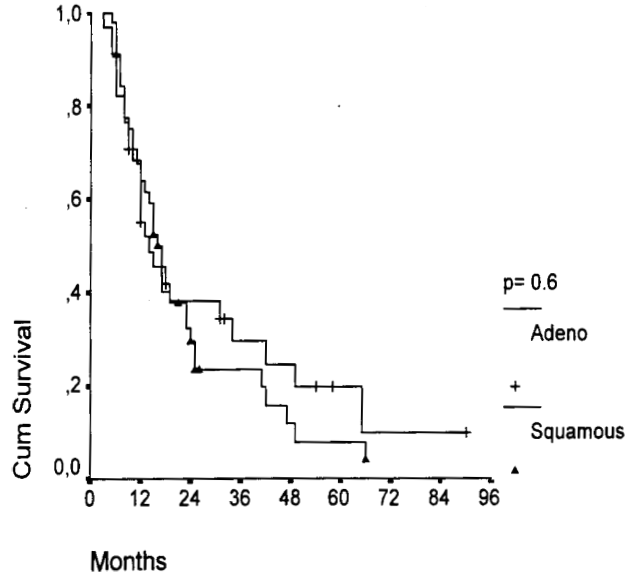

Fig. 1 — Survival curve according to histology

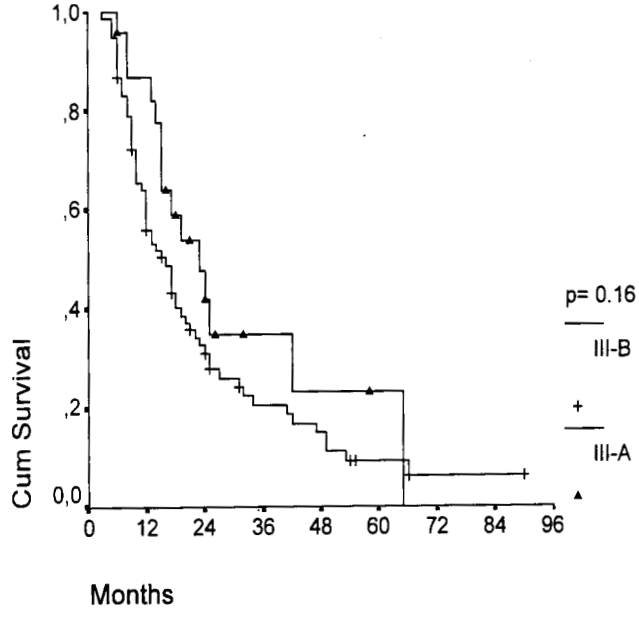

Fig. 2 — Survival curve according to stage

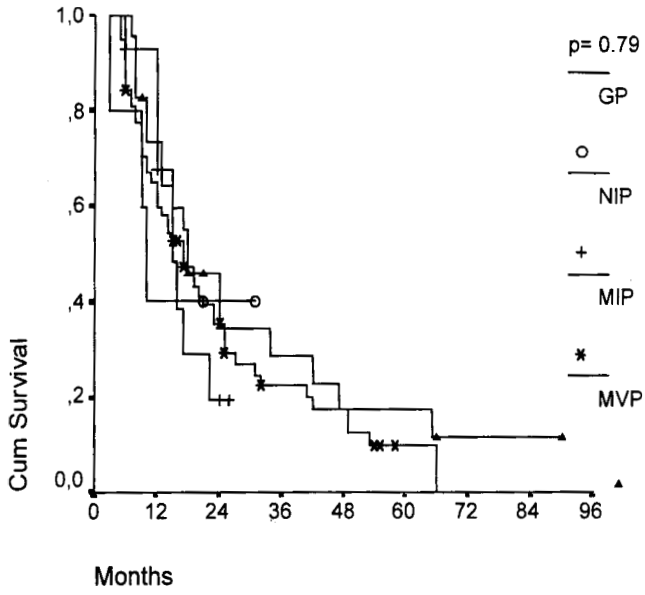

Fig. 3 — Survival curve according to CT schedule

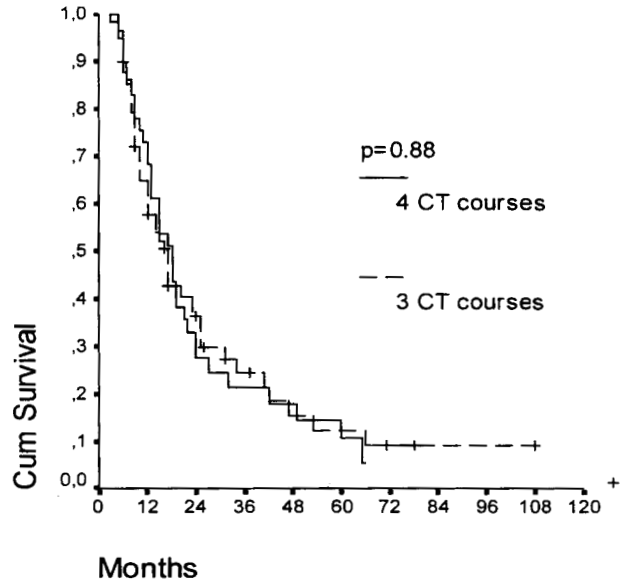

Fig. 4 — Survival curve according to number of CT courses

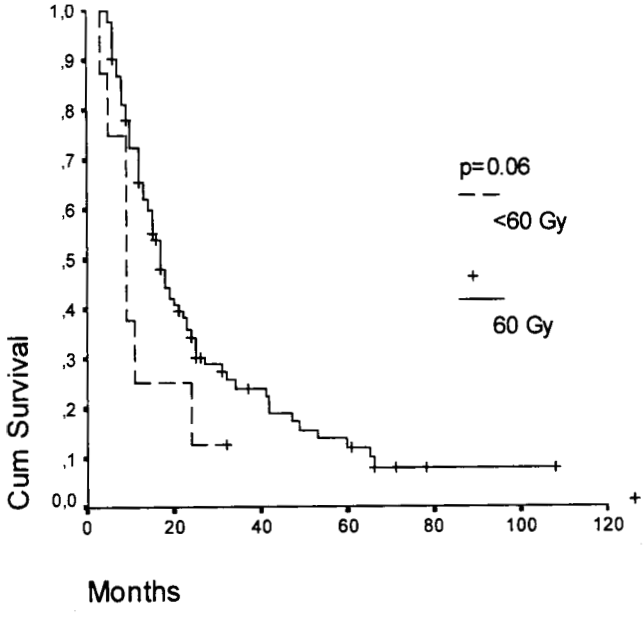

Fig. 5 — Survival curve according to RT dosis

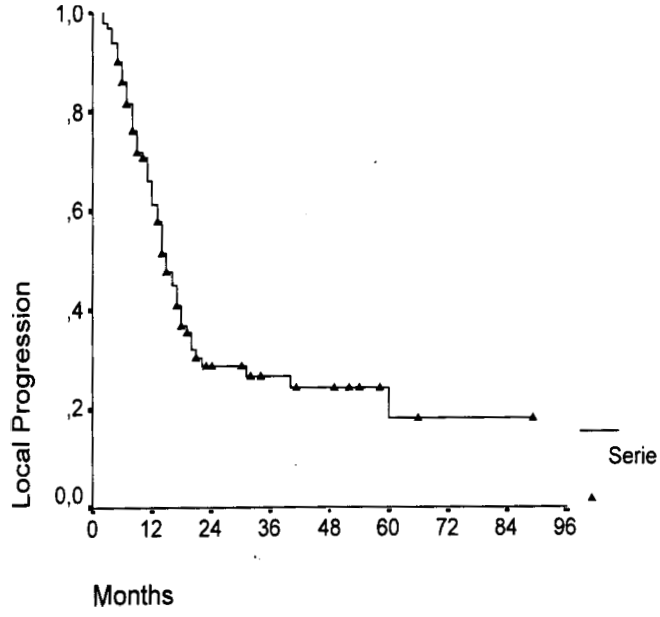

Fig. 6 — Overall survival

TABLE III
Results overview in differents series

AUTHOR	Nº PATIENTS	SURVIVAL			
		MEDIAN (months)	1 YEAR (%)	2 YEARS (%)	5 YEARS (%)
DILLMAN [11,12]*	78	13.8	55	26	19
LE CHEVALIER [21]*	176	12	50	21	
MATTSON [23]*	119	10.9	42	19	
SAUSE [28,29]*	164	13.8	60	31	8
FURUSE [14]*	160	13.3		27.4	8.9
TEJEDOR [34]	45	13		21	7
CRINO [8]	33	13		30	
GASPAR (current series)	100	17	69.2	36	11.6

* Randomized studies

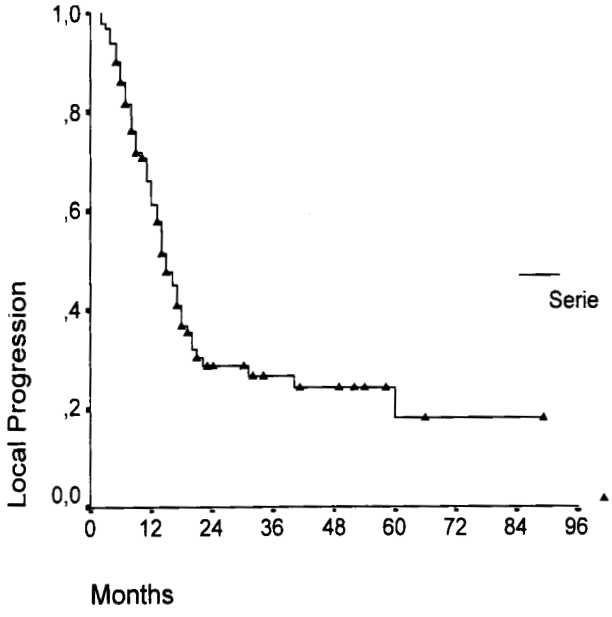

Fig. 7 — Local progression-free survival

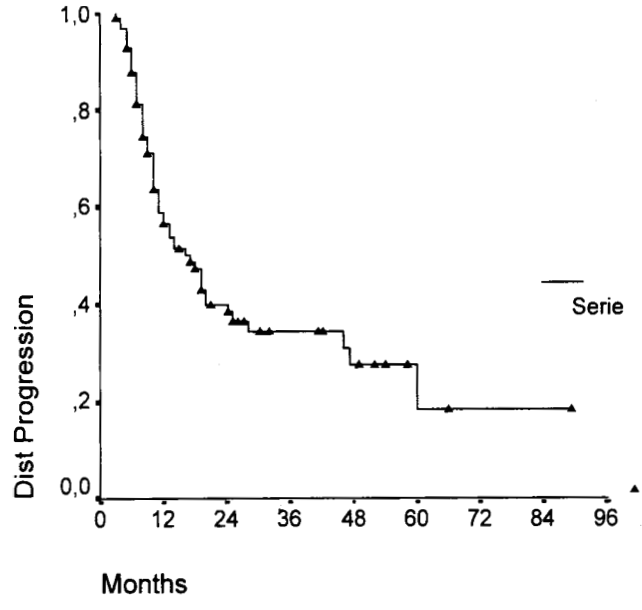

Fig. 8 — Distant progression-free survival

DISCUSSION

Today, combination of CT and RT is the standard treatment of unresectable NSCLC. Concerning CT, it has been demonstrated that cisplatin is the reference to combine with other drugs[18]. The sequential approach of CT and RT has been largely performed, showing an improvement of survival compared with RT alone[2,4,5,11,12,17,20,21.29,35.39].

Our series of 100 patients has 76% of cases with stage IIIB and a slight predominance of squamous cell carcinomas. CT consisted of 3 or 4 courses and two of the so-called new drugs — vinorelbine and gemcitabine — were introduced in our schedule in 1996 and 1997, respectively, leading to a smaller number of patients treated with those drugs. However, at this time, there is not any difference in survival results according to the CT scheme. Histologic type did not show either any prognostic relevance. The statistic difference between RT dosis, almost significant, probably means that 60 Gy might be the minimal dosis required in NSCLC, which perhaps means that dosis has prognostic value, as it is suggested in a recent recursive partitioning analysis[30].

The results of our series are quite similar to those published in literature with combined CT-RT in NSCLC (Table III) with 2- and 5-year survival rates of 36% and 11,6%, respectively. Nevertheless, better results could be achieved with improvements in both therapeutic modalities. Concerning CT a wider utilization of the new drugs seems to obtain promising results with more responses and longer survival, and this fact is more attractive if RT is given concurrently[9,14,36,37,38,40], in spite of more toxicity, mainly esophageal. What concerns RT, a sequential approach of CT-RT. in which part of RT was given with accelerated fractionation, obtained a 3-year survival rate of 26%[35], bringing to discussion the benefit of altered fractionation schemes. On the other hand, 3-dimensional planning and conformal RT have launched the debate about the optimal field size (is uninvolved elective areas irradiation needed?) and consequent escalation dosis, in order to reach better local control.

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