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RESEARCH ARTICLE

Patterns and management of distant failure in locally advanced rectal cancer: a cohort study

J. Arredondo[1] · J. Baixauli[2] · J. Rodríguez[3] · C. Beorlegui[4] · L. Arbea[5] · G. Zozaya[2] · W. Torre[6] · J. A. -Cienfuegos[2] · J. L. Hernández-Lizoáin[2]

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Abstract
Purpose To determine the long-term outcomes of locally advanced rectal cancer (LARC) treated with neoadjuvant chemoradiation (CRT) and surgery, and to analyze the management and survival once distant failure has developed.
Methods Data from LARC patients treated from 2000 to 2010 were retrospectively reviewed. CRT protocols were based on fluoropirimidines ± oxaliplatin. Follow-up consisted of physical examination, carcinoembryonic antigen levels, and chest-abdominal-pelvic CT scan.
Results The study included 228 patients with a mean age of 59 years. Forty-eight (21.1 %) patients had distant recurrence and 6 patients (2.6 %) had local recurrence. Median follow-up was 49 months. The 5- and 10-year actuarial disease free survival was 75.3 and 65.0 %, respectively. The 5- and 10-year actuarial overall survival (OS) was 89.6 and 71.2 %, respectively. Patients were classified as having liver (14 patients) or lung (27 patients) relapse according to the organ firstly metastasized. The variables significantly associated by univariate Cox analysis to survival were the achievement of an R0 metastases resection and the Köhne risk index, while the metastatic site showed a statistical trend. By multivariate Cox analysis, the only variable associated with survival was a R0 resection (HR = 16.3, $p < 0.001$). Median OS for patients undergoing a R0 resection was 73 months (95 % CI 67.8–78.2) compared to 25 months (95 % CI 5.47–44.5) in those non-operated patients ($p < 0.001$).
Conclusions Combined treatment for LARC obtains a 5-year OS rounding 90 %. Follow-up based on thoracic-abdominal CT scan allows an early diagnosis of metastatic lesions. Surgical resection of metastases, regardless of their location, greatly increases the patient's survival rate.

Keywords Locally advanced rectal cancer · Liver metastases · Lung metastases · Metastasectomy · Neoadjuvant treatment

✉ J. Arredondo
jarredondo@outlook.es

[1] Department of General Surgery, Complejo Asistencial Universitario de León, c/Altos de Nava s/n, 24008 León, Spain

[2] Department of General Surgery, Clínica Universidad de Navarra, Avenida Pío XII 36, 31008 Pamplona, Spain

[3] Department of Medical Oncology, Clínica Universidad de Navarra, Avenida Pío XII 36, 31008 Pamplona, Spain

[4] Department of Pathology, School of Medicine, Universidad de Navarra, Avenida Pío XII 36, 31008 Pamplona, Spain

[5] Department of Radiation Oncology, Clínica Universidad de Navarra, Avenida Pío XII 36, 31008 Pamplona, Spain

[6] Department of Thoracic Surgery, Clínica Universidad de Navarra, Avenida Pío XII 36, 31008 Pamplona, Spain

Introduction

Rectal cancer is a high-incidence disease, which accounts for almost 40,000 cases in the US and western countries [1]. Neoadjuvant chemoradiotherapy (CRT) followed by surgery—total mesorectal excision (TME)- and adjuvant chemotherapy (ChT) is currently the standard of care in locally advanced rectal cancer (LARC) [2]. Although this combined approach has resulted in a low local relapse rate, the incidence of distant metastases remains in the range of 20–30 %, and represents the main reason of treatment failure. Both, the liver and lung have been reported as the main sites of distant failure [3–7].

Surgical resection, when feasible, offers a potential for cure in a subset of relapsed patients. For the remaining patients, several strategies, such as two-stage hepatectomy, portal vein embolization, radiofrequency ablation or neoadjuvant systemic ChT, have been attempted to expand the number of them being candidates for resection [8]. Even in patients with both liver and lung metastases, an aggressive surgical management can also be offered if a complete resection is expected [9].

Since management and prognosis of metastatic disease is highly dependent on the tumor burden, an intensive follow-up after LARC surgery is warranted in an attempt to achieve early diagnoses of tumor relapse and to provide longer survival times.

The main aim of this study is to determine the long-term outcomes of LARC patients treated with neoadjuvant CRT and surgery. The secondary aim is to analyze the management and survival of these patients once distant failure has developed.

Patients and methods

Medical records from patients with LARC who underwent preoperative CRT followed by surgery at our institution in a 10-year period were analyzed. This retrospective study was approved by the Institutional Review Board.

Chemoradiotherapy protocols used in the present study have been reported elsewhere [7, 10], and were based on fluoropirimidines (5-fluorouracil or capecitabine) ± oxaliplatin. Concurrent radiotherapy (RT) was delivered by using a three-/four- or seven-field technique. TME according to a standardized technique was performed 5–6 weeks after the completion of CRT. Postoperative ChT was scheduled 4–6 weeks after surgery, depending on the pathological findings and the pretreatment TN-stage. According to their location primary tumors were classified as being in the lower (1–5 cm), middle (5.1–10 cm) or upper rectum (10.1–15 cm). Pathologic analyses were performed by a specialized gastrointestinal pathologist. Staging was performed according to TNM classification [11]. Tumor response grade was obtained according to the scale proposed by Memorial Sloan-Kettering Cancer Center (MSKCC), which classifies the degree of response in five groups taking into account to the percentage of tumor cells that remain visible in the surgical specimen [12]. A three-category pathologic scale that grouped grades 0–2, grade 3, and grades 3+ and 4 were used for statistical purposes.

Patients were followed-up every 4 months for 1 year, every 6 months for the next 2 years, and afterwards, yearly. Every evaluation consisted of physical examination, serum determination of carcinoembryonic antigen (CEA), and chest-abdominal-pelvic CT scan. Endoscopy was performed after 1 year from the surgery, and every 2 or 3 years afterwards. Local relapse was considered as any radiologic or clinical tumor regrowth within the prior pelvic treatment field, and distant relapse was defined as tumor growth in any other location. The criteria for diagnosing recurrence were a compatible image on CT, an elevation of serum CEA levels and/or a positive biopsy. At the moment of the first relapse, patients were divided into three prognostic categories according to the Köhne risk index [13].

Statistical analysis

Results were expressed as mean (standard deviation) or median (P_{25}–P_{75}) for quantitative variables. Proportion was applied to qualitative variables. Student's t or Mann–Whitney U and Chi-square tests were performed for comparing means and proportions, respectively. Disease-free survival (DFS), overall survival (OS) and survival after recurrence were estimated by the Kaplan–Meier method as cumulative survival rate. Survival curves obtained for different categories of a factor were compared by the Log-Rank test. Univariate Cox regression was used to identify factors related to recurrence and tumor-related death. All predictors with $p < 0.2$ in univariate analysis were entered in a multivariate Cox model with a semi-manual backward variable selection. All the statistical analyses were done using the SPSS/PC v.15 for Windows statistical package (SPSS, Chicago, IL, USA).

Results

Patients baseline characteristics

From January 2000 to December 2010, 228 LARC patients who received neoadjuvant CRT followed by surgical resection were retrospectively analyzed. The mean age was 59 years (10.8) and most of them were males (69.3 %). Seventy-five percent of the patients were classified as stage III and thirty-five percent as stage II in the baseline clinical workup. Concurrent RT, fluoropirimidines and oxaliplatin were used in 165 patients (72.4 %) whereas 63 patients (27.3 %) received RT and fluoropirimidines alone. In 132 (57.9 %) patients the number of RT fields was seven and in 96 patients (42.1 %) it was three or four. One hundred an seventy-four patients (76.3 %) underwent a low anterior resection, forty-eight (21.1 %) an abdominoperineal resection, and 6 patients (2.6 %) a Hartmann procedure. The median number of harvested nodes was 9 (5–15) and distal margin distance was 6 cm (0.5–8). Limphovascular or perineural invasion was observed in 35 and 43 patients,

respectively. After surgery, adjuvant ChT was administered to 155 patients (68 %).

Patients follow-up

Two and thirteen patients were lost to follow up after 1 and 3 years, respectively. Fifty-four (23.7 %) patients had disease recurrence including 6 patients (2.6 %) with local recurrence. Figure 1 summarizes the location of metastases developed all through the follow-up of the study. Whether the recurrence was the first one or not has not been taken into account in Fig. 1.

After a median follow-up of 49 months (range 30–73), the median DFS has not been reached. The 5- and 10- year actuarial DFS was 75.3 and 65.0 %, respectively. Twenty-five patients died due to disease progression, with a median time from primary surgery to death of 49.5 months (31–74). Median OS has not been reached and the 5- and 10-year actuarial OS was 89.6 and 71.2 %, respectively (Fig. 2).

Since liver and lung metastases are the most frequent sites of relapse, the outcome of these patients is reported in further detail. In this case, patients were classified as having liver (14 patients, 34.1 %) or lung (27 patients, 65.9 %) relapse according to the organ firstly metastasized. The studied variables in the univariate Cox analysis of survival after hepatic or pulmonary recurrence are outlined in Table 1. It should be noted that the only significant observed differences between the two groups were the tumor response grade ($p = 0.03$) and the resectability rate ($p = 0.003$). The other variables did not show statistically significant differences (data not shown).

Liver relapse ($n = 14$)

Ten patients (71.4 %) presented resectable liver metastases and one patient was turned into resectable after preoperative ChT. Eleven patients underwent surgical resection of liver metastases: eight directly from relapse diagnosis and three after neoadjuvant ChT. At the moment of the diagnosis, the median CEA level was 20 (3.1–64.2) ng/mL, and the median size of the bigger metastasis was 18 (10–37) mm.

Surgical procedures included three hemihepatectomies (27.2 %), four segmentectomies (36.3 %), three atypical resections (27.2 %) and one sectionectomy (9.0 %). Two patients (18.0 %) required two-stage hepatectomy to achieve a R0 tumor resection. Eight patients (72.0 %)

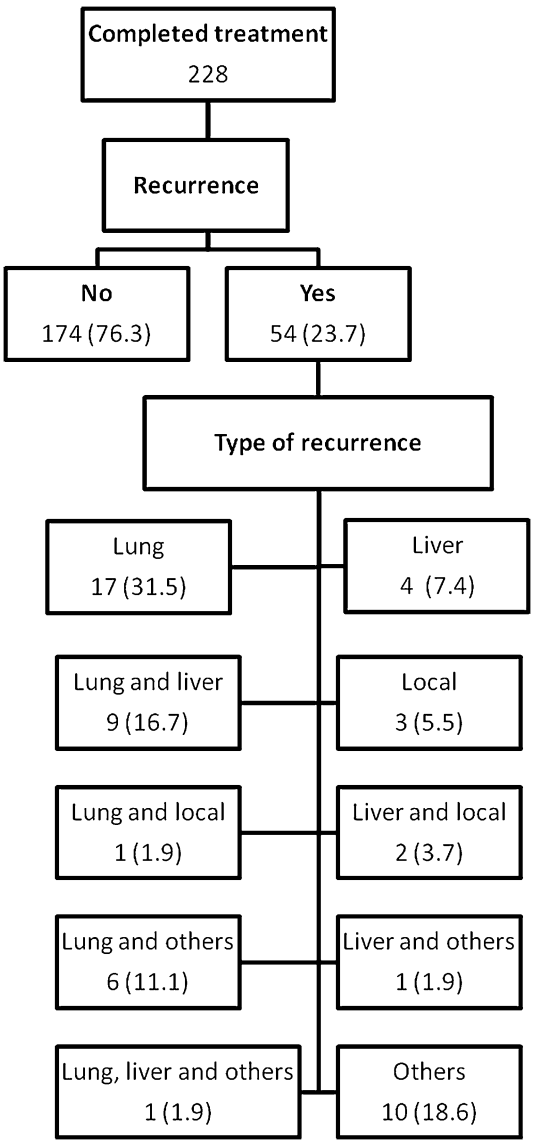

Fig. 1 Type of recurrences by location along all the follow-up of the study. Expressed as (%)

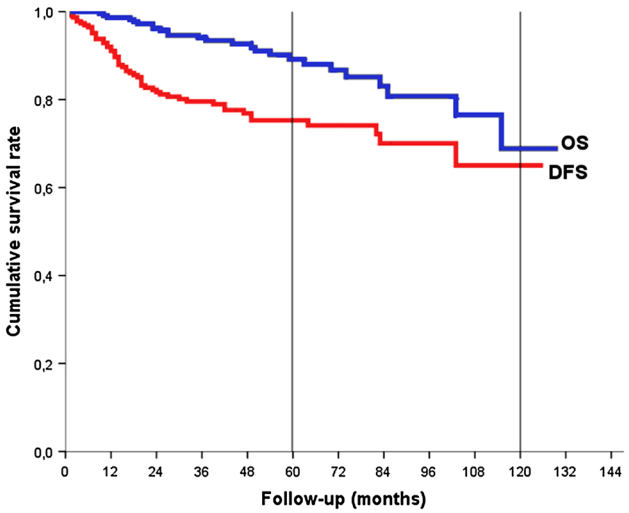

Fig. 2 Overall survival and disease free survival for the entire group of LARC patients

Table 1 Clinical characteristics of the patients at the time of liver or lung relapse

	Liver recurrence ($n = 14$)	Lung recurrence ($n = 27$)	Global liver or lung recurrence ($n = 41$)
Age[a]	62.7 (9.17)	58.3 (12.6)	59.8 (11.6)
Sex			
Male	11 (78.6)	16 (59.3)	27 (65.9)
Female	3 (21.4)	11 (40.7)	14 (34.1)
Baseline primary tumor clinical stage			
II	3 (21.4)	9 (33.3)	12 (29.3)
III	11 (78.6)	18 (66.7)	29 (70.7)
Primary tumor pathological stage			
I	4 (28.6)	6 (22.2)	10 (24.4)
II	4 (28.6)	7 (25.9)	11 (26.8)
III	6 (42.9)	14 (51.9)	20 (48.8)
Primary tumor regression grade (MSKCC)			
0–2	9 (64.3)	12 (44.4)	21 (51.2)
3	4 (28.6)	11 (40.7)	15 (36.6)
3+ , 4	1 (7.1)	4 (14.8)	5 (12.2)
Primary tumor rectal location			
Upper	1 (7.1)	0 (0)	1 (2.4)
Middle	5 (35.7)	6 (22.2)	11 (26.8)
Lower	8 (57.1)	21 (77.8)	29 (70.7)
Adjuvant chemotherapy after primary surgery	11 (78.5)	22 (81.5)	33 (80.5)
Köhne index			
Low risk	14 (100)	22 (81.5)	36 (87.8)
Intermediate risk	0 (0)	5 (18.5)	5 (12.2)
Disease free interval[b]	13.5 (6–30.7)	20 (12–27)	18 (9–27)
Recurrence resectability	11 (78.6)	10 (29.4)	21 (51.2)

Data expressed as *n* (%)

MSKCC Memorial Sloan Kettering Cancer Center

[a] Expressed as mean (standard deviation)

[b] Expressed as median (P_{25}–P_{75})

underwent resection of one lesion, two patients (18.0 %) of two lesions and one patient (9.0 %) of nine lesions. All patients were discharged uneventfully.

Lung relapse ($n = 27$)

Pulmonary metastases were detected either by CT scan (32 patients, 94.1 %), or by ^{18}FDG-PET/CT (2 patients, 5.9 %). Ten patients (29.4 %) presented resectable metastases and underwent surgery, three of them after neoadjuvant ChT. The median CEA level was 3.6 (1.7–10.3) ng/mL and the median size of the main metastasis was 8 (5–11) mm.

The surgical resection consisted on five lobectomies (50.0 %) and five metastasectomies (50.0 %). Seven patients (70.0 %) underwent resection of one lesion, two patients (20.0 %) of two lesions and one patient (10.0 %) of three lesions. There was no remarkable morbi-mortality. All patients received ChT.

Survival after first location recurrence

The median survival after distant recurrence was 36 months (95 % CI 28–44). Among the 41 patients who developed liver or lung relapse the only clinical variables significantly associated to survival after recurrence by univariate Cox analysis were the achievement of an R0 resection (HR 18.7, 95 % CI 4.04–86.4; $p < 0.001$) and the Köhne risk index (HR 6.07, 95 % CI 1.85–19.9; p 0.003), while the metastatic site showed only a statistical trend (HR 2.3, 95 % CI 0.93–5.78; p 0.07).

Median survival after liver or lung recurrence was 73 (95 % CI 65.5–80.5) and 32 months (95 % CI 20.5–43.5), respectively (Fig. 3).

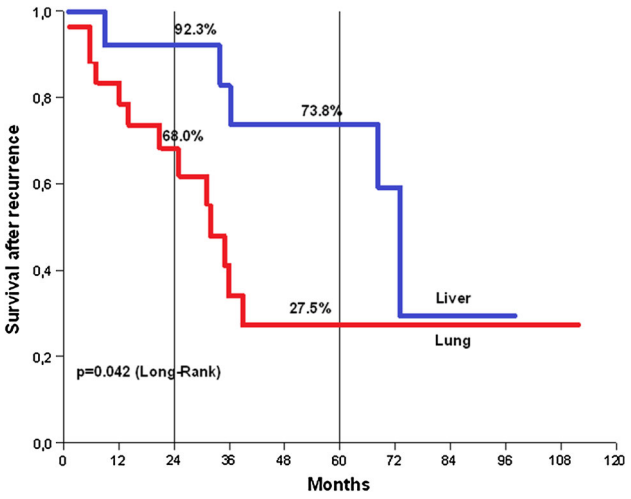

Fig. 3 Survival after recurrence in liver and lung. Survival rates at 24- and 60-months for each location were *highlighted*

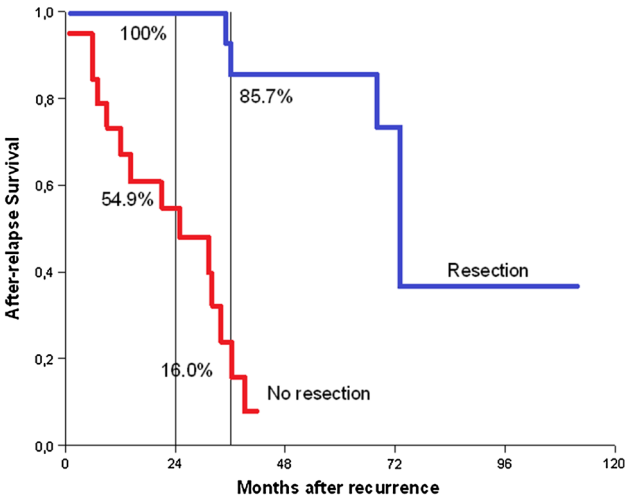

Fig. 4 Survival after recurrence according to surgical resection of metastases. Survival rates at 24- and 36-months were *highlighted*

Indeed, when a R0 resection was feasible and performed, median survival time was the same for both sites of relapse (73 months). When surgical resection was not performed, median survival time for liver and lung relapses was 25 (95 % CI 10.5–39.6) and 9 months (95 % CI 0–32.5), respectively.

By multivariate Cox analysis, the only variable significantly associated with an improved survival time was the achievement of a R0 resection of metastases (HR for no R0 resection = 16.3, 95 % CI 3.42–71.4, $p < 0.001$), while Köhne risk index showed only a statistical trend ($p = 0.094$).

Median OS for patients undergoing a complete surgical resection of their metastases was 73 months (95 % CI 67.8–78.2) compared to 25 months (95 % CI 5.47–44.5) in those non-operated patients ($p < 0.001$, Log–Rank) (Fig. 4).

Discussion

In the present study we report the long term outcome of LARC patients treated with a preoperative combined modality approach. While the local recurrence was low [14–19], the rate of distant metastases (21.1 %) is in agreement with that reported by other authors and remains the main cause of therapy failure [16, 17, 20, 21].

Despite a 5- and 10-year DFS of 75 and 65 % respectively, the 5- and 10-year OS remained at around 90 and 70 % respectively. This fact might be due to the early treatment of the recurrences.

Regarding to liver metastases, a curative surgical treatment could be offered to almost 80 % of patients. This resulted in a 5-year survival rate after hepatic relapse of 88.9 %, which highlights the importance of achieving a surgical excision of liver metastases, as commented by other authors [22–25].

As described in the literature, in many cases postoperative surveillance of rectal cancer patients is mainly focused on early detection of liver metastases by CT or ultrasound, while just a chest X-ray is the most frequently used test to rule out pulmonary metastases. In this study, the average size of lung metastases was less than one centimeter and, therefore, often undetectable by X-ray. The inclusion of chest CT scan in the follow-up has increased the detection of lung metastases. This has allowed early ChT administration and surgical salvage surgery in almost a third of them. Moreover, high definition CT was able to find poor prognostic factors such as small multiple lesions and/or lymph node involvement, thereby enabling a selection of those patients not eligible for an up-front surgical procedure. With a 5-year OS of 80 % after thoracic surgery, our data suggest that complete surgical resection of lung metastases is a potentially curative approach [26–28]. Moreover, our results are consistent with those of Chau and coworkers, who found a prolonged survival when a R0 surgical resection of pulmonary relapse was performed, as well as better results when the clinical monitoring was based on CT and CEA levels [4].

There is controversy in the literature about whether concurrent liver and lung metastases have a worse prognosis than in cases of metastases exclusively localized in the lung [9, 27–29]. In our study, as shown in Fig. 4, good survival is achieved if excision of all resectable metastases is accomplished, regardless of whether they affect only one organ. Therefore, surgical resection of synchronous metastases should be attempted if a complete removal is feasible.

Despite the NCCN guideline (version 4.2013) recommends the surveillance of patients at high risk of recurrence with chest-abdominal-pelvic CT scan annually for up to 5 years [30], in light of our findings, it might be reasonable to base the surveillance on an even more intense follow-up in selected patients.

In this study patients with not-resectable liver metastases presented a better survival than those with not-resectable pulmonary metastases. This fact could be in relation with the underlying biological background, such as the different expression of thymidilate synthase depending upon the tumor site that may be responsible of the different outcome of 5-FU-based chemotherapy in pulmonary metastases compared with liver metastases.

There are some limitations that deserve consideration. This is a single institutional study with few patients who developed metastases, requiring the results of the comparisons to be taken with caution. Therefore, further studies in larger series of patients are warranted to validate these results.

Conclusions

Treatment with neoadjuvant CRT and surgery for LARC can obtain good long-term oncological results, with a 5-year OS rounding 90 %. Follow-up based on thoracic-abdominal CT scan allows an early diagnosis of metastatic lesions, providing accurate data about their number and size and allowing for a more effective selection of patients to be treated. Surgical resection of metastases, regardless of their location, greatly increases the patient's survival rate.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This study has been approved by the appropriate ethics committee. For this type of study formal consent is not required.

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