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'Liver First' Approach in the Treatment of Colorectal Cancer with Synchronous Liver Metastases

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Advanced liver metastases · Reverse strategy · Liver sugery · Chemotherapy

Abstract
Background: In patients with synchronous colorectal liver metastases, an approach reversing the traditional therapeutic order – i.e. starting with chemotherapy first, doing the liver surgery second, and performing the colorectal surgery last – is theoretically appealing as it avoids the risk of metastatic progression during treatment of the primary tumor. The present series updates on a previously reported pilot experience. ***Patients and Methods:*** 35 patients with advanced synchronous colorectal metastases and nonobstructive colorectal tumors were treated with the reversed approach. Data were collected in a prospective database. ***Results:*** The median number of metastases was 6, the median size of the largest metastasis was 6 cm. Five patients could not complete the program (one death from sepsis during chemotherapy, 3 cases of progressive disease under treatment, and one case of vanishing liver metastases). The remaining 30 patients responded and underwent R0 liver resections with no major complications. One patient needed a Hartmann's procedure for obstruction after a first-step hepatectomy, and 1 patient had a rectal anastomotic leak. Median survival was 44 months. Overall survival rates of the 30 patients who completed the program at 1, 2, 3, 4 and 5 years were 100, 89, 60, 44 and 31%. ***Conclusions:*** The reverse approach appeared feasible and safe, with operability and survival rates better than expected for patients with similar severity. Potential problems, in particular regrowth of vanishing metastases and primary tumors, chemotherapy-associated liver damage, and large bowel obstruction, can be minimized by careful multidisciplinary selection, planning and execution.

Introduction

The standard treatment of synchronous colorectal liver metastases (CRLM) is removal of the primary tumor followed by 3–6 courses of chemotherapy and then, if the metastases are resectable, by liver surgery. However, only few patients can benefit from this strategy, mostly because either the metastases are considered unresectable from the beginning, or because they progress during treatment of the primary tumor.

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Over the last decade, major advances in chemotherapeutic agents substantially improved the chances of cure of patients with stage IV colorectal cancer. While the traditional treatment using 5-fluorouracil (5-FU) and leucovorin (LV) had low response rates (<25%), new agents like irinotecan, an inhibitor of topoisomerase I, or oxaliplatin, a non-nephrotoxic platinum complex, added to 5-FU-LV (FOLFIRI or FOLFOX combinations), obtained a tumor response in up to 40–50% of the patients [1, 2]. The use of triple associations with irinotecan, oxaliplatin and 5-FU-LV further increased the efficacy of systemic chemotherapy. Response rates as high as 70% were obtained in 3 different studies and the overall median survival improved to 26 months [3–5]. The more recent development of 2 monoclonal antibodies, cetuximab (Erbitux®), a monoclonal antibody against the epidermal growth factor receptor, and bevacizumab (Avastin®), a humanized antibody against the vascular endothelial growth factor [6, 7], has improved the response rates even further.

The growing efficacy of chemotherapy, accompanied by advances in liver surgery techniques and interventional radiology (hemi-portal embolization, radiofrequency thermal ablation), led to the development of new strategies to increase the number of patients who may benefit from a curative approach, and eventually to improve long-term survival [8].

One of these strategies is the so-called reverse treatment of advanced synchronous colorectal liver metastases (ASCRLM). In this strategy, a highly effective neoadjuvant chemotherapy directed against the liver metastases is given first, liver surgery is done next, and the colorectal resection is performed last. The rationale of such a strategy is to control the CRLM at the same time as the colorectal primary, optimize the chances of a curative liver resection, and allow unhurried chemoradiotherapy before rectal surgery when indicated. Our initial experience with this approach was published in 2006 [9]. The aim of the present study is to update on the initial series, and to share additional experience in the management of these patients.

Patients and Methods

Between January 1998 and December 2007, 35 consecutive patients with ASCRLM were offered the reverse treatment strategy with curative intent. Eligibility criteria were: age less than 70 years, performance status <2, a nonocclusive primary tumor, at least two liver segments without metastases, and no or resectable extrahepatic disease (lungs, lymph nodes). The definition of advanced metastatic disease was based on the clinical risk score described by Fong et al. [10]. Briefly, the score is based on 5 clinical criteria: positive lymph node status of the primary tumor, disease-free interval from the discovery of the primary to discovery of the liver metastases of less than 12 months, number of metastases greater than one, size of the larger tumor greater than 5 cm and preoperative CEA level greater than 200 ng/ml. A CRS of 3 or higher has been validated as defining more severe disease.

All patients had complete colonoscopy, endoscopic ultrasonography for rectal cancers, abdominal and chest computed tomography (CT) and magnetic resonance imaging (MRI) of the liver. After multidisciplinary evaluation, eligible patients were informed on the rationale of the strategy and accepted the protocol. Data were collected prospectively in an institutionally approved database.

Patients received 3–6 courses of chemotherapy before liver resection. The chemotherapy regimen used in our center was OCFL as described elsewhere [4]. Since 2006, bevacizumab was given to 7 patients and cetuximab to 2 patients as OCFL + bevacizumab or bevacizumab and cetuximab regimens.

Despite some differences in the chemotherapy regimens, all patients received state-of-the-art treatment for CRLM adapted to clinical circumstances and oncologist's/patient's choice.

Radiological studies to assess the response to chemotherapy were done during the third course. When the patient was considered resectable with a decrease in the CEA level, we planned the liver surgery 2–3 weeks after the third course of chemotherapy. Additional courses of chemotherapy were given only if further response was likely to confer a surgical advantage.

Because of the risks of chemotherapy-associated changes in the nontumoral parenchyma [11, 12], right portal vein embolization or, for patients with bilobar liver metastases, 2-step hepatectomy were considered if the calculated remnant liver volume represented less than 0.6% of the patient's weight. Two-step hepatectomy involved initial resection of all the metastases of the left liver with right portal vein ligation or with right portal vein embolization during the postoperative period. 4–6 weeks after the first procedure, a right or extended right hepatectomy was performed. Peroperative ultrasonography was used routinely. Liver surgery was based on the last CT scan or MRI, but also on the first CT scan before the chemotherapy to avoid the risk of not removing some metastases that could no longer be identified at imaging after chemotherapy (vanishing metastases). When possible, a surgical approach that favors conservative radical resections without undue sacrifice of functional liver tissue was chosen [13]. Only one simultaneous liver and rectal surgery was performed. However, simultaneous liver and colon surgery was performed if the liver resection was minor and considered without any risk of postoperative liver failure [14, 15]. In other cases, resection of the primary was planned within 4–8 weeks after liver surgery or after completion of pelvic radiotherapy in patients with T3 or N1 rectal tumors (dose of 50 Gy by a three-field technique).

Postoperatively, 2–3 courses of chemotherapy were added to the 3–4 courses of neoadjuvant treatment to complete the program. Follow-up consisted of monitoring of tumor markers, endoscopic surveillance and CT. Recurrences were treated with surgery, radiofrequency ablation and chemotherapy as appropriate.

Life-table curves were analyzed with the Kaplan-Meier method with the SPSS statistical software package (SPSS 10.0 for Windows, SPSS Inc., Chicago, Ill., USA).

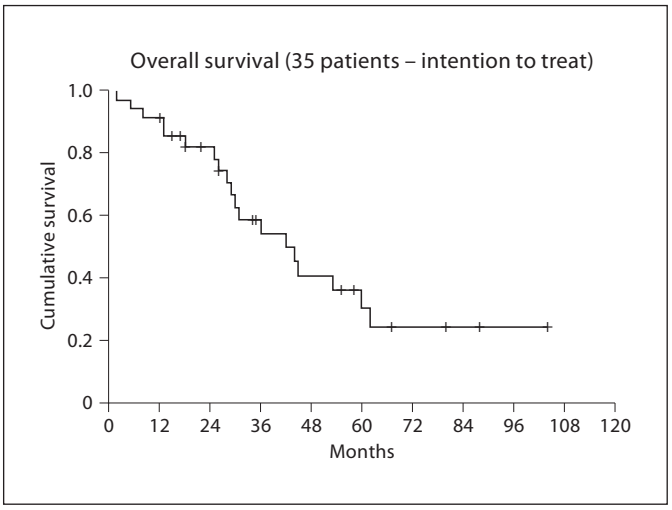

Fig. 1. Overall survival of all patients treated with the reverse strategy (intention to treat).

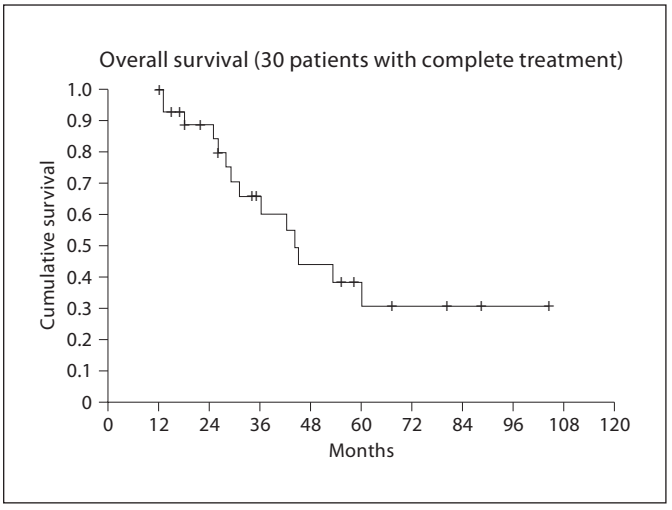

Fig. 2. Overall survival of the 30 patients who completed the treatment.

Results

Five of the 35 patients (14%) could not complete the program. One patient died of sepsis during chemotherapy, 2 patients had disease progression during the different surgical steps, 1 patient had rapid regrowth of liver metastases after the second phase of a 2-step hepatectomy to remove 18 bilobar nodules and was put again on chemotherapy without rectal surgery, and in the last patient who had 6 small metastases deeply located in left and right liver, the metastases had vanished after chemotherapy; this patient had resection of the primary without hepatectomy. All these patients died after 2, 5, 8, 30 and 62 months, the last 4 patients because of recurrence.

The program was completed in 30 patients. There were 16 men and 14 women with a median age of 52 years (range 32–69 years). Thirteen patients had a rectal primary. The median number of metastases was 6 (1–21, mean number 5.2). The median size of the largest metastasis was 6 cm (1–14, mean 7.3 cm). Three patients (10%) had resectable lung metastases at the time of diagnosis, one of whom with positive lymph nodes of the hepatic pedicle.

The median CEA level was 48 ng/l (range 2 to ≥5,000, mean 333 ng/l). The clinical risk score according to Fong's classification was 2 in 2 patients, 3 in 15 patients, 4 in 4 patients and 5 in 9 patients with a median of 3 (mean 3.7). Nine patients had a 2-step hepatectomy with a portal embolization or right portal vein ligation.

In 7 patients, the primary tumor could be removed at the same time as the liver metastases (or at the same time of the first liver resection for 2-step hepatectomies).

There was no peroperative mortality, and except for the patient who died of sepsis during chemotherapy, no patient died before completion of the therapeutic program. Complications of liver surgery involved 5 patients (17%).

Considering the colorectal surgery, there was one anastomotic leak converted to a Hartmann's procedure. One case of local rectal recurrence was observed in a patient who had a transanal resection at the site of a tumor that had vanished after chemoradiotherapy, and one further patient had late pelvic discrete peritoneal carcinomatosis. Overall, recurrences were observed in 20 patients.

At the end of the follow-up, 14 patients had died, 6 patients were alive with disease and 10 patients were alive with no evidence of disease.

Considering the 35 patients as intention to treat, the overall actuarial survival rates were 91, 82, 54, 41 and 30% at 1, 2, 3, 4 and 5 years from start of the treatment. The median survival was 44 months. For the 30 patients who completed the program, overall actuarial survival rates at 1, 2, 3, 4 and 5 years from the start of treatment were 100, 89, 60, 44 and 31% with a median survival of 44 months (fig. 1, 2).

Discussion

The present series illustrates and updates the pilot experience of our group with the 'liver first' approach for ASCRLM, an original concept that has been rendered possible by the very effective chemotherapies available today [9]. Indeed, we regard the approach more as a 'chemo first' than as a 'liver first' treatment, whose rationale lies on the assumption that at the stage of ASCRLM, patients have systemic disease, and that whatever the treatment, it should be systemic (immunologic, biologic, etc.) from the start. This goes without questioning that total removal of the cancer tissue in the liver remains a necessary step for long-term cure [16], and regardless of whether or not downstaging of the metastases is a prerequisite for surgery [17, 18].

The present series continues the initial study published in 2006 [9]. At present, a total of 30 patients have undergone all phases of the program (neoadjuvant chemotherapy, liver surgical clearance, pelvic radiotherapy if indicated and removal of the primary tumor, in that order). To the original 4 patients who dropped out of the program, only one additional patient could not complete the reverse strategy because of rapid regrowth of new liver metastases after the second step hepatectomy (a patient with 18 nodules and a CRS of 5 at presentation).

A relatively important change from the initial series was the addition of bevacizumab or cetuximab to the chemotherapy regimen. However, the chemotherapy used with alternatively given oxaliplatin and CPT11 was already very effective in a Swiss study [4].

A potential disadvantage of the strategy is that patients with resectable disease at presentation face the risk that CRLM becomes unresectable during chemotherapy. Based on our experience, we regard this risk as hypothetical, for two reasons: first that we did not encounter it; the disease progressed during chemotherapy in only 3 patients, none of whom was resectable upfront. The second reason is that nonresponders are a subgroup of patients with aggressive tumors who can hardly be helped by surgery [19]. Indeed, it was recently shown by our group and by others that the histological response to chemotherapy was in itself a prognostic factor [20, 21].

More concrete pitfalls of upfront chemotherapy came into light with practice. The first was that response to chemotherapy cannot be assumed to persist. The possibility of progression after initial response has to be anticipated, and surgery scheduled as early as possible after initial systemic control and when the patient is considered resectable.

The second was the problem of vanishing metastases, concerning in particular small nodules beside primarily unresectable metastases for which chemotherapy is pursued. The risk of regrowth of these lesions is very high, and we actively search and excise them on the basis of intraoperative ultrasound or landmark-oriented anatomical resections.

The third was chemotherapy-associated parenchymal damage. While it is indisputable that this renders liver surgery more difficult and hazardous, problems and complications can be diminished by attention to surgical detail [8] and liberal use of progenerative techniques such as portal vein ligation and embolization.

These three pitfalls contributed to identify the concept of a window of resectability that opens and closes for each patient, and that has to be anticipated from the initial multidisciplinary discussion. In practice, we measure the CEA and obtain a new imaging after 2.5–3 months after the start of chemotherapy: as soon as the CEA decreases and the metastases are considered resectable or a response is shown for the resectable metastases, we perform the liver surgery followed 1 month later by colorectal surgery (preceded by pelvic radiotherapy if needed).

Nonobservance to these probably contributed to a poor outcome in one of the earliest patients for whom surgery was deferred until the 6th cycle because of patient's preference and logistical reasons, with the combined difficulties of progressive metastatic disease and chemotherapy-associated parenchymal damage.

The other original aspect of the reversed approach, namely operating on the liver metastases before the colorectal surgery, rests on the assumption that the vital outcome is dictated by the liver metastases which in the traditional bowel-first approach can progress while attention is given to the primary. On the contrary, with the reverse approach, removing all known liver metastases at the first surgical intervention protected the patients from regrowth of the liver metastases and was an element of peace of mind if state-of-the-art radiotherapy had to be given to rectal tumors.

The risks of progression of the liver metastases in the traditional colon-first approach are real, in particular if septic complications occur. Septic complications, whether related to surgery or associated conditions, are not a rare event even in experienced centers [22, 23], especially in patients with stage IV CR cancer. The realism of our assumptions on the risk of a period without chemotherapy if the primary was resected first was demonstrated by a randomized study, showing that only one half of pa-

tients with rectal cancer could have a full dose of the postoperative chemotherapy, for whatever reasons [24].

The risk of the primary becoming obstructive was taken into account from the beginning of the protocol, but in fact this event was rare, and a Hartmann's procedure was needed only in the patient mentioned above, in whom the window of resectability was missed for logistic reasons [9].

A more real risk is the disappearance of the primary tumor, a potential problem that must be anticipated by the colorectal surgeon. We now advocate tagging the tumor by tattooing the distal margin with China ink at colonoscopy if this complication is likely.

Respecting the above-mentioned caveats, and the modern principles of specialized rectal surgery such as total mesorectal excision, patients did not seem to suffer from doing the colorectal surgery last. In particular, only one anastomotic leak was observed in a patient with very advanced disease (lymph-node invasion of the hepatic pedicle and pelvis, eventually with a poor outcome, arguably a poor candidate for curative treatment), and the only local recurrence was due to misjudgement and insufficient radicality in excising a lesion that had responded completely.

The survival figures in our series have to be interpreted in the light of the severity of the disease at presentation. According to the clinical risk score (CRS), validated in large series of patients [10, 25, 26], only 2 patients had a CRS of 2, 28 had a CRS of 3 or more, including 9 patients with a CRS of 5. Patients with a CRS from 3 to 5 were considered as good candidates for experimental therapies because their expected 3-year survival was so poor (40%) [10]. In this series, the mean CRS was 3.7, the median number of metastases was 6, the size of the largest one was 6 cm and the median CEA level was 48 ng/l. Half of the patients were technically unresectable before chemotherapy.

While our experience does not allow a direct comparison, we found that resectability and survival were better than expected, with 86% of the patients who could undergo the total program of treatments, and for these patients the 3- and 5-year survival was 60 and 31% (fig. 1). However, only 10 patients are alive with no evidence of disease after a mean follow-up of 44 months. This figure demonstrates that despite the fact that we are now able to prolong survival of patients with severe disease who would have had only palliative treatments 10 years ago, we are still unable to offer cure to the majority of them, and that further progress is needed.

Conclusions

High-impact chemotherapy followed by resection of liver metastases before removal of the primary tumor is a feasible and safe approach with an appealing rationale. The strategy appears to be associated with an increased rate of curative resection and to improve long-term survival without detrimental effect on the evolution of the primary, provided that careful planning and a precise schedule are respected.

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