Colorectal cancer with non-resectable synchronous metastases: should the primary tumor be resected?

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SUMMARY

Objectives — In asymptomatic patients presenting with non-resectable synchronous metastatic disease from colorectal adenocarcinoma, the beneficial effect of resecting the primary tumor remains to be documented. The aim of this study was to compare survival of patients with metastatic colorectal cancer who underwent elective resection of the primary tumor to those who did not.

Methods — A retrospective analysis of patients with metastatic colo-rectal cancer treated between June, 1996 and December, 1999 was performed. Overall survival was compared between patients who underwent first-line resection of the primary colorectal tumor (group 1) or those who did not undergo elective resection of the primary (group 2). The probability of surgical resection of the primary tumor for gastrointestinal complications in group 2 was evaluated.

Results — Thirty-one and 23 patients were included in groups 1 and 2 respectively. Five patients (21.7%, 95% confidence interval CI 95% 4.9-38.5%) in group 2 required surgical treatment for intestinal obstruction due to the primary tumor. Two clinical characteristics were significantly different between groups 1 and 2: rectal localization (9.7% versus 34.7%; P = 0.03) and presence of fewer than three metastases (29.0% versus 4.3%; P = 0.03). Survival curves were not significantly different (log-rank). Median duration of survival was 21 and 14 months, respectively (P = 0.718).

Conclusion — In patients with non-resectable synchronous metastatic disease, non-surgical management of the primary tumor is a rational alternative if asymptomatic. A prospective randomized trial integrating the quality-of-life factor should be organized.

RÉSUMÉ

Métastases synchrones non résécables d’origine colorectale : faut-il systématiquement réséquer la tumeur primitive ?

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Objectif — Le bénéfice de la résection de la tumeur primitive colorectale n’est pas connu chez les malades asymptomatiques ayant des métastases synchrones non résécables. Le but de cette étude a été d’évaluer l’évolution après résection initiale ou non résection de la tumeur primitive colorectale.

Méthodes — Les données de 54 malades consécutifs ayant des métastases hépatiques synchrones d’un cancer colorectal, pris en charge au CHU de Rouen entre le 1/6/1996 et le 31/12/1999, ont été revues et réparties en deux groupes : groupe 1 : (n = 31) ; malades opérés de première intention, groupe 2 (n = 23) : malades non opérés de première intention. La nécessité de recourir dans un second temps à une chirurgie de la tumeur primitive a été évaluée dans le groupe 2. La survie des 2 groupes a été comparée.

Résultats — Au cours du suivi, 5 malades du groupe 2 (21.7 %, intervalle de confiance à 95 % IC 95 % 4,9-38,5 %) ont été opérés pour un syndrome occlusif. Les différences significatives entre les groupes 1 et 2 étaient respectivement la localisation rectale (9,7 % versus 34,7 % ; P = 0,03) et le nombre de métastases inférieur à 3 (29,0 % versus 4,3 % ; P = 0,03). Les courbes de survie (Log-Rank) n’étaient pas significativement différentes entre les 2 groupes. La médiane de survie était respectivement de 21 et 14 mois dans les groupes 1 et 2 (P = 0,718).

Conclusion — La non résection de la tumeur colorectale primitive est une attitude possible chez les malades ayant des métastases synchrones non résécables, sans symptôme critique. L’organisation d’une étude prospective randomisée est justifiée.

The full text is available in English, free of charge, on the web on: www.e2med.com/gcb.

Approximately 33,000 new cases of colorectal cancer are diagnosed every year in France, accounting for 15% of incident cancers [1]. Twenty to thirty percent of these patients have stage IV disease (International Union Against Cancer classification) with distant metastases which are accessible to potentially curative resection in 2.8 to 30% of the cases [3, 4]. When metastases are unresectable, chemotherapy is indicated if compatible with the patient’s general status. Chemotherapy improves the chances of survival at one year by 50% without deteriorating quality-of-life [5]. Moreover, metastases become resectable after chemotherapy in 3 to 34% of patients, depending on the series [6-9]. In recent studies, median survival of patients with unresectable metastases given chemotherapy ranges from 16 to 21 months [6, 10-12]. Elective resection of the primary tumor is generally proposed for patients with cancer of the colon or rectum with synchronous unresectable metastases [13, 14], but postoperative mortality is high, even when considering only scheduled procedures [15]. Surgery always induces transient immunodepression and activation of growth factors which may favor tumor growth [16]. The beneficial effect of resection of the primary tumor is unknown and little work has been devoted to the analysis of outcome in metastatic patients with an unresected primary tumor [17, 18].

The purpose of the present study was to analyze outcome in a series of patients with colorectal cancer with non-resectable synchronous metastases, comparing patients who underwent surgical resection or not of the primary tumor.
Patients and methods

Study population

The medical files of patients admitted to the Gastrointestinal Disease Unit of Rouen University Hospital between June 1st, 1996 and December 31st, 1999 for stage IV cancer of the colon or rectum (liver metastases) were reviewed retrospectively using the French disease group coding system (Programme de Médicalisation des Systèmes d’Information, PMSI) (colonic cancer: C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C19, rectal cancer: C20, liver metastasis: C78.7). The selected files were studied to identify patients with synchronous metastases. The non-resectable nature of synchronous metastases was determined during a multidisciplinary meeting of gastrointestinal cancer specialists including a liver surgeon. Pathological proof of colorectal adenocarcinoma was available in all cases. The files of all patients with non-resectable metastases of colonic or rectal adenocarcinoma were retained for analysis. Patients who underwent first-line surgery because of serious complications related to the gastrointestinal tumor (intestinal obstruction, pain, hemorrhage) were excluded from the analysis. The patients remained for analysis were divided into two groups: group 1 included patients who underwent first-line surgery for resection of the primary tumor, and group 2 included patients who did not undergo first-line surgery.

The following clinical and biological data were recorded: age, gender, general health status (WHO classification), weight loss, past history, serum hemoglobin, serum albumen, serum carcinoembryonic antigen (CEA), time of initial management. Data noted from the pathology report were: localization of the primary tumor, number and localization of metastases, and measurable surface area of the metastases estimated as the product of the two largest perpendicular diameters (> 1 cm). Treatments delivered—surgery, chemotherapy (schemes, number of protocols, number of cycles) — were recorded as well as the number of hospitalization nights required for treatment or for management of complications. Duration of follow-up was defined as the time from first consultation to death or end of follow-up (October 1, 2002).

Statistical analysis

The Mann-Whitney test was used to compare quantitative variables and non-parametric tests or the exact Fischer test as appropriate to compare qualitative variables. Kaplan-Meier survival plots were compared with the logrank test. Statistical analysis was performed with Statview 5.0. Comparisons were performed between groups 1 and 2 and between subgroups defined by number of treatments (< 3 versus ≥ 3) because of a suggested relationship between the number of treatments and survival [19]. Similarly, comparisons were performed between subgroups of patients defined by number of metastases (< 3 versus ≥ 3 and < 5 versus ≥ 5), the latter a recognized prognostic factor [3, 20].

Results

Files of 77 patients with non-resectable metastases from colonic or rectal cancer were identified. Files of 13 patients who underwent first-line surgery for a gastrointestinal complication (intestinal obstruction or acute abdomen) were excluded from the analysis. The study population thus included 54 patients, 21 men and 33 women, mean age 59.4 years (range: 26-77) with a primary colonic (n = 43) or rectal (n = 11) tumor. According to the WHO classification the patients’ general health status was: class 1 (n = 8), class 2 (n = 38), class 3 (n = 7) and class 4 (n = 1). At the first visit, median weight loss was 5 kg. None of the patients had contraindications for surgical resection of the primary tumor. Mean size of the liver metastases was 70.7 cm² (range: 3-2633); 18.5% of patients had fewer than three metastases and 37% had more than four. Serum CEA was elevated (Nl = 5 ng/mL) in 90% of patients. Mean duration of hospital stay was 16.8 days. At the time of data analysis, 52/54 patients (95%) had died (1 living, 1 lost to follow-up). Mean survival in this population was 19.4 months (range: 2-81, median 16.5). Median survival in patients with five liver metastases or more was shorter than that in patients with fewer than five liver metastases (7 versus 21 months, P = 0.004). Mean survival was not different between subgroups with < 3 or ≥ 3 liver metastases. Median survival was significantly longer in patients given at least three treatment lines (medical or surgical treatment) than those given less than three treatments (22 versus 7 months, P < 0.0018).

There were 31 patients in group 1 (elective resection of the primary) and 23 in group 2 (without elective surgery). Patient characteristics are given in table I. For patients in group 1, time in hospital for surgery was 10.9 days (mean). Peritoneal involvement was noted during surgery in 13 of these 31 patients (41.9%, 95% confidence interval (CI95%): 24.5-59.3%). There were no operative deaths. One patient died 31 days after surgery due to progression of the neoplasia without surgery-related complication. Postoperative chemotherapy was performed in all 30 patients who survived one month after surgery. Oxaliplatin and/or irinotecan was administered in 80% and 33% of patients

Table I. – Characteristics of the study population.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
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<tbody>
<tr>
<td>N = 31</td>
<td>N = 23</td>
<td></td>
</tr>
<tr>
<td>Male gender, %</td>
<td>54.8</td>
<td>69.6</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>59.8</td>
<td>58.9</td>
</tr>
<tr>
<td>Primary rectal tumor, %</td>
<td>9.7</td>
<td>34.7</td>
</tr>
<tr>
<td>WHO health status class 0-1, %</td>
<td>80.5</td>
<td>91.3</td>
</tr>
<tr>
<td>Weight loss, kg</td>
<td>4.5</td>
<td>7.8</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>33.5</td>
<td>29.8</td>
</tr>
<tr>
<td>Serum hemoglobin &lt; 7.5 mmol/L, %</td>
<td>45.2</td>
<td>52.2</td>
</tr>
<tr>
<td>CEA &gt; 5 ng/mL, %</td>
<td>87.1</td>
<td>95.6</td>
</tr>
<tr>
<td>Tumor surface area, cm²</td>
<td>59.6</td>
<td>88.2</td>
</tr>
<tr>
<td>At least three liver metastases, %</td>
<td>29.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Five liver metastases or more, %</td>
<td>35.5</td>
<td>39.1</td>
</tr>
<tr>
<td>Lung metastases, %</td>
<td>16.1</td>
<td>13.0</td>
</tr>
</tbody>
</table>

Group 1: surgical resection of the primary tumor; group 2: without first-line surgery. NS: not significant.
in group 1, respectively. In group 1, 71% of the patients were given two chemotherapy regimens. Four of these 31 patients underwent surgery for resection of metastases (12.9%, CI95%: 1.1-23.7%).

In the group not undergoing elective surgery of the primary (group 2), all 23 patients were given chemotherapy. Oxaliplatin and/or irinotecan was administered in 82% and 40%, respectively. At least two chemotherapy regimens were given to 70% of patients in group 2. Seven patients in group 2 underwent surgery: eight (21.7%; CI95%: 4.9-38.5%) for tumor-related intestinal obstruction and two (8.7%; CI95%: 0-20%) for complete resection (R0) of the neoplasia subsequent to reduction in size of the metastatic tumors. In patients who underwent surgery for intestinal obstruction during the course of disease, two had a tumor of the ascending colon and three of the descending colon. Right sided colectomy was performed in two patients, segmentary left colectomy in one, and left colostomy in two. The obstruction developed four months (range 2-8) after instituting therapeutic management. Time in hospital was 13.8 days (mean 22.1 days for eight patients with rectal cancer given radiotherapy and 4.1 days for the 14/15 patients given chemotherapy alone). The fifteenth patient, who was blind and lived alone, remained in hospital for the entire period of treatment (74 nights).

Comparison between the two groups demonstrated that two factors were significantly different: tumor location and number of hepatic metastases (table I). In group 1, rectal tumors were less frequent (9.7% versus 34.7%) and the proportion of patients with ≥ 3 liver metastases was higher (29.0% versus 4.3%). The survival curves were not significantly different between the two groups (P = 0.718) (table II). Using a five metastases threshold (≥ 5), stratification of groups 1 and 2 did not reveal any difference in median survival. Duration of hospitalization was not significantly different between the two groups, 16.3 and 13.8 days in groups 1 and 2, respectively.

Discussion

In this population, seven (30.4%) of the 23 patients who did not undergo first-line surgery for resection of the primary tumor underwent a secondary operation. Five patients (21.7%, CI95%: 4.9-38.5%) developed intestinal obstruction which was treated surgically. This result is comparable with data reported in the literature: 8.7% (CI95%: 0-28.7%) for Scoggins et al., 20.8% (CI95%: 4.6-37%) for Sarela et al. and 10% (CI95%: 3-17%) for Tebbut et al. [17, 18, 21]. Looking at these data, the overall incidence of intestinal obstruction in patients with non-resectable synchronous metastases of colorectal adenocarcinoma varies from 7% to 18%. The location of the tumor does not appear to predict development of obstruction. In our series, two of the five patients who developed obstruction had a tumor of the right colon while all six of the patients reported by both Scoggins et al. and Sarela et al. had a tumor of the left colon [17, 18]. Two patients (8.7%) underwent secondary complete resection (R0) of their neoplasia after reduction of the size of the metastases. In the series cited above, secondary surgery for curative resection (R0) was performed in 0/23 and 1/24 patients [17, 18]. Data from prospective therapeutic trials including unselected patients have yielded rates ranging from 6% to 14%, but the synchronous nature of the metastases is not mentioned [6, 7].

In our group of 31 patients who underwent first-line surgical resection, peritoneal involvement was found at surgery in 13 (41.9%, CI95%: 24.5-59.3%). This rate is rather high compared with data in the literature. Intra-operative discovery of carcinomatosis was 3.3% in a recent series of 416 patients undergoing surgery for resection of hepatic metastases [22].

Mean survival in our cohort was 16.5 months; 21 months and 14 months for groups 1 and 2, respectively (not significant). Median survival in comparable series in the literature has ranged from 10.3 to 16.6 months [17, 18]. Median survival of patients with unresectable metastases was 16 to 21 months in recent therapeutic trials [6, 10-12]. These studies included patients with metachronous or synchronous metastases, the latter known to be a factor of poor prognosis [3].

There was no significant difference in mean hospital stay between the two groups defined in this study, a result which is difficult to interpret because group 2 included two types of patients: those with cancer of the rectum treated with radiotherapy (generally delivered in an in-hospital setting in our unit) and those with cancer of the colon given chemotherapy (generally delivered on an out-patient basis). A multicentric prospective study would be useful to clarify this point.

The principal limitation of the present study was the retrospective nature of the data. We were unable to find any prospective data in the literature on this topic and few retrospective data have been published [17, 18]. The only comparative study included retrospective patients treated between 1985 and 1999 [17]. This long inclusion period introduced a supplementary bias due to variable treatment modalities and changing diagnostic and therapeutic practices between 1985 and 1999. We restricted our analysis to a shorter period (1996-1999) during which management practices (chemotherapy and surgery) did not generally change. Most of the patients (80%) were given a chemotherapy protocol including oxaliplatin and 70% received at least two different chemotherapy regimens. Future developments in endoscopic techniques will undoubtedly lead to a smaller number of surgical interventions for obstruction [23]. Comparison of two groups of patients demonstrated an imbalance which could explain the trend toward longer survival after first-line surgery. The two groups were significantly different for number of metastases, a known prognostic factor [3, 20]. More operated

Table II. – Clinical course in the patients with non-resectable synchronous liver metastases of colorectal cancers with (group 1) and without (group 2) first-line resection of the primary tumor.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Median survival, months</td>
<td>21</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Mean survival, months</td>
<td>20.1</td>
<td>18.4</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital stay, days*</td>
<td>16.3</td>
<td>13.8</td>
<td>NS</td>
</tr>
<tr>
<td>At least 3 treatments, %**</td>
<td>71.0</td>
<td>56.5</td>
<td>NS</td>
</tr>
<tr>
<td>Secondary surgery for gastrointestinal complication, %</td>
<td>–</td>
<td>21.7</td>
<td></td>
</tr>
</tbody>
</table>

* A night spent in hospital was counted as one hospital day; ** Chemotherapy or surgery. NS: not significant.
patients in group 1 (29%) than non-operated patients in group 2 (4.3%) had at least three liver metastases.

In conclusion, the results of this analysis suggest that non-resection of the primary tumor is a rational approach for patients with non-resectable synchronous metastases of a colorectal adenocarcinoma who do no have signs of intestinal obstruction. The absence of prospective data on this topic emphasizes the need for a randomized clinical surgical study integrating the quality-of-life factor.

REFERENCES