Rare hepatic metastases of colorectal cancer in livers with symptomatic HBV and HCV hepatitis

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Rare hepatic metastases of colorectal cancer in livers with symptomatic HBV and HCV hepatitis

AIM: *The liver is the most common site of metastases in colorectal cancer but metastases seem to be less common in patients with a chronically liver damage. The aim of our study was to assess the development of metachronous liver metastases in patients affected by HBV or HCV related liver diseases.*
MATERIAL OF STUDY: *We retrospectively evaluated above all the development of liver metastases and the 5-year disease free in 457 patients radically treated for colorectal cancer with healthy liver and in 31 patients radically treated for colorectal cancer affected by liver damage (HBV or HCV related).*
RESULTS: *Overall incidence of liver metastases was 9% (44/488), in particular 3.2% in infected patients and 9.4% in non-infected patients (p= 0.34).*
Our results revealed that there is no statistically significant difference between the number of positive lymph nodes of primary colorectal cancer and the number of indifferentiated cancers in infected compared with non-infected patients (29% vs 34.1% and 9.7% vs 13.6% respectively), and the 5-year disease free is better for infected patients (93% and 80%, p = 0.17).
DISCUSSION: *In infected patients we registered a better crude 5-year disease free interval and a fewer incidence of metachronous liver metastases. This difference is in agreement with other results mentioned in literature.*
CONCLUSION: *In the light of the reported data, the authors consider that the recent pathogenetic theory of the "metalloproteinase inhibitor" should be taken in account.*

KEY WORDS: Colorectal cancer, Hepatitis chronic, Metachronous metastases, Pathogenesis.

Introduction

The liver is the most common site of metastases in colorectal cancer and autopsies performed on patients who died with metastatic bowel cancer revealed in over 50% of the cases metastases only in this organ [1]. However, in colorectal cancer the presence of metastases in chronically infected livers seems to be markedly reduced. In fact, in a systematic literature review Seymour [2] reported liver metastases in 37% of healthy livers and in 23.7% in patients with diseased livers, these incidences being homogeneous in Eastern (Japan) and Western (Europe and USA) populations. Moreover, in 5,092 autopsies in patients with malignant tumors Lieber [3] reported liver metastases in 28.6% of the patients with healthy livers but only in 4.5% of patients affected by cirrhosis.

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The aim of our study was to assess the development of metachronous liver metastases in patients affected by HBV or HCV related liver diseases against patients with healthy liver who had undergone radical surgical treatment for colorectal cancer.

Methods

A total of 662 patients were surgically treated for colorectal adenocarcinoma in 1993-2005 period at our Department. We studied 488/662 (73.7%) patients who:
– underwent radical surgical resection (complete resection of the primary tumor and regional lymphadenectomy) of colorectal cancer (65 stage A according Astler-Coller, 68 stage B1, 190 stage B2, 18 stage C1, 147 stage C2);
– did not have liver synchronous metastases;
– with no prior chemotherapy or radiotherapy;
– initially adhered to the follow-up protocol, at three monthly intervals for the first three years, at six monthly intervals until the fifth year and then at 12 monthly intervals until the tenth year [4].
From this group we extrapolated 31/488 (6.3%) patients who, before developing colorectal cancer, were already affected by an ascertained symptomatic hepatitis for HBV (45.2%), HCV (48.4%) or HBV + HCV (6.4%) related infection at admission. All patients gave their informed consent to receive tests to confirm the diagnosis of HBV/HCV infection. Chronic liver insufficiency was confirmed preoperatively by hematochemical data (elevated bilirubin and transaminase concentrations and reduced albuminemia levels) and by liver ultrasonography and/or computed tomography (CT) imaging. Sixteen patients were classified in A Child group; 11 in B Child group and 4 in C Child group. Diagnosis of liver disease was confirmed by intraoperative biopsy, while no signs of preoperative liver distress (hematochemical data, HBV and HCV tests, radiologic findings) were observed in the remaining 457.
Last follow-up was December 2010. Median follow-up of the entire study series (488 patients) was 9.0 years (95% CI=8.2-9.9), in particular:
– 62.9% (307 patients) regularly attended to the follow-up between five and ten years after the surgical procedure without relapse;
– 13.5% (66 patients) dropped out at some time during the follow-up without relapse;
– 5.9% (29 patients) died during follow-up for causes not related to colorectal cancer without relapse;
– in 17.6% (86 patients) cancer relapse.
We compared the following parameters in the infected patients and the non-infected control group: a) cancer staging [patients with negative lymph nodes (N-) i.e. patients A + B1 + B2 according to Astler Coller vs. patients with positive lymph nodes (N+) i.e. patients C1 + C2 according to Astler-Coller]; b) percentage of indifferentiated carcinomas, c) delayed diagnosis (time lapse between onset of symptoms and diagnosis of colorectal cancer); d) incidence of metachronous liver metastases or metastases in other areas; e) time interval between surgical management of primary tumor vs. onset of metachronous liver metastases; f) the disease free interval.
During the study period the strategy to diagnose liver metastases was always the same: determination of blood carcinoembryonic antigen, liver ultrasound and abdominal CT according to the our scheduled follow up [5]. All liver metastases were histologically confirmed (re-surgery or biopsy) except 8 non-infected patients who did not given consent for further treatment.
Statistical analysis: chi-square test (or Fisher exact test when adequate) was used to compare groups of infected and non-infected patients according to qualitative variables such as grading and presence of metastases. Student t-test was used to compare quantitative data between groups. The median duration of follow-up was calculated using Schemper's method [6].
Disease-free interval (DFI) was calculated using the Kaplan-Meier method [7] and Rothman's 95% confidence intervals (95%CI) [8]. DFI was computed from the date of primary tumor resection to the date of liver metastasis or death or last follow-up. All tests were two-sided. Univariate analyses were performed using the logrank test[9].

Results

In the entire study series (488) who underwent radical surgical treatment for colorectal cancer 279 patients (57.2%) were men and the remaining 209 were women (42.8%). Patients' median age was 65.7 years (61.0 and 66.0 median age respectively for infected and non-infected patients, p=0.01); 165/488 (33.8%) were N+ and 65/488 (12.5%) presented an indifferentiated carcinoma. Comparison of positive lymph nodes and percentages of indifferentiated carcinomas between infected and non-infected patients is reported in Table I.

TABLE I - *A comparison of clinicopathological features between infected and non infected group*

Factors	infection n=31	noninfection n=457	chi-square
N-	22 (71%)	301 (65.7%)	p=0.56
N+	9 (29%)	156 (34.1%)	
Undiffer.	3 (9.7%)	62 (13.6%)	p=0.78
Differ.	28 (90.3%)	395 (86.4%)	

Legend: n: number of patients; N: lymph nodes; undiffer.: undifferentiated; differ.: differentiated.

Overall delayed diagnosis was 5.3 months (range 1 – 24 months), being 5.6 months (range 1 – 18 months) and 5.2 months (range 1 – 24 months) in infected and non-infected patients, respectively.
Overall incidence of metachronous liver metastases was 9% (44/488), being 3.2% (1/31; after 88 months) in infected patients and 9.4% (43/457; range 6 – 77 months) in non-infected patients, respectively (p = 0.34).
Overall incidence of metachronous metastases (liver, lungs, peritoneum) was 17.6% (86/488), being 9.7% (3/31; range 30 – 88 months) and 18.2% (83/457; range: 6 – 77 months) in infected and non-infected groups, respectively (p = 0.23).
In the non-infected patient series the 38.9% (178/457) underwent adjuvant chemotherapy, whereas only the 22.6% (7/31) in the group of infected patients (p=0.10).
Finally the 5-year disease free interval was 93% and 80% respectively for infected and non-infected patients (p = 0.17).

Discussion

After the first experience reported on hepatic metastases in cirrhotic livers in the literature more than sixty years ago [10], in the following decades only few authors have focused on liver metastases in colorectal cancer patients affected by HBV or HCV related liver diseases [11-15] and recently only in the Chinese literature probably due to the high incidence of endemic HBV infection [16,17] (PubMed search using key words: colorectal cancer, hepatic metastases and hepatitis or cirrhosis).
The incidence of patients radically treated for colorectal cancer and presenting chronic liver damage varies between 1.6% [12], 4.1% [13], 13.7% [15] to 18.4% [11], and in our study series the incidence was 6.3%. In this regard it must be stressed that the series of these authors were similar by numbers to ours; it is inevitable a numerical difference between the number of patients treated for colorectal cancer with liver healthy and patients with chronically liver damage both in our series (457 patients vs. 31) and in the rare series published in the literature (i.e. 430 patients vs. 37 [12]; 438 patients vs. 74 [13]; 635 patients vs 87 [15]; 1150 patients vs. 26 [16]).
We assessed solely subjects with chronic liver damage even if some authors [12,16] report that this difference also is present in non-symptomatic patients affected by viral hepatitis, as Song [13] underlines that such difference is much more evident when HBV infected patients present viral replication. Furthermore, Uetsuji [11] reported that while he never observed liver metastases in patients with conclaimed cirrhosis, 10% of the patients with metastases was positive for the hepatitis B surface antibody.
In our study the incidence of metachronous liver metastases in patients with chronic liver damage was lower than observed in the non-infected group. We are aware that this difference did not reach statistical significance, probably because of the inevitable smaller size of the infected group, but, in our opinion, this gap (3.2% vs. 9.4%) seems equally interesting and especially this finding is in agreement with findings reported by other authors [11-14] and by Iascone [15] and Qian [16] who report similar results for the synchronous liver metastases too.
It should also be underlined that in our infected group adjuvant chemotherapy cannot even justify the lower incidence of liver metastases. In fact in this series, as it is logical to think, we recorded a smaller number of patients receiving adjuvant chemotherapy.
In our series the only infected patient who developed metachronous liver metastases did so at 88 months after primary surgery, this being the longest disease free interval in the entire study cohort (infected and non-infected). Although other authors [12-14] did not report the time interval between the development of the primary carcinoma and metastases, we recommend follow-ups for longer than 5 years postoperatively. Song [13] and Utsunomya [12] did not mention mean duration of follow-up, whereas Gervaz [14] reported mean follow-up lasted 28 months and Qiu [17] a median follow-up time of 57 months that is much shorter than our median follow-up interval (108 months).
The mechanism by which patients with liver disease present fewer metastases than non-infected patients is still not clear. It has been suggested that the former may have a shorter life expectancy than the latter [18]. This hypothesis does not agree with our results where 6.4% of non-infected patients died during follow-up from intercurrent pathologies at a median postoperative interval of 16 months (range: 3 – 96 months). Diversely, only one of our infected patients (3.2%) died from complications related to cirrhosis 73 months after primary surgery. Moreover, results reported in other series [14] have agreed with our findings.
We have also recorded that 5-year disease free interval seems to be higher in infected patients (93% vs 80%; p=0.17); these data are supported by a lower overall number of metachronous metastases (liver, lung, peritoneum) in infected compared with non-infected patients. "*Also in this case*" we know that the difference is not statistically significant, but "*also in this case*", other authors report similar data to ours [12,13]. As age was statistically lower in infected patients respect to non-infected we completed the analyses to test whether age modified effect of infection on liver metastasis development but it did not modify the association. Furthermore, if in our series we recorded higher percentages of DFI than those reported in the literature, we like to emphasize that, overall, almost 70% of patients (323/488) are N-. In this regard only Qiu [17], in literature, refers no difference in terms of disease free interval but it is necessary to remember that his series largely consists of patients with synchronous liver metastases and he reports a higher incidence of extra-hepatic metastases in the group of infected patients.

It has been suggested that primary colorectal tumors are less aggressive in infected patients [12,13]. In reality, even if delayed diagnosis of primary colorectal cancer was overlapping in the two groups of patients studied, our results revealed that there is no statistically significant difference about N+ colorectal carcinomas and indifferentiated carcinomas between the two series (Table I).
Other pathogenic theories address the: i) opening of portosystemic shunts in cirrhotic livers [19] whereby the hepatic bed may be bypassed, even if this hypothesis has not been confirmed [14] by an increase in the number of metastases in other areas; or ii) cytotoxic liver activity on metastastic cells from T lymphocytes, Kupfer cells or tumor necrosis factor α synthesized by the same liver cells [13,17,20,21].
Recently, a noteworthy hypothesis focused on metalloproteinase, proteolytic enzymes promoting tumoral invasion. These enzymes are antagonized by some tissue inhibitors that may reduce tumor aggression and are found in greater numbers in the tissues surrounding less advanced colorectal tumors. These inhibitors have also been isolated inside myofibroblasts of diseased livers but not in the healthy liver myofibroblasts and may clarify the lower incidence of metastases observed in damaged livers [22,23].

Conclusions

In conclusion we registered in patients radically treated for a colorectal cancer and presenting chronic liver damage (HBV or HCV related) a fewer incidence of metachronous liver metastases and a better crude 5-year disease free interval respect to the non-infected group. This difference did not reach statistical significance (probably due to the different size of the two groups) but it is in agreement with other results mentioned in literature.
Further in-depth studies are required to investigate the pathogenic theories and among these particularly interesting is that relating to metalloproteinase.

Riassunto

OBIETTIVO: L'incidenza di metastasi epatiche in pazienti radicalmente trattati per un cancro colorettale sembra essere minore nei pazienti affetti da un danno epatico cronico da infezione HBV o HCV. Scopo del lavoro è stato pertanto quello di confrontare l'incidenza di metastasi epatiche metacrone in pazienti trattati per un cancro colo-rettale senza e con danno epatico.
METODI: Sono stati valutati 488 pazienti trattati per un carcinoma del colon-retto, 457 con fegato sano e 31 con fegato danneggiato da un'infezione HBV o HCV; obiettivo principale è stato il confronto tra i due gruppi di stadiazione della neoplasia, insorgenza di metastasi epatiche metacrone ed intervallo libero da malattia a 5 anni.
RISULTATI: L'incidenza globale di metastasi epatiche è stata del 9% (44/488). Nel gruppo dei pazienti infetti è stata del 3.2% e in quello dei non-infetti del 9.4% (p=0.34). Non abbiamo registrato differenze statisticamente significative tra il gruppo di infetti e quello di non-infetti per quanto riguarda il numero di pazienti con linfonodi metastatici e quello con carcinomi indifferenziati (29% vs 34.1% and 9.7% vs 13.6% rispettivamente). Abbiamo registrato un intervallo libero da malattia a 5 anni del 93% e del 80% rispettivamente per i pazienti infetti e non-infetti (p=0.17).
DISCUSSIONE: Nel gruppo dei pazienti infetti abbiamo registrato una minore incidenza di metastasi epatiche ed un migliore intervallo libero da malattia a 5 anni. Anche se questi risultati non raggiungono la significatività statistica, probabilmente a causa dell'inevitabile minore dimensioni del campione dei pazienti infetti, i risultati confermano i dati dei rari lavori presenti in letteratura.
Conclusione:Alla luce della disamina effettuata, riteniamo che la teoria patogenetica degli "inibitori delle metalloproteinasi" debba essere ulteriormente approfondita dalla futura letteratura scientifica.

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