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Original research

Liver resection for metastases from colorectal cancer in very elderly patients: New surgical horizons

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ABSTRACT

Introduction and aim: Patients with colorectal cancer (CRC) may develop liver metastases. Surgical resection remains the best treatment of choice for colorectal liver metastases (CRLM) according to resectability criteria, with a long-term survival of 25% up to 41% after 5 years. Advanced age is associated with a higher incidence and co-morbidity, particularly cardiovascular disease, as well as deteriorating physiological reserves. The aim of this study was to analyse the overall and disease-free survival for patients with CRLM according to their chronological age.

Methods: Patients with CRLM were enrolled in the study. Data on gender, age, co-morbidity, metastasis characteristics (number, size and total metastatic volume (TMV)), use of perioperative chemotherapy and operative and post-operative complications were collected. Then, according to recent World Health Organization (WHO) guidelines, the patients were grouped by age. Statistical analysis was performed using the software R (ver. 2.14.1).

Results: Hepatic resection was performed in 149 patients (21 patients in the very elderly group, 79 in the elderly group and 49 in the younger group). The three groups were comparable in terms of operative duration, transfusion rate, length of high-dependency unit (HDU) stay and post-operative hospital stay. The very elderly group showed a non-significant increase in post-operative morbidity. The 30-day and 60-day/inpatient mortality rates increased with age without any significant statistically difference between the three groups (very elderly group 4.8% and 4.8%; elderly group: 2.5% and 3.8%; and younger group 0% and 2%). At 5 years, the overall survival was 28.6% for very elderly patients (≥75 years), 33.3% for elderly patients (≥65 to <75 years) and 43.5% for younger patients (≤65 years). The 1-, 3- and 5-year disease-free survival was similar across the groups.

Conclusions: Liver resection for CRLM in carefully selected patients above the age of 75 can be performed with acceptable morbidity and mortality rates, similar to those in younger patients. Moreover, the severity of CRLM in elderly patients is proven to be lesser than in younger patients. Thus, we can

Abbreviations: CRC, Colorectal Cancer; CRLM, Colorectal Liver Metastases 3; CEA, Carcinoembryonic Antigen; CA125, Carbohydrate Antigen 125; CA19.9, Carbohydrate Antigen 19.9; DFS, Disease-Free Survival; IOUS, Intraoperative Ultrasound; OS, Overall Survival; PET, Positron Emission Tomography; SD, Standard Deviation; TMV, Total Metastatic Volume; TNM, Tumour Node Metastasis.

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conclude that advanced chronological age cannot be considered a contraindication to hepatic resection for CRLM.

1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy worldwide and the second leading cause of cancer deaths in developed countries. Moreover, it is the fourth leading cause of cancer and cancer-related deaths among both men and women in Western countries and the third most prevalent cancer in men after prostate and lung cancer, and the second in women after breast cancer [1–4].

Approximately 50–60% of patients with CRC develop metastases [5–7]: the liver is often a site of metastases, about 15% of which are synchronous (SLM) [8–10]. Resection of SLM can be performed at the time of colorectal surgery (combined resection), or several weeks later (delayed resection), depending on the complexity of the procedures and the availability of experienced liver surgeons [14,15]. Colorectal liver metastases (CRLM) may also develop metachronously, primarily within 3 years after resection of primary CRC [16].

Surgical resection remains the best treatment of choice for CRLM according to resectability criteria, with a long-term survival of 25% up to 41% after 5 years [17–19]. The 10-year survival rate is about 90% for patients with stage I disease but only 5% for patients with unresectable stage IV disease [5–14]. Patients with potentially resectable liver disease who did not undergo hepatectomy previously had poor prognosis, with a 5-year survival rate of only 0–2% [20–22].

It is well known that advanced age is associated with elevated levels of co-morbidity, particularly cardiovascular disease, as well as deteriorating physiological reserves. Several studies have reported the resection of CRLM in only 8–20% [23,24] of patients above the age of 70 [23]; however, hepatic resection and other major procedures are considered to be of high risk in these patients [25]. However, several studies in elderly patients have shown that surgery resection should be the preferred therapeutic option for CRLM [26–30].

The aim of this study was to analyse the overall survival (OS) and disease-free survival (DFS) for patients with CRLM according to their chronologic age.

2. Methods

2.1. Study design

We conducted a retrospective study between January 2008 and January 2015 (a 7-year period). The study involved surgeons from the Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna; Department of Surgery, Annunziata Hospital of Cosenza; and Department of Medical and Surgical Sciences of University "*Magna Graecia*" of Catanzaro. This study was approved by the ethics committee of the Annunziata Hospital of Cosenza, Italy, in accordance with the Declaration of Helsinki and the Guideline for Good Clinical Practice. Before the study was begun, all participants provided written informed consent.

2.2. Population

Patients diagnosed with CRLM were enrolled and grouped by age according to the recent World Health Organization (WHO) guidelines [31]: ≤65 years (younger group), ≥65–74 years (elderly group), and ≥75 years (very elderly group).

Clinical data were collected from the hospital electronic medical record system. The selective diagnostic workup for these patients included evaluating the liver function; measuring the serum levels of carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA-125) and carbohydrate antigen 19.9 (CA-19.9); performing ultrasonography, chest X-ray, abdominal computed tomography (CT), magnetic nuclear resonance (MNR), colonoscopy and fluorine-18-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET); determining the number and size of metastases; and calculating the total metastatic volume (TMV) with the expression $V=(4/3)\cdot\pi\cdot r^3$ and, in patients with multiple lesions, as the sum of the volume of each metastasis [32].

The type of procedure was defined based on the classification of liver segments by Coinaud [33]. Resection of three or more segments was defined as major hepatectomy. Liver resection was defined as 'curative' when no extrahepatic disease was detected, and when the entire hepatic tumour was removed with a sufficient surgical margin macroscopically, which was confirmed as being free from cancer infiltration under microscopic examination. Intraoperative ultrasound (IOUS) was used to guide resection [34].

The surgical technique of liver resections and different methods of vascular control to reduce intraoperative bleeding were performed [35–37]. All resections were performed with R0 intent.

The metastases that were not eligible for surgical resection were treated by radiofrequency ablation with RITA Model 1500 RF Generator (RITA Medical Systems, Inc., Mountain View, CA, USA) and excluded from this study.

In accordance with the guidelines [38–40], chemotherapy was offered to all patients based on clinical picture, volume and number of metastases, preoperative value of tumour biomarkers and performance status. The patients received systemic chemotherapy based on fluorouracil and folinic acid combined with oxaliplatin or irinotecan.

Death within 30 days from the surgical procedure was defined as operative mortality. Death after 30 days from the surgery and before discharge was defined as hospital mortality.

2.3. Statistical analysis

The chi-squared test was used to test for differences between groups. Continuous variables were expressed as mean ± standard deviation and were compared using the Mann–Whitney *U* test.

Univariable logistic regression analyses were used to assess the effect of age on post-operative outcomes. Multivariable analyses for post-operative morbidity and mortality were conducted using logistic regression models.

Continuous data were expressed as median value and range, and discrete variables as absolute and relative frequencies. To compare discrete variables, the Pearson χ^2 test and Fisher's exact test were used, as appropriate. After comparing the demographic data between the different groups, we performed age-stratified survival