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Liver resection in elderly: comparative study between younger and older than 70 years patients. Outcomes and implications for therapy

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SUMMARY: **Liver resection in elderly: comparative study between younger and older than 70 years patients. Outcomes and implications for therapy.**

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Background and aim: *to identify the factors that could influence the outcome of the old aged patients underwent liver resection for hepatocellular carcinoma (HCC) or colorectal liver metastases (LMCRC).*

Patient and methods: *the Authors identified 51 patients older 70 years-old over 12-years period underwent resection for HCC (n 26) or for LMCRC (n 25). This group was compared with a cohort of 93 patients younger than 70 years who underwent resections in the same period. We have evaluated the results in terms of peroperative morbidity and mortality.*

Results: *the mean age of 51 elderly patients was 74 years-old. Thirty-five were treated with anatomical resection. Cirrhosis was present in 26 patients while 27 had co-morbidities. Thirteen patients developed complications and the mean age of these were 76 years compared with 73 of the patients who have not (p= .01). No mortality was registered. The cirrhosis, blood transfusions, anatomical resection and diameter of the lesion did not influence the outcome.*

Conclusions: *our results indicate the age per se should not be considered a contraindication for surgery, that proved to be safe and curative therapy, but showed that old age, using 75 years as a cut-off, in association with at least one comorbid medical condition could be considered as relevant factor of morbidity.*

RIASSUNTO: **La resezione epatica negli anziani: studio comparativo tra soggetti più giovani e più anziani di 70 anni. Prognosi e considerazioni terapeutiche.**

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Obiettivi: *identificare i fattori di rischio che possono influenzare la prognosi postoperatoria dei pazienti anziani operati di resezione epatica per carcinoma epatocellulare (HCC) o metastasi da cancro del colon-retto (LMCRC).*

Pazienti e metodi: *gli Autori hanno selezionato 51 pazienti con più di 70 anni in un periodo di 12 anni, che sono stati trattati con resezione epatica per HCC (n 26) o per LMCRC (n 25). Questo gruppo è stato comparato con un altro di 93 pazienti più giovani di 70 anni. Abbiamo valutato i risultati in termini di morbilità e mortalità.*

Risultati: *l'età media dei 51 pazienti anziani era di 74 anni. Trentacinque sono stati trattati con resezione anatomica. La cirrosi epatica era presente in 26 mentre 27 avevano fattori di comorbidità. Tredici pazienti hanno avuto complicanze: l'età media di questi era di 76, comparata con 73 di quelli che non ne hanno avute (p= .01). Nessuna mortalità. La cirrosi, le trasfusioni di sangue, la resezione anatomica ed il diametro del tumore non hanno influenzato la prognosi.*

Conclusioni: *i risultati indicano che l'età non deve essere considerata una controindicazione per la chirurgia epatica che è provato essere efficace e terapeutica, ma abbiamo osservato che 75 anni sono un limite che in associazione di comorbidità può essere considerato fattore di rischio di complicanze.*

KEY WORDS: Hepatocellular carcinoma - Liver metastases - Colorectal cancer - Liver resection - Elderly.
Carcinoma epatocellulare - Metastasi epatiche - Cancro del colon-retto - Resezione epatica - Anziani.

Introduction

The worldwide improvement of social conditions, an incessant development and advances in medical knowledges, have contributed to a constant and progressive increase of the average life expectancy which is currently greater than 70 years. Elderly patients are becoming much more frequent candidates to undergo surgery both emergently and electively. In spite of this, there is a certain reluctance to schedule these patients for operation because they often have lower life expectancy, cognitive decline and co-morbidities that increase perioperative risk.

On the other hand, the frequency of cancer is si-

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gnificantly higher in the elderly and liver is involved by two leading worldwide cancer as a primary site for hepatocellular carcinoma (HCC) or as a site of metastasis by colorectal cancer (LMCRC). For these patients, the resection is the gold standard treatment.

We present in this study 51 patients older than 70 years treated with liver resection for HCC (n = 26) and for LMCRC (n = 25). We have analysed the clinical and pathological features, pointing out the characteristics of two groups of patients and describing the surgical approach and matching these with an homogeneous group of patients (n 93) younger than 70 years. The aim of the study is to identify the factors that could influence the outcome in the elderly patients.

Patients and methods

This is a retrospective study. The Authors present a review of 392 patients who underwent liver resection in the period January 1993 through June 2005 at the IV Unit of Surgery at Regional Hospital in Treviso, Italy. The patients were selected from a prospective hepato-biliary database and a registry of hepato-biliary surgery. Patients were grouped according to age older (O group) or younger (Y group) than 70 years. Ninety patients were excluded: 71 because treated for trauma and 19 due to incomplete clinical records. All patients in this study underwent complete resection of the gross tumour. The patients in O group underwent resection for HCC or LMCRC. The tumour histology of the patients in Y group was more heterogeneous and includes the following categories: HCC, cholangiocarcinoma, metastases from breast cancer, gastrointestinal cancers, reproductive tract cancers (primary testicular or gynaecologic), melanoma, renal cancer, or miscellaneous. Liver cirrhosis was present in 73 cases, 26 in O group (51%) and 47 in Y group (51%).

The data included patient's age, gender, co-morbid diseases, diagnosis, operative procedure, transfusion requirement, pathologic features, morbidity and mortality. For all patients the following tests were carried out: blood tests with AFP values, CEA and Ca 19.9 oncoantigens, hepatitis B surface antigen (HbsAg) and hepatitis C antibody (HCVAb), ECG, chest X-ray, right upper quadrant ultrasonography (US) and CT scan and\or RMN.

The cirrhotic patients were previously selected using the Child classification. For all patients older than 70 years, except those who underwent urgent operations, a detailed evaluation of cardiovascular function was carried out. All patients were treated with prophylactic broad-spectrum antibiotic. Prophylaxis for deep venous thrombosis with low-molecular weight heparin was employed in all patients. Postoperative pain control was obtained using neuroleptoanalgesia (tramadol, ketorolac and morphine) for 3 days, and then only in case of need. A right hockey-stick incision was used as favoured laparotomy.

Staging laparoscopy was performed in selected patients. Intraoperative US was performed as the first step. The liver resections were also described by the Couinaud segments resected (1-3). Non anatomic resection denotes a non segmental resection of the liver surrounding the cancer. The liver dissection was usually performed with Kelly-clasia and each vessel was legated or clipped. During the last two years, the Ultracision® dissector (Ethicon Endo Surgery) was used. The Argon beam coagulator was used on the cut surface of the liver. Macroscopic and microscopic histopathological tests were carried out on the specimen. The grade of cell differentiation in case of HCC was classified according to Edmondson's system. The AJCC and TNM staging system were used for classification. Maximal diameter of the specimen was taken as the tumour size; in case of multiple HCC or LMCRC, the size of the largest tumour was considered as the maximal diameter.

Oral intake was started as soon as tolerated. The abdominal drains were removed as soon as possible unless a biliary fistula was documented. Postoperative complications were documented and classified as minor or major. Wound infections and urinary tract infections were considered minor complications. Bleeding, biliary fistula, pulmonary infections and deep venous thrombosis were considered major complications. Perioperative mortality was defined as death in the same admission hospital or within 30 days of the date of operation. All the operations were carried out by experienced hepato-pancreato-biliary surgeons. All patients older than 70 years and all patients with major hepatic resection were monitored in the intensive care unit over the immediate postoperative period.

The patients over 70 with underlying liver condition or judged ASA 4 were excluded from surgery and directed to alternative procedures such as radiofrequency ablation, percutaneous ethanol injection, cryotherapy and chemoembolization.

Statistical analysis

The main purpose of the study was to evaluate in-hospital morbidity and the outcomes with respect to age. These results obtained were then compared to the ones achieved in patients younger than 70 years.

The following factors were assessed as prognostic factors: age, comorbidity, type and extent of hepatic resection (anatomic vs. non anatomic resection, < 3 segments or more than 3), allogenic blood transfusions, and postoperative complications. The patients' baseline characteristics are expressed as mean ± standard deviation (SD) for continuous data and as frequency for categorical data. The study population was divided in two groups according with to age (younger and older than 70 years). The O group was the study group. After matching for year of resection, sex, and underlying liver disease, 93 younger than 70 who underwent liver resection were selected as control group (Table 1). The main outcomes were: hospital stay, early (< 30 days) postoperative morbidity, mortality and outcomes (Table 2). Early postoperative outcomes was compared between the groups (Table 3). After this first analysis, the study group was divided in two subgroups according to the presence of postoperative complications: thus 13 patients were in the "morbidity group" and 38 in the "non morbidity group" (case–control study). In the comparison of different subgroups, continuous variables were compared using logistic regression. Categorical variables were compared using Chi-squared or Fisher's exact tests as appropriate. A receiver operating characteristic (ROC) curve was used to identify the most sensitive and specific cut-off point of patient age in predicting the occurrence of post operative complications (Fig. 1). The calculations were done with the JMP package (1989-2003 SAS Institute Inc.).

TABLE 1 - PATIENTS CHARACTERISTICS.

Variable	Patients > 70 years (n=51)	Patients < 70 years (n=93)
Sex (male)	37 (73%)	62 (67%)
Mean age ±SD (years)*	74±3.4	58±1.0
Mean size of tumor	9±11.8	12±16.7
Cirrhosis	26 (51%)	47 (51%)
Anatomical resection	35 (69%)	60 (65%)
Blood transfusions	21 (41%)	31 (33%)
Comorbidity	27 (53%)	33 (33%)

TABLE 2 - PATIENTS CHARACTERISTICS. COMPARISON BETWEEN THE "MORBIDITY" AND "NON MORBIDITY" GROUPS.

Variable	O group (n=51)	Morbidity group (n=13)	Non morbidity group (n=38)	P value
Sex (male)	37 (73%)	9 (70%)	28 (74%)	.73
Mean age ± SD (years)	74 ± 3.4	76 ± 4.1	73 ± 2.9	.01
Mean size of specimen ± SD (cm)	9 ± 11.8	10 ± 14.8	9 ± 10.8	.73
Cirrhosis	26 (51%)	18 (47%)	8 (61%)	.52
Anatomical resection	35 (69%)	8 (62%)	27 (71%)	.73
Blood transfusions	21 (41%)	7 (54%)	14 (37%)	.33
Comorbidity	27 (53%)	9 (69%)	18 (47%)	.21
Hospital stay ± SD (days)	10 ± 4.6	14 ± 6.4	9 ± 3.0	<01

TABLE 3 - EARLY POSTOPERATIVE OUTCOMES OF CASE (O GROUP) AND CONTROL GROUP (< 70 YEARS).

Variable	Patients > 70 years (n=51)	Patients < 70 years (n=93)	P value
Hospital stay	37 (73%)	62 (67%)	0.06
Mortality	0	0	ns
Morbidity	13 (25%)	9 (10%)	.01

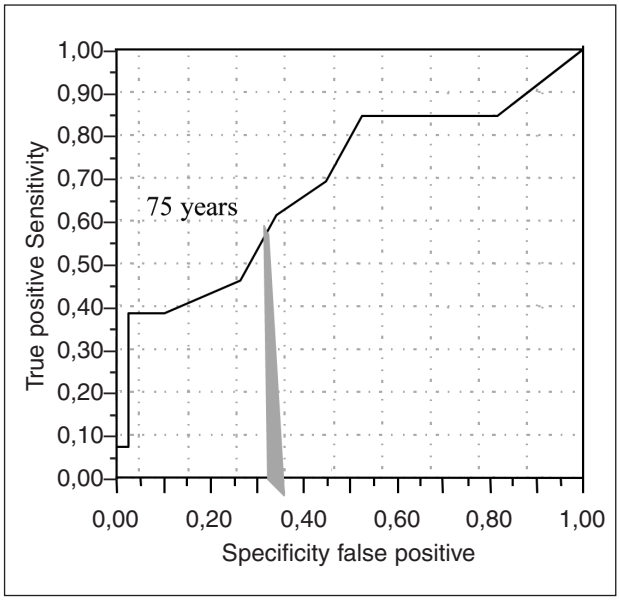

Fig. 1 - Determination of the best cut-off value of patient age in determining the risk of postoperative complications by means of the ROC curve method.

Results

Over a 12-year period 392 patients underwent liver resection in our Unit. Fifty-one were older than 70 year (O group). There were 37 males and 14 females with median age of 74±3.17 (max 84, min 70). The clinical features of these patients were compared with patients younger than 70 years (Y group, 93 patients) who also underwent liver resection. In Y group there were 62 males and 31 females with median age of 58±1 (max 69, min 19). Thirty-five comorbidities were present in 27 patients in O group and the most common comorbid condition was cardiovascular diseases (21 pts) followed by diabetes mellitus (6 pts). The complete list of comorbidity is listed in Table 4. Liver cirrhosis was associated with HCC in 22 cases and was related to virus C infection in 11 patients, while 10 patients had alcoholic cirrhosis; 1 patient had mixed cirrhosis (alcoholic and hepatitis C virus infection). All patients but 3 were in Child class A; the 3 patients in Child class B underwent surgery after haemoperitoneum due to rupture of HCC. In O group 14 right lobectomies, 2 left lobectomies, 19 anatomical segmentectomies and 17 non anatomic resections were performed; twenty-one patients received 69 units of red blood cells (Table 4). A total of 6 patients in O group underwent urgent surgery for HCC rupture. Two patients in O group underwent repeated resection for LMCRC. The anatomic resections were slightly higher in O group respect Y group (69% vs. 65%, p=*ns*) while the need to transfuse was higher in Y group (41% vs. 31%, p=*ns*). Postoperative complications were 15 (14.7%) in Y control group and 13 (25%) in O study group and this difference was statistically significant (p= *.01*). The median age of the cohort of the

TABLE 4 - PREOPERATIVE ASSOCIATED CONDITIONS AND INTRAOPERATIVE PROCEDURES IN OLDER AGE PATIENTS (O GROUP).

Type of resection	Liver resections (n=26) for HCC	Liver resections (n=25) for metastases	Condition associated	HCC (n)	Metastases (n)
Right hepatectomy	6	9	Arterial hypertension	6	7
Left hepatectomy	1	1	Diabetes mellitus	3	3
Segmentectomy*	12	7	Peripheral arterial obstruction	2	-
Non anatomic	9	8	Heart insufficiency	1	-
Diameter of specimen (cm)	10.9	21.11	Cardiosclerosis	1	1
Diameter of tumour (cm)	4.31	4.41	Myocardial infarction	1	2
Pedicle clamping			AF	1	1
Yes	14 (53%)	8 (32%)	Ictus cerebri	1	-
Mean duration (min)	19.21	11.6	Gastric ulcer	1	-
PBRC transfusions			Hypothyroidism	1	-
Yes	10 (38%)	11 (44%)	Deep vein thrombosis	-	1
Number of units	34	35	Pulmonary tuberculosis	1	-

**One or more than one segment.*

patients with postoperative complications (Morbidity group) was 75.9 years-old. Three patients required reoperation for bleeding (O group 1 patient, Y group 1 patient) and for bile leak (Y group 1 patient). Subfrenic abscess with biliary fistula and fluid collection were observed in 10 patients (5 in O group and 5 in Y group). Five of these required ultrasonography guided percutaneous drainage.

The only statistically significant difference between the study groups was patient age older than 75 years (p= *.01*) and is marked when we have analyzed the morbidity and non morbidity subgroups (either in O group, Table 2). The best cut-off value of patient age in predicting postoperative morbidity was 75 years (Fig 1). In fact, among 21 patients (41%) older than 75 years, the postoperative morbidity was 38% versus only 17% of the 30 (59%) younger than 75 years.

The postoperative stay in hospital was 10,8 days for O group and 9,68 days for Y group (p= *ns*). No significant difference in terms of complications was found between anatomic vs. non anatomic resections (p= *ns*). The significant difference in hospital stay (p< *0.01*) between morbidity and non morbidity groups, is evidently a consequence of postoperative morbidity.

Discussion

The improved global knowledge in medicine, a better understanding of the segmental liver anatomy as well as the refined surgical techniques in controlling haemorrhage, have combined to cause a meaningful drop in the morbidity and mortality post resection and, as a result, the surgical treatment of liver malignancies has increased worldwide. In the last decade similar results were obtained even in elderly (4, 5). In our experience, patients older than 70 years were treated in the same manner as the younger ones and the results are in line with those reported in literature. We have zero mortality, but interestingly, the average age of the 38% of the patients who developed complications was 75.9 years-old versus 73.3 of the patients who have not and this difference was statistically significant (p= *.01*).

Although the elderly patients usually have alterations due to the advancing age or a variability of comorbidities, it is quite clear that only cirrhosis itself may increase morbidity and mortality. Several studies report that liver surgery gives similar results for all age group (6-10). The mortality rate reported by specialized centres is less than 5 % while the experience with grafts has demonstrated that aging does not affect meaningful liver function with acceptable results after transplant of an elderly liver (11-14).

Heavy alcohol abuse and HCV infection are two of leading causes of cirrhosis and both in elderly stands out above all the others while considering Italy an intermediate risk-area, the distribution of HCC is increasing and mean age nowadays is 67.3 years (15, 16).

More than 50 per cent of the patients treated for colorectal cancer are older 70 years and 33-50 per cent of all these develop LMCRC after the first operation. In spite of this, only 8-20 per cent underwent resection and it is worth remembering that untreated patients have an average survival of only 4.5 to 5.6 months (17, 18)

As both life expectancy and the prevalence of these malignancies are steadily increasing at the same time as the malignancies, the benefits obtainable with liver re-

section should be reconsidered. To achieve better results in our elderly population a proper selection of patients in terms of liver functional reserve and co morbid conditions is mandatory. An effective evaluation of these two parameters may be of great help in reducing morbidity and mortality. Child status, liver disposition of volumes and indocyanine tests are used to estimate liver residual function but different considerations are related to the comorbidities.

In fact the majority of the elderly may suffer from more than one comorbid disease or for many reasons do not have a good performance status. Cardiovascular diseases and diabetes mellitus are two of the more frequent conditions and were also reported to be significant risk factors, especially when associated with cirrhosis and advanced age (19-21).

The alterations due to the advancing age together with comorbidities should play a fundamental role in poor outcomes. In over 12 year's period, only 51 patients older than 70 years underwent surgery after assessment of by our liver team. It is therefore clear that we are considering a highly selected group of patients.

The exclusion from surgery of the high risk patients allows us to avoid useless treatment but some Authors, after retrospective analysis of 297 patients who underwent resection for LMCRC, reported that no subgroups of elderly patients ruled out on principle from surgery were found (22).

In a recent review of 82 patients, the outcomes obtained on patients treated with surgical resection of HCC larger than 10 cm were compared to those of patients treated with surgical resection of HCC lower than 10 cm. The results achieved in the two groups in terms of overall survival proved similar and the Authors emphasized the role of the control of intraoperative bleeding as well (23). In fact it is well known that haemorrhage and needs for transfusions are closely associated with worse prognoses (24). Actually, in our study group, tumour dimension did not influence the outcome (p= *ns*).

In O group of the present experience, the anatomic resection was used more frequently than in Y group; accordingly the need of transfusion was lower (19 patients vs. 39 with 65 units vs. 119 respectively). But the transfusion rate and the anatomical resection not influenced the outcome (p= *ns*).

Although anatomical resection should be considered the treatment of choice due to the greater oncological value and a lower incidence of bleeding, as well reported in literature, there are not difference in terms of morbidity and mortality after anatomic or non anatomic resections. Therefore some groups of patients could profit by limited non anatomical resection as long as an R0 resection is still achieved (25-29).

In the present study 6 patients (24 % of the patients with underlying cirrhosis) underwent urgent resection after rupture of HCC. The rupture of HCC which is a life-threatening condition is quite impossible to prevent and remains the second most common cause of spontaneous haemoperitoneum with a variable incidence from 4 to 24 % and frequently oblige to carry out an urgent operation (30, 31).

Liver surgery has a relatively high incidence of postoperative complications and a proper treatment of these is mandatory to lower mortality. In fact many complications can be treated conservatively or with percutaneous maneouvres (drainage of abscess or biliary fistula). A second operation near the first-one or in patients with sepsis may be devastating in the elderly.

Therefore appropriate selection as well as a proper treatment of the complications might dramatically improve the results. The above considerations along with the absence of competitive therapies, would suggest that elderly patients suitable for liver resection, should be directed to a high volume center.

Our study, provides further evidence that the aged *per se* should not be considered a contraindication for liver resection: it is safe, effective and curative therapy in elderly in elderly as well. However age greater than 75 years, in association with more than one medical comorbidity could be considered relevant factor morbidity.

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