



Elderly and very elderly patients with hepatocellular carcinoma.

Strategy for a first line treatment

Ann. Ital. Chir.
Published online 29 April 2013
pii: S0003469X13020368
www.annitalchir.com

Stefania Brozzetti*, Mario Bezzi**, Giuseppe Maria De Sanctis***, Gian Marco Andreoli**, Monica De Angelis*, Michelangelo Miccini*, Francesca Galati**, Valentina Panetta°, Caterina Furlan***, Domenico De Santis*, Giorgio De Toma*, Adriano Tocchi*

“Sapienza” University of Rome Medical School, Rome, Italy

**Department of Surgery “P. Valdoni”*

***Department of Radiology*

****Department of Infectious and Tropical Disease*

°L'altrastatistica s.r.l., Consultancy & Training, Biostatistics office, Rome, Italy

Elderly and very elderly patients with hepatocellular carcinoma. Strategy for a first line treatment

AIM: Health-status of elderly patients with hepatocellular carcinoma (HCC) may limit surgical approach; other options are thus auspicious.

METHODS: The authors reviewed 98 selected patients, aged 65 to 90 years, with 149 HCC treated between 2002 and 2011. According to the extent of malignancy, health status and treatment, patients were divided into 3 groups. Sixty-one, submitted to major and minor curative resections, were in group A and B while group C included 37 patients, unsuitable for high-risk procedures and percutaneous ablation, submitted to intraoperative-radiofrequency ablation (IRFA) alone or combined with minor resections. Assessment of safety and therapeutic efficacy of this management was evaluated.

RESULTS: A postoperative mortality rate of 1,02% and an overall survival rate at 5 years of 62.3% were observed. Indeed matched post-operative morbidity and mortality rates of A, B, C groups were 45%, 8%, 16.21% ($p < 0.004$) and 9 %, 0%, 0% ($p = 0.112$) respectively. 3 years overall-survival was not statistically different ($p = 0.585$). However 5 years survival rate and disease-free-survival rate were significantly higher in patients of group A and B ($p = 0.003$; $p < 0.001$).

CONCLUSION: Treatment strategies to minimize treatment-related morbidity and mortality have resulted satisfactory for early and late outcomes of an heterogeneous group of elderly patients with HCC.

KEY WORDS: Elderly and very elderly patients, First line treatments, Hepatocellular carcinoma.

Introduction

Hepatocellular carcinoma is the fifth more common cancer in the world and its incidence is increasing¹⁻³ in par-

ticular in elderly population⁴. In the West Countries, HCC incidence peaks in men aged 70-74 years⁵ and patients older than 75 years, account for 22% of HCC patients⁶.

Surgical resections of HCC, in patients unsuitable for liver transplantation, still provide the best opportunity for long-term results, including disease-free and overall survivals⁷⁻¹⁰.

Aging of population with HCC have led hepatobiliary surgeons to evaluate and operate on increasingly older patients and to develop different criteria to treat these individuals. Even if specific operative complications are a concern, advanced age is no longer necessarily con-

Pervenuto in Redazione Settembre 2012. Accettato per la pubblicazione Dicembre 2012

Correspondence to: Stefania Brozzetti, MD, Department of Surgery “P. Valdoni”, University of Rome “Sapienza” Medical School. Via Michele di Lando 72, 00162 Rome, Italy (e-mail: stefania.brozzetti@uniroma1.it)

sidered a contraindication for hepatic surgery in elderly¹¹⁻¹³. However, the prevalence of comorbid conditions increases with aging and confers a risk for adverse outcomes after major hepatic resection, especially in patients with underlying chronic liver diseases^{1,14,15}. Otherwise minor liver resections could result inadequate in many patients because of the extent or location of malignancies. The opportunities for treating patients with HCC have been significantly increased by the development of technologies¹⁶⁻¹⁹. Radiofrequency ablation (RFA) has emerged as the most powerful, effective, and well-tolerated procedure for tumor destruction and as the primary modality to treat patients who cannot withstand surgery²⁰⁻²². However, not all lesions are suitable for percutaneous RFA because of size or location in the liver^{21,23}. Intraoperative radiofrequency ablation (IRFA) has enlarged the number of patients candidates for ablation because this procedure enables the treatment of critically sited lesions^{21,24,25}. The objective of this study was to analyze the effectiveness of different first line treatments in a surgical setting developed to minimize procedure-related risks in different elderly patients with HCC, unsuitable for transplantation or percutaneous RFA.

Material and Methods

PROCEDURES

Clinical, operative, pathologic data, immediate and long-term outcomes were collected using a prospective, single-institution database of patients over age 65 with HCC admitted for treatment at Department of Surgery "P. Valdoni" University of Rome "Sapienza", between January 2002 and December 2011. A multidisciplinary team of hepatobiliary surgeons, interventional radiologists, oncologists, and anesthesiologists, all members of an Italian Oncologic Geriatric Group (GOGI) study, cooperated in planning the treatment of these patients. Information was collected with regard to sex, age, comorbidities, alcohol abuse, and positive serology for hepatitis B or C virus (Table I). All patients underwent routine baseline examinations, including complete blood chemistry tests, standard chest x-ray, analyses of blood gases, respiratory function tests, electrocardiography, and second-level tests, such as echocardiography with estimation of ventricular kinetics and ejection fraction¹⁵. Additional investigations, such as exercise tolerance electrocardiography or perfusion myocardium scintigraphy, were done only in patients with a medical history of coronary artery disease or if required by results of baseline or second-level examinations. Carotid vessel color doppler echo-ultrasonography was performed in patients with a positive history of cerebral vascular disease. Anesthesiologic risk according to American Association of Anesthesiologists (ASA) scale²⁶, geriatric risk according to Comprehensive Geriatric Assessment (CGA) scale

²⁷⁻²⁹, and surgical risk according to a score used during previous 10 years at our Institution (Table III) were determined in all patients. CGA scale²⁷ divides elderly patients in three classes. Class 1: fit patients with good nutritional status and physical performance, who have the same therapeutic indications as younger patients. Class 2: intermediate patients with not life threatening comorbidities, in whom therapeutic indications should be adapted. Class 3: frail patients with severe comorbidities and constant limitation of daily life. In these patients the only therapeutic indications is a supportive care. Patients classified as ASA Class IV, CGA Class 3 and with a Surgical Risk score exceeding 15 were considered unsuitable for any surgical treatment and were excluded from the present study. Liver function was evaluated by means of Child-Turcotte-Pugh classification. A score greater than 8 was considered an absolute contraindication for surgery, as were total serum bilirubin levels of 3 mg/dL, prothrombin activity less than 50%, an international normalized ratio (INR) of 1.7 or greater. In patients candidate to major resection, preoperative workup included the study of hepatic venous pressure gradient and the indocyanin green plasma disappearance test. No patient submitted to major resections had hepatic venous pressure gradient > 10 mmHg nor indocyanin green plasma disappearance rate at 15 min less of 15%, (by LiMON[®], impulse Medical System). The stage of tumor disease was evaluated by imaging, including B-type ultrasonography (US), helical computed tomography (CT), and magnetic resonance imaging (MRI), and by the serum level of α -fetoprotein.

The volume of remnant liver parenchyma was calculated, based on planned resection, by means of CT scanning according to Nagino and colleagues³⁰. Patients were divided into three groups. Group A included patients with large or central lesions, defined "Fit Patients" (CGA 1; ASA I-II), suitable for high-risk procedures (right/left or extended hepatectomies), with an estimated residual liver volume of more than 35%. Group B included patients with tumor requiring minor surgery (less than three segments of Couinaud), "Fit or Intermediate Patients" (CGA 1-2) with ASA scale I-II-III. Patients with more than one lesions or with lesion of the dome, classified as "Intermediate Subjects" according to CGA criteria (CGA 2) not having "severe" functional frailty, ASA II-III, but for whom the risks of major or central resections were considered to overwhelm the potential benefits, were included in group C. These patients, because would not benefit from minor surgery for location or number neither from percutaneous RFA because of size or location of tumor, were treated with IRFA either alone or combined with limited peripheral resections. All three groups had no more than 3 lesions. The Brisbane 2000 system nomenclature was adopted to describe anatomic liver resection in three groups³¹. Wedge resections with maximal sparing of liver parenchyma were used only to remove superficial, central, small

Table I - Demographic and clinical data

	Group A (n=11)	Group B (n=50)	Group C (n=37)
AGE, Y, MEAN (SD) [RANGE]	66.8 (2.1) [65-71]	72.8 (5.9) [65-90]	74.4 (5.9) [65-89]
SEX			
Male	10	36	15
Female	1	14	22
Aetiology			
Hepatitis C virus	6	33	17
Hepatitis B virus	3	20	20
Alcohol	0	0	2
Other	2	0	0
Comorbidity			
Cardiovascular			
Hypertension	4	23	30
Coronary Heart disease	0	4	7
Miocardial Infarction	0	1	3
Valvular heart disease	0	2	2
Cardiac Arrhythmias	1	2	7
Vascular			
Cerebrovascular disease (TIA)	0	1	2
Stroke	0	1	0
Pulmonary			
COPD	4	10	9
Asthma	0	5	2
Diabetes			
Insulin-dependent	0	2	3
Non Insulin-dependent	0	3	1
Renal Insufficiency	0	0	1
Overweight/obesity	0	3	3
Underweight	0	1	1
ASA class			
I	7	17	0
II	4	32	9
III	0	1	28
CGA CLASS			
1 ^a	11	41	0
2 ^b	0	9	37
Treated nodules, n, (mean), [range]	17 (1.5) [1-2]	55 (1.1) [1-3]	77 (2.0) [1-3]
Size of lesions, cm	1.0-6.0	1.5-6.0	1.0-8.0
No. resected nodules	17	55	18
No. ablated nodules	0	0	59
Type of resection			
Extended right hepatectomy	2	0	0
Right hepatectomy	5	0	0
Left hepatectomy	4	0	0
Bi-segmentectomy	0	4 (sg 2,3); 5 (sg 6,7); 1 (sg 4b,5)	2 (sg 6,7); 1(sg 5,6)
Segmentectomy	0	35	11
Wedge	0	7	1
Median intraoperative blood loss, mL [range]	400 [300-650]	150 [50-200]	100 [50-450]
Use of portal clamping	6	0	2 RFA/2 resection
Median length of portal clamping, min, [range]	20 [15-30]	0	18 [12-25]
Median length of surgery, min, [range]	280 [240-350]	210 [150-350]	170 [100-270]

ASA, American Society of Anesthesiologists; CGA, Comprehensive Geriatric Assessment; COPD, chronic obstructive pulmonary disease; ^a Class 1 -fit patients - of CGA with no functional dependence in Activity of Daily Living (ADLs) and in Instrumental Activity of Daily Living (IADLs), no relevant comorbidities and no geriatric syndrome (dementia, delirium, depression).

^b Class 2 -intermediate patients -of CGA Comorbidities present but not life-threatening, dependence in one or more IADLs but not in ADLs, mild memory disorder and depression, no geriatric syndromes.

^c Exophytic lesion.

Table II - Location of lesions (Couinaud segments)

Group A (n=17)		Group B (n=55)		Group C (n=77) Resected and/ or ablated	
Location	No lesions	Location	No lesions	Location	No lesions
II	1	I	1	I	1/3
II-III	2	II	4	II	2/4
II-III-IV	1	III	7	III	2/0
III-IV	1	IVa	1	IVa	0/16
IVa	2	IVb	2	IVb	0/3
IVb	1	V	9	V	4/8
V-VI	1	VI	24	VI	7/0
VI	2	VII	9	VII	2/4
VII	1	VIII	2	VIII	0/21
V-VIII	2				
V-VIII - IVa	1				
V-VII-VIII	2				

tumors. No procedure was performed laparoscopically. Intraoperative ultrasonography was performed routinely to confirm data of preoperative imaging, to mark the plane of parenchymal transection³², and to guide, in case of IRFA, the placement of electrode. IRFA was performed according to a standard protocol by means of a Cool-tip Radiofrequency System (Radionics, Tyco Healthcare Group, Burlington, MA USA). A single electrode with a 2 or 2.5 cm exposed tip was used for tumors of 2 cm or smaller in diameter, and a cluster electrode consisting of 3 parallel electrodes was used for tumors about 3 cm in diameter. Each ablation cycle lasted from 10 to 12 minutes. The Pringle maneuver was adopted during ablation of lesions proximate to large portal vessels. Data related to size, number, and distribution of HCC, number and type of resections, number of IRFA treatment, operative time, intraoperative blood loss, use and length of portal clamping were also collected (Table I, Table II). All patients were admitted to a sub-intensive postoperative care unit for 12 to 48 hours. Major operative morbidity was defined as the occurrence of one or more potentially life-threatening events. Minor operative morbidity was defined as the occurrence of non-life-threatening events. Length of hospitalization and immediate outcomes were registered (Table IV). Treatment was defined as "cleared" when tumor was completely removed with a surrounding clear margin of at least 1 cm, either when the complete tumor coverage was assessed by postoperative CT in case of IRFA.

US and α -fetoprotein serum level controls were performed every six months after treatment. MRI or CT scanning was performed one month after IORF, then at the first year after procedures and successively every two - three years or when recurrence was suspected at US. In very small (≤ 0.5 cm) suspected recurrence, US was

Table III - Surgical risk

		Scoring system (1-3)
Age, y	≥ 65	1
	≥ 75	2
	≥ 80	3
Health status and functional reserve	ASA I-III; CGA 1-2	1-3; 1-2
Type of surgery	Minor	1
	Intermediate	2
	Major	3
Surgical experience	Good	1
	Intermediate	2
	Little	3
Staff experience	Good	1
	Intermediate	2
	Little	3
Postoperative course (hospitalization, difficulties in postoperative course)	Easy and short	1
	Long with difficulties	2

ASA, American Society of Anesthesiologists; CGA, Comprehensive Geriatric Assessment.

adopted for a very intensive three months follow up, to control the growing. Distant intra-hepatic recurrence was defined as a new tumor occurring away from the resected or ablated area. Long-term outcomes including overall survival, disease-free survival, distant recurrence, local or disseminated recurrence, were compared.

STATISTICAL ANALYSIS

Comparisons between groups were examined by χ^2 tests for dichotomous variables (or the Fisher exact test when appropriate), and ANOVA or Student *t* test for continuous variables. To compare non-parametric data, the Kruskal-Wallis test was used, and each group was compared with the others by the Mann-Witney test.

In survival analysis, patients were censored if they had not experienced the end-point of interest at the end of the follow-up period. Kaplan-Meier estimates of overall survival time and disease-free survival (without recurrence) were compared using the log-rank test. Bonferroni's correction was applied when appropriate. Stata 12.0 was used for all analysis. $p < 0.05$ was considered statistically significant.

Results

The study included 61 men and 37 women, with hepatocellular carcinoma, aged 65 to 90 years (mean 72.7 \pm

Table IV - Comparison of groups A, B, and C

	Group A (n=11)	Group B (n=50)	Group C (n=37)	P value
MORBIDITY	45% (n=5)	8% (n=4)	16.21%(n=6)	<0.004 0.095 C vs A 0.313 C vs B 0.007 B vs A
<i>Major operative morbidities</i>	No. patients	No. patients	No. patients	
Transient Liver failure	1	–	–	
Intra-abdominal hemorrhage	1 ^b	–	–	
Biliary fistula	1 ^c	–	–	
Infected ascites	–	–	1 ^f	
Cardiologic failure	1 ^a	1 ^e	–	
Respiratory failure	1 ^d	1 ^e	–	
<i>Minor operative morbidities</i>				
Transient partial portal vein thrombosis	–	–	2	
Ascites	2	2	2	
Pleural effusion	3	1	2	
Temporary renal impairment function	–	1 ^e	1	
Re-operation	9.1% (1 ^b)	–	–	
MEDIAN HOSPITAL STAY, D [RANGE]	15 [12-30]	10 [9-13]	9 [9-22]	<0.001
POSTOPERATIVE RE-ADMISSION	9.1% (1 ^c)	–	2.9% (1 ^f)	
MORTALITY (30 D)	9,09% (1)	–	–	0.112

^aDeath; ^bReoperation; ^cBiliary stenting; ^dProlonged mechanical ventilation; ^{e,f} same patient.

SD 6.0 years). All patients except 2 had an underlying liver disease, usually Child –Pugh A and related to a virus hepatitis. Group A included 11 patients, group B 50, and group C 37. Demographic and clinical data of three groups are shown in Table I, II.

Eleven major resections and 55 minor resections were performed in group A and B, respectively. Seventeen lesions were removed in group A and 55 in group B; 77 lesions (range 1-3, mean 2) were treated in group C. The type of resection performed in groups A, B and C are listed in Table I. Fifty-nine lesions in group C were removed by IRFA and 18 were resected; 14 patients received combined treatment and 23 underwent isolated IRFA. Five nodules, missed at preoperative imaging, were detected at intraoperative ultrasonography and required to change planned treatment. An intermittent Pringle maneuver was used in cirrhotic patients, during major resections, during a right posterior resection, a bi-segmentectomy (5 to 6 sg), and in 2 cases of IRFA next to a main portal branch. The latter 2 patients had an asymptomatic, partial portal vein thrombosis that lasted 3 months (Table IV). Median blood loss and median operating times are listed in Table I. Rates of operative morbidity and mortality, reoperation, hospital stay are listed in Table IV. The difference of morbidity and hospital stay, was statistically significant ($p < 0.004$; <0.001), not that of mortality ($p=0.112$) (Table IV). All specimens except two, met defined requisite for a “clear” treat-

ment. In 2 wedge resections microvascular spread was observed ; an intensive imaging follow up (US, MRI or CT) was therefore performed at 3-4 month interval. Assessment of tumor destruction by ablation, with no residual contrast-enhancing area, was observed at 1 month in all patients except three. In these patients, in order to obtain complete ablation of the nodules, a chemoembolization (TACE) with DC Bead TM of residual pathological tissue was performed 2 months later. Median follow-up was 38 months (range 3-60 months). Overall 1-year survival was 100% in all groups. Three and five-year survival rates were 100%, 88.3%, 84.6% ($p= 0.585$) and 100%, 79.5%, 38.2% ($p = 0.003$) in groups A, B and C respectively (Fig. 1a). One- and 3-year disease free survival (DFS) rates were 100%, 93%, and 97% ($p =0.911$) and 71.4%, 75.9%, and 52.8% ($p = 0.374$) in group A, B, and C, respectively. Five-year DFS rates were 57%, 56% and 0% ($p < 0.001$) in groups A, B and C, respectively (Fig. 1b) The results of survival after Bonferroni's correction achieved borderline significance comparing group A and C ($p=0.033$) and B and C ($p=0.030$). The DFS achieved significance comparing A and C ($p=0.029$) and highly significant between B and C ($p<0.001$). Survival and disease-free survival was significantly higher in patients who had intended curative resections, A and B versus C ($p <0.001$; $p <0.001$) (Figg. 2a, 2b). Recurrences occurred in 3 patients in group A, 11 in group B, and 23 in group

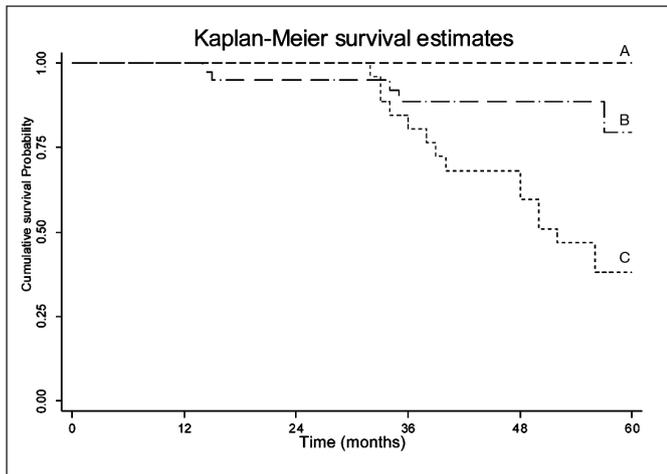


Fig. 1a: This Kaplan-Meier plot illustrates overall survival in the 3 groups: group A who underwent large resections, group B who had small resections, and group C who had IRFA or IRFA ± small resections. Log-rank test: $\chi^2_{(2)} = 11.83$, $P = 0.003$. IRFA, intraoperative radiofrequency ablation.

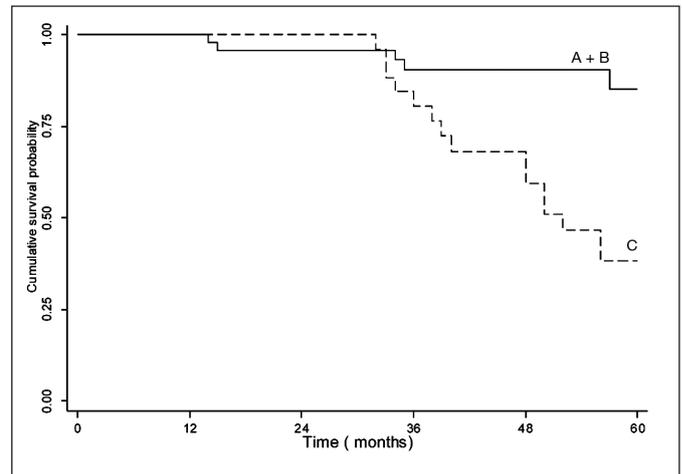


Fig. 2a: This Kaplan-Meier plot illustrates overall survival in 2 groups: group A and B combined who underwent large and small resections vs group C who had IRFA or IRFA ± small resections. Log rank test: $\chi^2_{(1)} = 11.07$; $P < 0.001$. IRFA, intraoperative radiofrequency ablation.

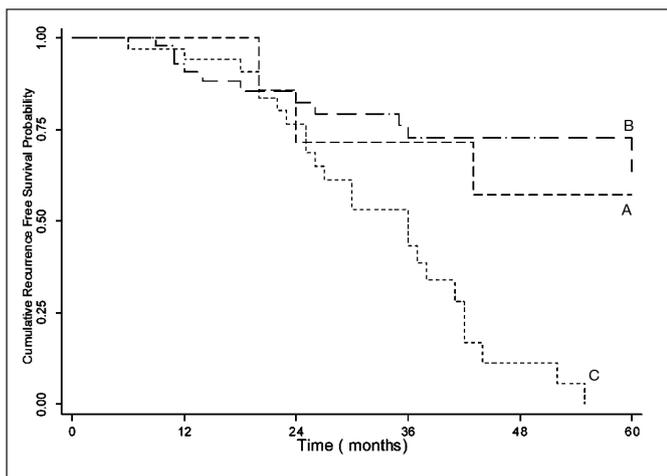


Fig. 1b: This Kaplan-Meier plot illustrates disease-free survival in 3 groups: group A who underwent large resections, group B who had small resections, and group C who had IRFA or IRFA ± small resections. Log-rank test: $\chi^2_{(2)} = 17.59$, $P < 0.001$. IRFA, intraoperative radiofrequency ablation.

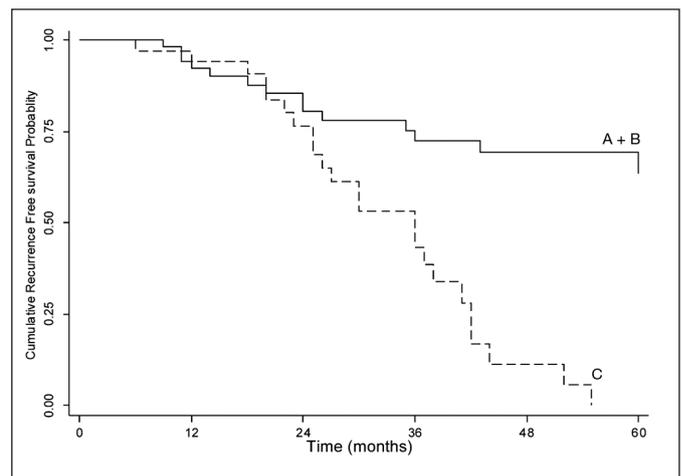


Fig. 2b: This Kaplan-Meier plot illustrates disease-free survival in 2 groups: group A and B combined who underwent large and small resections vs group C who had IRFA or IRFA ± small resections. Log-rank test: $\chi^2_{(2)} = 17.59$, $P < 0.001$. IRFA, intraoperative radiofrequency ablation.

C, with significant difference ($p=0.001$) (Table V). Six patients with recurrence, 3 in group A and 3 in group C, are alive at follow-up and disease free after multimodal repeat treatments. They were considered recurrent disease patients.

Discussion

HCC is the most common malignancy of the liver. Prolonged life expectancy, increasing incidence of hepatitis B and C virus in geriatric individuals, and improvement in medical care of hepatitis and cirrhosis contribute

to increase the number of elderly patients affected by HCC requiring treatment. However, the most adequate treatment for these patients is debated even though liver transplantation and liver resection remain as first-line choice^{7,8,16,33-36}. Despite the outcome of liver transplantation in rigorously selected septuagenarians has been recently reported as satisfactory as that in general population³⁷, elderly patients have been virtually excluded from transplantation^{38,39}.

Number of liver resections, on the other hand, is steadily increasing because advances in anesthesia and medical care have lowered the operative risk^{7,40}, risk of postoperative liver failure, independently from age¹³.

Table V - Recurrence in the liver

Type	Group A (n=9)	Group B (n=50)	Group C (n=37)	Total	P value
Distant from area of treatment	3	8	12	23 (62.2%)	0.150
Near area of treatment	0	1	2	3 (8.1%)	
Disseminated in the liver	0	2	9	11 (29.7%)	C vs A+B =0.309
Totale	3 (33.3%)	11 (22.0%)	23 (62.2%)	37 (37.8%)	0.001

In group A and B 14 patients had recurrence (14.3% disseminated) and in group C 23 patients had recurrence (39.1% disseminated). P=0.150

Although age 70 is presently considered as the threshold for old age, physiologic changes associated with aging are a gradual and extremely individual process²⁹. The elderly include a heterogeneous group of individuals, some of whom are in extremely good health, but many others are affected by concurrent diseases, associated disabilities, and reduced functional reserve in multiple organs²⁷. Furthermore, an outstanding feature of aging is reduced adaptability to stress, and surgery represents a major stressor^{43,44}. Hepatic physiologic changes peculiar to aging are represented by decreased blood perfusion and reduced regenerative capacities of the liver parenchyma⁴⁵. A larger residual liver mass is therefore required to avoid the risk of postoperative hepatic failure and underlying liver disease more than restricts the resectability in elderly patients⁴⁶. The major controversies regarding very old patients, aged 80 and over, are primarily based on issues related to a shorter life expectancy balanced against extent of treatment necessary to achieved prolonged survival and risk it related. Although many studies have shown that older age is not an independent predictor of morbidity and mortality in liver surgery, other studies have demonstrated that "longer operative time" and a weighted comorbidity index score had a statistically significant odds ratio for 30-day mortality and morbidity¹². People aged 80 and over candidate to surgical higher risk treatments require an extreme caution. At present, there are no definite criteria for selecting elderly patients, though careful assessment of individual operative risks is recommended to reliably predict which patients will benefit from resective surgery^{13,42}. Variables associated with higher surgical risk are unclear. Some centers have started, therefore, to set their own individual rules based on the concept of "physiologic age."⁴² Most widely adopted predictors are no longer age itself, but include comorbid associated illnesses, severity rather as the number of co-morbid illness, functional frailty with reduced adaptability to stress, underlying liver disease, and the extent of the planned resections⁴⁴. Different classes or categories of elderly patients may be created, each requiring a different approach to avoid overwhelming the potential benefits by therapeutic risks. The conventional ASA score

and CGA scale were the basic selection criteria adopted in our study. ASA and CGA have been both reported as excellent criteria in predicting life expectancy and evaluating functional reserve and operative risk in elderly patients in different surgical settings^{28,29}. The comprehensive analysis of surgical risk, anesthesiological (ASA) and geriatric (CGA) risk together with liver-related functions risk, have resulted, in our experience, as effective criteria to refer different elderly patients to different treatments. We sought to establish a relationship among results of strategy treatments in different elderly patients. Radical liver anatomic resections ensured the best long-term outcome. We experienced significantly higher five years overall survival and a better DFS (Fig. 1a, 1b). However, high risk procedures, entailing long operative times, heavy blood loss, high cardiopulmonary stress, complex and prolonged postoperative care, exceed the tolerance of unfit elderly patients because of their reduced functional reserve^{29,44}. Approximately 60% of our patients had cardiovascular diseases. Diabetes mellitus was seen in about 10% and thirty percent had chronic pulmonary diseases. Most of the patients, 71%, were preoperatively staged (ASA II-III) as representing for a moderate operative risk but an high percentage of them (53%), for number or localization of the malignancies, should had required an extensive or at high risk liver surgery.

Thermal RFA represents an effective and well-tolerated procedure for tumor destruction and a valid alternative for the treatment of small favourably -sited liver lesions and it has a comparable 3-year overall survival rate but a poorer disease-free survival rate^{18,20,21}. IRFA has enlarged the number of patients candidates for ablation because this procedure enables the treatment of critically sited lesions^{20,21,24,25}. This procedure was adopted in our series of 37 unfit patients with multifocal malignancies and with malignancies that carried a high surgical risk. IRFA either alone or combined with minor resections has effectively cleared the disease and provided good control of tumor progression. Reduced operative morbidity, no mortality, good control of tumor progression, and satisfactory survivals are the results achieved in these series of patients who would have been other-

wise considered not amenable to effective treatment because of their poor baseline condition, the extent of their disease, and their reduced life expectancy. Unusual high rates of radicality following both surgical resection and RFA are a possible bias consequent the enrolment criteria adopted in our study. As a matter only patients with lesion of about 3 cm were considered suitable for RFA, whereas only patients with marginal lesions were submitted to small resections. A selection bias related to number and location of lesions may be responsible for higher recurrence in group C patients. In conclusion, although only weak statistical significance was reached, possibly because of the small size of our sample, our results strongly support that differentiated treatments should be tailored for different elderly patients. Liver resection can be performed in patients aged 70 or more years safely, Surgical strategy should be optimized to minimize postoperative morbidity and mortality. Accordingly, IRFA, either alone or associated with minor liver resection, is the best option to treat elderly patients with HCC with severe comorbidities, unsuitable for external RF or for higher risk resections. We are completing larger series to confirm the reported results.

Riassunto

SCOPO: Lo stato di salute di pazienti anziani affetti da epatocarcinoma (HCC) può limitare l'approccio chirurgico; perciò altre opzioni sono auspicabili.

METODI: Gli autori hanno rivisto 98 pazienti selezionati con età tra i 65 e i 90 anni, con 149 HCC trattati tra il 2002 e il 2011. A seconda dell'estensione della malattia neoplastica, dello stato di salute e del trattamento, i pazienti sono stati divisi in tre gruppi. Sessantuno, sottoposti a resezioni curative maggiori e minori, erano nel gruppo A e B il gruppo C includeva 37 pazienti non candidabili a procedure ad alto rischio nè a procedure ablative esterne, sottoposti a trattamento ablativo intra-operatorio associato o meno a resezioni minori. La sicurezza e l'efficacia terapeutica di queste scelte strategiche sono state valutate.

RISULTATI: Una mortalità post-operatoria dell'1,02% e una sopravvivenza complessiva a 5 anni del 62,3% sono stati osservati. Però i tassi di morbilità e mortalità dei gruppi A,B,C sono stati del 45%, 8%, 16,21% ($p < 0,004$) e 9%, 0%, 0% ($p = 0,112$) rispettivamente. La sopravvivenza complessiva a 3 anni non era statisticamente diversa ($p = 0,585$). Tuttavia i tassi di sopravvivenza e di sopravvivenza libera da malattia a 5 anni erano significativamente più alti nei pazienti del gruppo A e B ($p = 0,003$; $p < 0,001$).

CONCLUSIONI: Strategie di trattamento volte a ridurre la morbilità e la mortalità trattamento-correlata sono risultate soddisfacenti in termini di risultati immediati e a distanza in un gruppo eterogeneo di pazienti anziani affetti da HCC.

References

- 1) Parkin DM, Bray F, Ferlay J, Pisani P: *Global cancer statistics*. 2002. CA Cancer J Clin, 2005; 55:74-108.
- 2) El-Serag HB, Rudolph KL: *Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis*. Gastroenterology, 2007; 132:2557-576.
- 3) *World Health Organization. Globocan 2008 (IARC2010). Section of cancer information*
- 4) Hashem B El-Serag: *Epidemiology of Viral Hepatitis and Hepatocellular Carcinoma*. Gastroenterology, 2012; 142:1264-273.
- 5) Borie F, Tretarre B, Bouvier AM, Faivre J, Binder F, Launoy G, Delafosse P, Tisot J, Peng J, Grosclaude P, Guizard AV, Gras-Aygon C: *Primitive liver cancer: Epidemiology and geographical studies in France*. Eur J Gastroenterol Hepatol, 2009; 21:984-89.
- 6) Borie F, Bouvier AM, Herrero A, Faivre J, Launoy G, Delafosse P, Velten M, Buemi A, Peng J, Grosclaude P, Trétarre B: *Treatment and prognosis of hepatocellular carcinoma: A population based study in France*. J Surg Oncol, 2008; 98(7):505-09.
- 7) Poon RTP: *Optimal initial treatment for early hepatocellular carcinoma in patients with preserved liver function: transplantation or resection?* Ann Surg Oncol, 2007; 14:541-47.
- 8) Thomas MB, Jaffe D, Choti MM, Belghiti J, Curley S, Fong Y, Gores G, Kerlan R, Merle P, O'Neil B, Poon R, Schwartz L, Tepper J, Yao F, Haller D, Mooney M, Venook A: *Hepatocellular carcinoma: consensus recommendations of the National Cancer Institute Clinical Trials Planning Meeting*. J Clin Oncol, 2010; 28(25):3994-4005.
- 9) Smoot RL, Nagorney DM, Chandan VS, Que FG, Schleck CD, Harmsen WS, Kendrick ML: *Resection of hepatocellular carcinoma in patients without cirrhosis*. Br J Surg, 2011; 98(5):697-703.
- 10) Makuuchi M, Donadon M, Torzilli G: *Hepatic resection for hepatocellular carcinoma in cirrhosis*. Ann Ital Chir, 2008; 79(2):111-15.
- 11) Ferrero A, Viganò L, Polastri R, Ribero D, Lo Tesoriere R, Muratore A, Capussotti L: *Hepatectomy as treatment of choice for hepatocellular carcinoma in elderly cirrhotic patients*. World J Surg, 2005; 29: 1101-105.
- 12) Cho SW, Steel J, Tsung A, Marsh JW, Geller DA, Gamblin TC: *Safety of liver resection in the elderly: how important is age?* Ann Surg Oncol, 2011; 18(4):1088-95.
- 13) Bockhorn M, Sotiropoulos GC, Sgourakis G, Neuhaus JP, Molmenti EP, Lang H, Frilling A, Broelsch CE: *Major liver resections in the elderly-is an aggressive approach justified?* Int J Colorectal Dis, 2009; 24:83-86.
- 14) Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O: *Seven hundred forty-seven hepatectomies in the 1990s: An update to evaluate the actual risk of liver resection*. J Am Coll Surg, 2000; 191:38-46.
- 15) Older P, Hall A: *Clinical review: How to identify high-risk surgical patients*. Crit Care, 2004; 8(5):369-72.
- 16) Belghiti J: *Resection and liver transplantation for HCC*. J Gastroenterol, 2009; 44 Suppl 19:132-35.
- 17) Vullierme MP, Paradis V, Chirica M, Castaing D, Belghiti J, Soubrane O, Barbare JC, Farges O: *Hepatocellular carcinoma. What's new?* J Visc Surg, 2010; 147(1): e1-e12.

- 18) Jarnagin WR: *Management of small hepatocellular carcinoma: A review of transplantation, resection, and ablation.* Ann Surg Oncol, 2010; 17(5):1226-333.
- 19) Takayama T, Makuuchi M, Kosuge T, Yamamoto J, Shimada K, Inoue K: *Preoperative portal embolization.* Ann Ital Chir, 1997; 68(6):745-50.
- 20) Gravante G, Overton J, Sorge R, Bhardwaj N, Metcalfe MS, Lloyd DM, Dennison AR: *Radiofrequency ablation versus resection for liver tumors: An evidence-based approach to retrospective comparative studies.* J Gastrointest Surg, 2011; 15:378-87.
- 21) Lencioni R, Crocetti L: *Radiofrequency ablation of liver cancer.* Tech Vasc Interv Radiol, 2007; (1):38-46.
- 22) Nishikawa H, Inuzuka T, Takeda H, Nakajima J, Matsuda F, Sakamoto A, Henmi S, Hatamaru K, Ishikawa T, Saito S, Nasu A, Kita R, Kimura T, Arimoto A, Osaki Y: *Comparison of percutaneous radiofrequency thermal ablation and surgical resection for small hepatocellular carcinoma.* BMC Gastroenterol, 2011; 11:143-55.
- 23) Brunaud L, Bresler L: *Radiofrequency ablation of unresectable liver tumors: factors associated with incomplete ablation or local recurrence.* Am J Surg, 2010; 200:435-39.
- 24) Kim HO, Kim SK, Son BH, Yoo CH, Hong HP, Cho YK, Kim BI: *Intraoperative radiofrequency ablation with or without tumorectomy for hepatocellular carcinoma in locations difficult for a percutaneous approach.* Hepatobiliary Pancreat Dis Int, 2009; 8(6): 591-96.
- 25) Stella M, Minuto MN, Pasqualini M, Percivale A, Profeti A, Serafini G, Gandolfo N, Marengo G, Azzola E, Pellicci R: *Intraoperative use of radiofrequency thermoablation of liver tumors: Considerations on indications and related therapeutic aspects.* Ann Ital Chir, 2002; 73(5):511-16; discussion 517.
- 26) ASA Physical Status Classification System. *American Society of Anesthesiologists.* Available at: HYPERLINK "<http://www.asahq.org/clinical/physicalstatus.htm>" <http://www.asahq.org/clinical/physicalstatus.htm> Accessed December 10, 2010.
- 27) Basso U, Monfardini S: *Multidimensional geriatric evaluation in elderly cancer patient: A practical approach.* Eur J Cancer Care, 2004; 13:424-33.
- 28) Extermann M, Hurria A: *Comprehensive geriatric assessment for older patients with cancer.* J Clin Oncol. 2007; 25:1824-831.
- 29) Balducci L, Yates J: *General guidelines for the management of older patients with cancer.* Oncology, 2000; 14(11A):221-27.
- 30) Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y: *Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: Surgical outcome and long-term follow-up.* Ann Surg, 2006; 243:364-72.
- 31) Terminology committee of the IHPBA (Authors). *The Brisbane 2000 terminology of liver anatomy and resections.* HPB. 2000; 2:333-39.
- 32) Torzilli G: *Intraoperative ultrasound in surgery for hepatocellular carcinoma.* Ann Ital Chir, 2008; 79(2):99-106.
- 33) Bruix J, Sherman M: *American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma.* Hepatology, 2005; 42(5):1208-236.
- 34) Bruix J, Sherman M: *American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: An update.* Hepatology, 2011; 53(3):1020-22.
- 35) Poon RTP: *Liver transplantation for solitary hepatocellular carcinoma less than 3 cm in diameter in Child A cirrhosis.* Dig Dis, 2007; 25:334-40.
- 36) Agrawal S, Belghiti J: *Oncologic resection for malignant tumors of the liver.* Ann Surg, 2011; 253(4):656-65.
- 37) Lipshutz GS, Hiatt J, Ghobrial RM, Farmer DG, Martinez MM, Yersiz H, Gornbein J, Busuttill RW: *Outcome of liver transplantation in septuagenarians: A single-center experience.* Arch Surg, 2007; 142:775-84.
- 38) OPTN: *Organ Procurement and Transplantation Network available at HYPERLINK "<http://optn.transplant.hrsa.gov/lorganDataSource/about.asp?display=Liver>" <http://optn.transplant.hrsa.gov/lorganDataSource/about.asp?display=Liver> Accessed January, 10, 2011.*
- 39) Surveillance, Epidemiology and End Results (SEER) Program of National cancer institute. Available at: HYPERLINK "<http://www.seer.cancer.gov>" www.seer.cancer.gov Accessed January, 7, 2011.
- 40) Dokmak S, Paradis V, Vilgrain V, Sauvanet A, Farges O, Valla D, Bedossa P, Belghiti J: *A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas.* Gastroenterology, 2009; 137(5):1698-705.
- 41) Belghiti J, Kianmanesh R.: *Surgical treatment of hepatocellular carcinoma.* HPB (Oxford). 2005; 7(1):42-49.
- 42) Aldrighetti L, Arru M, Catena M, Finazzi R, Ferla G: *Liver resection in over 75 years old patients: Surgical hazard or current practice?* J Surg Oncol, 2006; 93:186-93.
- 43) Pasetto LM, Lise M, Monfardini S: *Preoperative assessment of elderly cancer patients.* Crit Rev Oncol Hematol, 2007; 64:10-18.
- 44) Vaitkevicius VP, Kirsh MM, Orringer MB: *Perioperative evaluation and management.* In: Hazzard WR, Blass JP, Halter JB (eds): *Principles of Geriatric Medicine and Gerontology.* 5th ed. New York, NY: McGraw Hill; 2003; 361-71.
- 45) Carli F, Zavorsky GS: *Optimizing functional exercise capacity in the elderly surgical population.* Curr Opin Clin Nutr Metab Care, 2005; 8:23-32.
- 46) Mullin EJ, Metcalfe MS, Maddern GJ: *How much liver resection is too much?* Am J Surg, 2005; 190:87-97.

