Is Liver Resection Justified for Patients With Hepatic Metastases From Breast Cancer?

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Objective: The purpose of this study was to examine our experience with hepatic resection (HR) in a relatively unselected group of patients with breast cancer liver metastases (BCLM).

Background: Although medical therapies provide limited survival benefit (median survival, 3–15 months), inclusion of HR into the multimodality treatment of patients with BCLM remains controversial. Our approach has been to offer HR to all patients with BCLM, provided that curative hepatic resection was feasible and extrahepatic disease was controlled with medical and/or surgical therapy.

Methods: Outcomes for 85 consecutive patients (all female, median age, 47 years) with BCLM treated with HR from 1984 to 2004 were reviewed. Extrahepatic metastases had been treated prior to HR or were synchronously present in 27 patients (32%). BCLM were solitary in 32 patients (38%) and numbered more than 3 in 26 patients (31%). The prognostic value of each study variable was assessed with log rank tests for univariate analysis and Cox proportional hazard models for multivariate analysis.

Results: Within 60 days of major hepatectomy (≥3 segments, 54 patients) or minor hepatectomy (<3 segments, 31 patients), there was no mortality. The median hospital stay was 9 days with complications occurring in 26% of patients. Microscopically and macroscopically positive margins were present in 18% (R1) and 17% (R2) of patients. Following HR, 28 patients (33%) developed isolated hepatic recurrences, 12 of whom were treated with repeat hepatectomy. At a median follow-up interval of 38 months, 32 patients were alive, yielding median and 5-year overall survivals of 32 months and 37%. Median and 5-year disease-free survivals were 20 months and 21%. Study variables independently associated with poor survival were failure to respond to preoperative chemotherapy ($P = 0.008$), an R2 resection ($P = 0.0001$), and the absence of repeat hepatectomy ($P = 0.01$).

Conclusions: For patients with BCLM, HR is safe and may provide a significant survival benefit over medical therapy alone. Response to preoperative chemotherapy, resection margin, and rehepatectomy for intrahepatic recurrence are key prognostic factors. Importantly, favorable outcomes can be achieved even in patients with medically controlled or surgically resectable extrahepatic disease, indicating that surgery should be considered more frequently in the multidisciplinary care of patients with BCLM.

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Approximately 50% of breast cancer patients will develop distant metastases,[1,2] accounting for breast cancer's ranking as a leading cause of cancer-related mortality for women.[3,4] Although significant progress has been made in the multimodality treatment of patients with breast cancer, including the use of more effective systemic chemotherapy (anthracyclines and taxanes), antihormonal therapy (aromatase inhibitors), and directed biologic agents (trastuzumab), the development of distant metastases continues to be associated with a very poor prognosis. Liver metastases (breast cancer liver metastases [BCLM]) are present in 15% of patients newly diagnosed with metastatic breast cancer and are the only site of distant disease in one third of these patients.[5,6] Ultimately, as many as 50% of patients with stage IV disease will develop liver metastases, with associated median survivals ranging from 3 to 15 months.[7–9]

Although one half of stage IV breast cancer patients will develop liver metastases, there are 2 main reasons why patients with BCLM are rarely referred for surgical evaluation. First, most patients with breast cancer liver metastases also have extrahepatic metastases,[10] a finding that has traditionally been considered a contraindication to hepatic resection (HR). Second, due to the perception that BCLM are associated with a particularly poor prognosis, in many cases treatments with a minimal toxicity profile have been preferred to aggressive treatments, including systemic chemotherapy and HR.[11] Based largely on these 2 factors, the reports that comment on the role of HR in patients with BCLM contain very few cases (Table 1.). In point of fact, the literature contains only one report that examines outcomes following HR in more than 34 patients.[12] Moreover, because of small sample sizes, few independent prognostic factors for postoperative recurrence and/or survival have been identified.[12–14]

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TABLE 1. Presentation of Studies Documenting Long-term Outcome Following Hepatic Resection in Patients With Breast Cancer Liver Metastases (Inclusion Criteria >5 Patients Reported)

Author	Year	Dates	n	Postoperative Mortality (%)	Median Survival (mo)	5-Year Survival (%)
Stehlin[24]	1974	—	9	—	28	11
Schneebaum[25]	1994	—	6	—	42	—
Lorenz[26]	1995	—	8	—	15	12
Elias[20]	1995	1986–1994	21	0	26	22
Raab[27]	1998	1983–1993	34	3	27	18
Seifert[22]	1999	1985–1997	15	0	57	18
Kondo[21]	2000	1990–1999	6	0	36	40
Maksan[28]	2000	1984–1998	9	0	—	51
Selzner[29]	2000	1987–1999	17	6	25	22
Yoshimoto[30]	2000	1985–1998	25	—	34	—
Pocard[12]	2001	1988–1999	65	0	47	46*
Carlini[31]	2002	1990–1999	17	0	53	46
Vlastos[13]	2004	1991–2002	31	0	63	61
Sakamoto[14]	2005	1985–2003	34	0	36	21
d'Annibale[32]	2005	1984–1999	18	0	32	30
Ercolani[33]	2005	1990–2003	21	0	42	25

*Four-year survival.

Recognizing the limitations of other therapies to treat patients with BCLM and the possibility that the presence of BCLM does not necessarily indicate a significantly poorer prognosis than other sites of distant metastases,[2] we have taken an aggressive surgical approach to the treatment of these patients. When presented with a breast cancer patient with technically resectable BCLM who has been treated with systemic therapy, we have offered HR, even in the presence of extrahepatic disease, provided the extrahepatic disease was resectable and/or well-controlled. In addition, early in our experience, we did not view the response of intrahepatic tumors to preoperative systemic therapy as an inclusion or exclusion criteria for HR. This approach has allowed us to acquire experience with HR for the treatment of a relatively unselected group of patients with BCLM. The purpose of this study was to determine the recurrence patterns and long-term outcomes in this large cohort and to identify prognostic factors that may allow for optimal patient selection in the future.

METHODS

Patient Inclusion Criteria

A search of our prospective database identified 108 patients with the diagnosis of hepatic metastases from breast cancer primary tumor treated surgically at our institution from 1984 to 2004. To diagnose the presence of unresectable extrahepatic disease and to confirm that resection of all radiographically apparent intrahepatic disease was feasible, each patient underwent a preoperative staging evaluation, including axial imaging (brain, chest, and abdomen), liver sonogram, and bone scintigram. Despite this radiologic staging evaluation, in 23 of the 108 patients (21%), initial abdominal exploration revealed unresectable hepatic or intra-abdominal disease not identified on preoperative imaging. The remaining 85 (79%) patients, who underwent HR, comprise the study cohort analyzed in this report.

Immunohistochemical Analysis of Liver Metastases

Immunostaining was performed on a Ventana NexES platform, according to standard methods. Briefly, 4-μm-thick sections from formalin-fixed, paraffin-embedded liver metastasis tissue blocks were deparaffinized. These sections were then stained with antibodies for estrogen receptor (NCL-ER 6F11, Novocastra, Newcastle Upon Tyne, UK; dilution, 1:25), progesterone receptor (NCL-PRG 312, Novocastra; dilution, 1:50), and *c-erbB2* (NCL-CBF11, Novocastra; dilution, 1:100). For hormone receptor analysis, antigen retrieval was accomplished after deparaffinization by placing slides into 0.01 mol/L citrate buffer (pH 6.0) for 10 minutes in a pressure cooker. Viable tumor cells were present in the resected specimens and, therefore, available for assessment of receptor status for 76 of the 85 study patients (89%).

Statistical Considerations

For statistical analysis, multiple clinical, operative, postoperative, and pathologic factors were recorded. To facilitate comparisons, several variables were dichotomized. The presentation of hepatic metastases was considered synchronous when diagnosed within 6 months of primary tumor treatment and metachronous when the hepatic disease-free interval was greater than 6 months. The magnitude of HR was classified as major ($\geq$3 hepatic segments) or minor ($<$3 hepatic segments), according to Couinaud's classification.[15] Postoperative complications were classified as local when occurring near the field of liver surgery (eg, biliary fistula) and general when occurring distant from the field of liver surgery (eg, pneumonia) as per our previous reports.[16–18]

Recurrence-free, disease-free, and overall survivals (OS) were calculated by the method of Kaplan and Meier. Disease-free survivals were determined by the recurrence status of the patient at the latest follow-up date. Univariate associations between study factors and outcomes were determined by the finding of a log-rank test P value ≤ 0.05. All study variables with a significance level of $P \leq 0.10$ in univariate analysis were then entered into a Cox proportional hazard model. In multivariate analysis, independent statistical significance was determined by a P value ≤ 0.05. All statistical analyses were performed using SPSS software, version 12.0 (SPSS, Inc., Chicago, IL).

RESULTS

Clinical Characteristics

All patients were female with a median age of 47 years (range, 27–70 years). In all patients, the primary breast tumor histology was adenocarcinoma (ductal, 86%; lobular, 14%; well differentiated, 11%; moderately differentiated, 50%; poorly differentiated, 39%). To be considered for HR, all patients were required to have received stage-appropriate therapy for their primary tumor. These treatments included partial or total mastectomy in 82 (96%) and radiotherapy in 70 of the 85 study patients (82%), respectively. At diagnosis, 11% were treated with systemic therapy prior to mastectomy, 66% received postmastectomy systemic chemotherapy, and 31% received postmastectomy hormonal therapy. Immunohistochemical data on the primary tumor hormone receptor status (estrogen [ER] and progesterone [PR]) was available for 44 study patients, including 24 ER+PR− tumors (55%), 3 ER−PR+ tumors (7%), 9 ER+PR+ tumors (20%), and 8 ER−PR− tumors (18%).

BCLM presentation was synchronous (within 6 months of primary tumor treatment) in 9 patients (11%) and metachronous in 76 patients (89%). The median time from treatment of the breast primary tumor to diagnosis of liver metastases was 34 months (range, 0–147 months). Tumors were solitary in 32 patients (38%) and numbered more than 3 in 26 patients (31%). The median maximal tumor size was 2.8 cm (range, 1–19 cm). Metastases distribution was unilobar in 52 (61%) patients and bilobar in 33 (39%) patients. In anticipation of extended HR, 1 patient underwent preoperative portal vein embolization.

Prior to HR, 19 (22%) patients had been curatively treated for a local-regional breast cancer recurrence. In addition, extraabdominal distant metastases (ie, bone, lung, brain) had been diagnosed in 16 (19%) patients, 11 of which were curatively resected or in remission following systemic treatment prior to hepatectomy. Each of the remaining 5 patients, who underwent hepatectomy with extraabdominal disease present, had bone metastases well controlled with systemic therapy and local radiotherapy.

Chemotherapy Details

Seventy-one patients (84%) received a median of 8 cycles (range, 2–22) of systemic therapy during the interval between diagnosis of liver metastases and HR, with only 23% of patients receiving more than one line of chemotherapy. For patients receiving prehepatectomy systemic treatment, regimens included anthracyclines in 40%, taxanes in 62%, vinorelbine in 18%, antihormonal treatment in 1%, and trastuzumab in 7%. Intrahepatic tumor response to chemotherapy was measured in all patients but was not used to determine eligibility for HR. Using WHO criteria,[19] 55 (78%) of the 71 patients who received prehepatectomy systemic chemotherapy had an objective response, 10 (14%) had stable disease, and the remaining 6 (8%) patients progressed while on therapy.

Following HR, 71 of the 85 study patients (83%) received systemic therapy. For those patients receiving posthepatectomy systemic treatment, chemotherapy regimens included anthracyclines in 39%, taxanes in 63%, vinorelbine in 13%, and trastuzumab in 18%. In addition, 34% of patients were treated with antihormonal therapy. The majority of these patients were treated with aromatase inhibitors following completion of systemic chemotherapy.

Operative Management

Following thorough preoperative evaluation, 108 patients were first explored under general anesthesia through a right subcostal minilaparotomy incision. This allowed assessment for intra-abdominal spread of disease and access to the liver for ultrasound examination. In 15 of these 108 patients (14%), previously undiagnosed extensive intrahepatic disease that contraindicated resection was identified. In an additional 22 patients (20%), peritoneal or perihepatic nodal disease was identified. In 14 of these 22 patients, complete resection of both the intra-abdominal and intrahepatic disease appeared feasible and was performed. In the remaining 8 patients with higher volume intra-abdominal disease, the procedure was terminated. Therefore, 85 (79%) of the 108 patients initially explored were resected (Fig. 1).

When no contraindication to liver resection was identified during the initial examination, the incision was enlarged and HR commenced. Major hepatectomies ($\geq$3 segments) were performed in 54 (64%) patients and minor resections ($<$3 segments) were performed in 31 (36%) patients. Anatomic, nonanatomic, and combined anatomic/nonanatomic resections were completed in 26 (31%), 30 (35%), and 29 (34%) patients, respectively. HR was paired to radiofrequency ablation in 3 (4%) patients and to cryoablation in 4 (5%) patients.

Postoperative Course

There was no mortality within 60 days of resection. During recovery, 19 (22%) patients developed a total of 21 local complications. Biliary fistula, exteriorized by the routinely placed perihepatic drain, developed in 6 (7%) patients. Each fistula resolved spontaneously without need for further intervention. Infected intra-abdominal fluid collections developed in 2 (2%) patients, requiring percutaneous drainage and intravenous antibiotic therapy. An additional 11 (13%) patients developed noninfected perihepatic fluid collections; all of which resolved without need for intervention. One patient experienced postoperative hemorrhage from the liver resection bed, requiring urgent reoperation for control, and 1 patient experienced transient hepatic insufficiency. Twenty

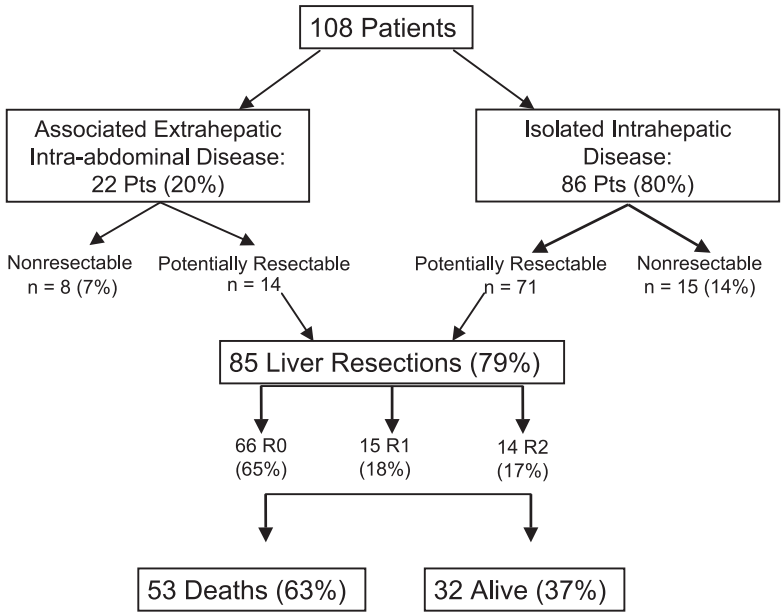

FIGURE 1. Diagram of treatment outcome in 108 patients undergoing abdominal exploration for breast cancer liver metastases.

(24%) patients experienced general complications. The median postoperative length of inpatient hospitalization was 9 days (range, 5–22 days).

Pathologic Evaluation

The median number of hepatic metastases in the resected specimen was 2. Thirty-two patients (37%) had solitary tumors, 27 patients (32%) had 2 or 3 tumors, and 26 patients (31%) had >3 tumors. The median size of the largest metastasis was 25 mm (range, 4–170 mm). Microscopically positive margins (R1) were present in 15 patients (18%). In an additional 14 patients (17%), margins were macroscopically positive or small volume disease remained in the remnant liver following resection (R2). In each of these cases, the residual disease was addressed with postoperative hepatic arterial chemotherapy via an infusion pump placed at the end of the procedure.

Liver metastases immunohistochemistry to determine ER, PR, and *c-erbB2* status revealed that 52% of patients had ER+ tumors, 25% had PR+ tumors, and 28% had *c-erbB2*+ tumors.

Overall Survival

At a median follow-up interval for the entire cohort of 38 months after the first HR, the median and 5-year overall survivals from the date of diagnosis of liver metastases were 46 months and 41% and from the date of first HR were 32 months and 37%, respectively (Fig. 2). Eight patients were alive 5 years after first hepatectomy and 4 of these patients were alive 10 years after first hepatectomy.

Prognostic Factors of Overall Survival

All recorded study variables were analyzed to determine associations with survivals (Table 2). In univariate

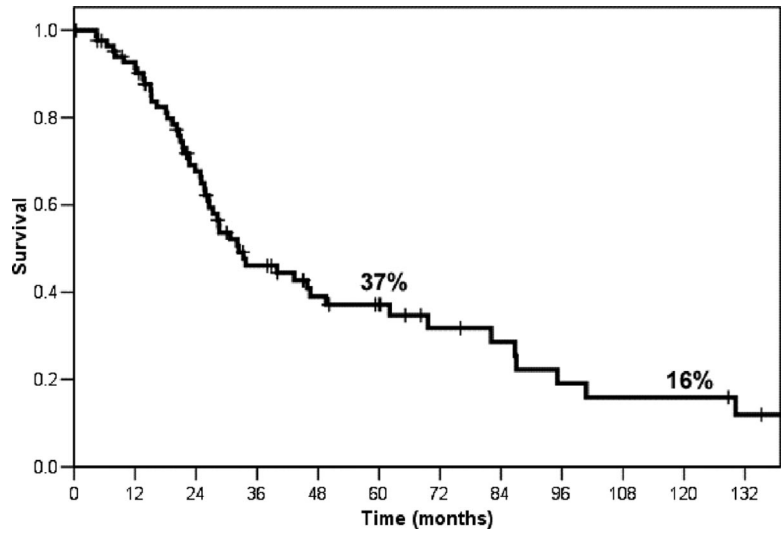

FIGURE 2. Overall survival following hepatic resection for patients with breast cancer metastases.

TABLE 2. Univariate and Multivariate Analysis of Study Factors for Overall Survival

	n	Median (mo)	5-yr (%)	Univariate *P*	Multivariate *P*	Odds Ratio (95% CI)
Age						
≤50 yr	52	33	41	0.98	—	
>50 yr	33	31	32			
Primary tumor						
T stage						
T1-2	57	33	42	0.10	NS	
T3-4	8	130	74			
N stage						
N0	39	46	44	0.26	—	
N1-2	36	29	37			
Differentiation						
Well	6	130	83	0.39	—	
Moderate	27	46	49			
Poor	21	29	40			
Hormone receptor status						
Positive (ER and/or PR)	36	29	41	0.76	—	
Negative (both ER and PR)	8	40	51			
Surgical treatment						
Breast conservation	47	32	45	0.47	—	
Mastectomy	35	28	28			
Liver metastasis						
Interval from primary treatment						
≤12 mo	12	21	38	0.10	NS	
>12 mo	73	33	38			
Tumor number						
Solitary	32	50	48	0.09	NS	
>1	53	27	32			
Maximal tumor size						
≤5 cm	71	32	39	0.68	—	
>5 cm	14	21	32			
Distribution						
Unilateral	52	40	41	0.07	NS	
Bilateral	33	26	32			
Prehepatectomy chemotherapy						
Present	71	31	35	0.07	NS	
Absent	14	43	50			
Response to prehepatectomy chemotherapy						
Partial response	55	40	42	0.004	0.008	
Stable disease	10	21	12			3.5 (1.4–8.8)
Progression	6	18	0			
Metastases hormone receptor status*						
ER positive	44	50	49	0.10	NS	
ER negative	32	27	23			
PR positive	21	87	53	0.12	—	
PR negative	55	29	30			
c-erbB2 positive	24	32	38	0.83	—	
c-erbB2 negative	52	32	39			
Posthepatectomy chemotherapy						
Present	71	50	47	0.73	—	
Absent	14	32	43			
Posthepatectomy anti-hormonal therapy						
Present	29	41	33	0.22	—	
Absent	66	23	21			

(*Continued*)

TABLE 2. (*Continued*)

	n	Median (mo)	5-yr (%)	Univariate *P*	Multivariate *P*	Odds Ratio (95% CI)
EHM history at or prior to hepatectomy						
Local breast recurrence						
Present	19	26	23	0.40	—	
Absent	66	40	42			
Extra-abdominal metastases						
Present	16	29	13	0.07	NS	
Absent	69	34	43			
Intra-abdominal metastases						
Present	14	21	22	0.07	NS	
Absent	71	33	41			
Overall metastasis status						
No history of EHM	58	40	45	0.004	NS	
All EHM treated prior to hepatectomy	10	32	23			
EHM present at hepatectomy	17	20	18			
Hepatic resection						
Treatment era						
1983–1993	25	26	36	0.78	—	
1994–2004	60	32	30			
Extent						
Minor	31	43	40	0.86	—	
Major	54	32	36			
Type						
Anatomic	26	46	51	0.40	—	
Nonanatomic	30	29	41			
Both	29	27	24			
Pathology						
Margin						
R0	56	43	43	0.00001	0.0001	
R1	15	46	42			
R2	14	16	10			5.6 (2.5–12.8)
Repeat hepatectomy						
Present	11	95	81	0.01	0.01	
Absent	74	28	29			2.4 (0.8–7.0)

*Nine of 85 patients with no immunohistochemical analysis due to complete pathologic response to preoperative chemotherapy.

CI indicates confidence interval; T, tumor; N, node; ER, estrogen receptor; PR, progesterone receptor; EHM, extrahepatic metastases; R0, margin-negative; R1, margin microscopically positive; R2, gross residual intrahepatic disease; NS, not significant.

analysis, study variables that were associated with poor overall survival were a lack of response to prehepatectomy chemotherapy ($P = 0.004$, Fig. 3A), the presence of extrahepatic metastases at the time of hepatectomy ($P = 0.004$, Fig. 3B), an R2 resection ($P = 0.00001$, Fig. 3C), and the absence of repeat hepatectomy ($P = 0.01$, Fig. 3D).

Subsequent multivariate analysis determined that 3 of these 4 study variables were independently associated with poor outcome. Patients with intrahepatic disease progression (5-year OS, 0%) and those with stable disease (5-year OS, 12%) during preoperative chemotherapy administration were 3.5 times more likely to die compared with patients responding to preoperative systemic therapy (5-year OS, 42%; $P = 0.008$). Patients with an R2 resection (5-year OS, 10%) were 5.6 times more likely to die than patients with R1 (5-year OS, 42%) or R0 (5-year OS, 43%) resections ($P = 0.0001$). In addition, patients who were not candidates for rehepatectomy (5-year OS, 29%), either because they did not recur in the liver or their hepatic recurrences were not resectable, were 2.4 times more likely to die than patients who developed intrahepatic recurrences in a resectable pattern and underwent repeat hepatectomy (5-year OS, 81%; $P = 0.01$).

Recurrence Rates and Treatment of Recurrences

Following HR, 59 patients (69%) developed additional metastatic disease with a median time to recurrence of 10 months (range, 1–132 months). For this group, recurrences were limited to the liver in 28 patients (48%), were limited to extrahepatic sites in 9 patients (15%), and involved both intrahepatic and extrahepatic sites in 22

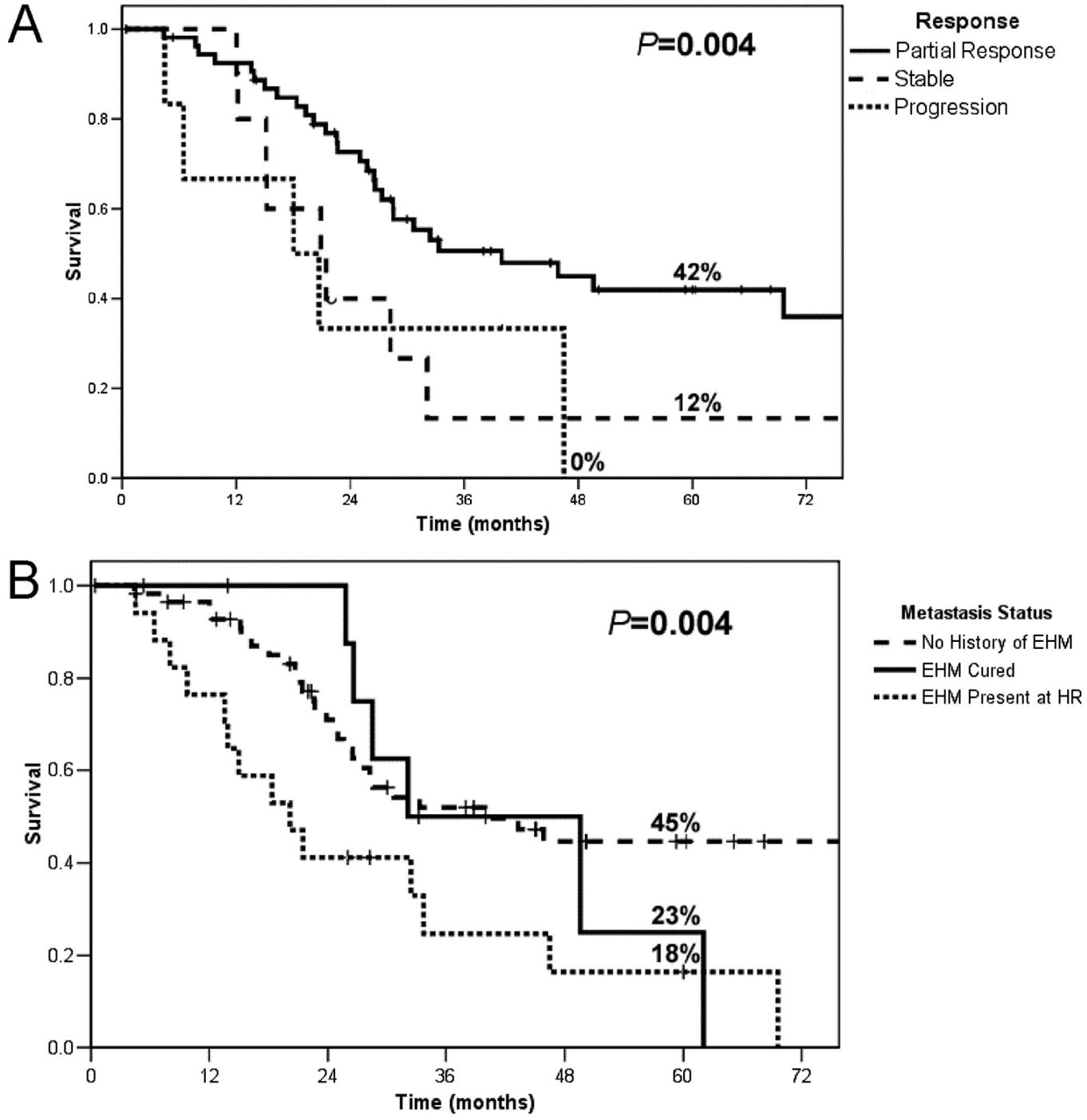

FIGURE 3. Overall survival following hepatic resection based on (A) response to preoperative chemotherapy, (B) status of extrahepatic disease at hepatectomy, (C) the margin of resection, and (D) repeat hepatectomy. EHM indicates extrahepatic metastases.

patients (37%). The median time to intrahepatic recurrence was 10 months (range, 1–47 months). Twelve of the 25 patients (48%) with intrahepatic recurrence underwent second hepatectomies, and 4 of these 12 rerecurred in a resectable pattern and underwent a third hepatectomy. Following repeat hepatectomy, 6 of these 12 patients were disease free at follow-up intervals from 1st hepatectomy ranging from 14 to 166 months. Of the 32 patients who were alive at latest follow-up, 19 were free of disease. The median and 5-year recurrence-free survivals for the entire study group of 85 patients were 15 months and 12%. In multivariable analysis, the only study factor with a significant association to recurrence was bilateral liver metastases (0.013, odds ratio: 1.9, 95% CI, 1.1–3.2).

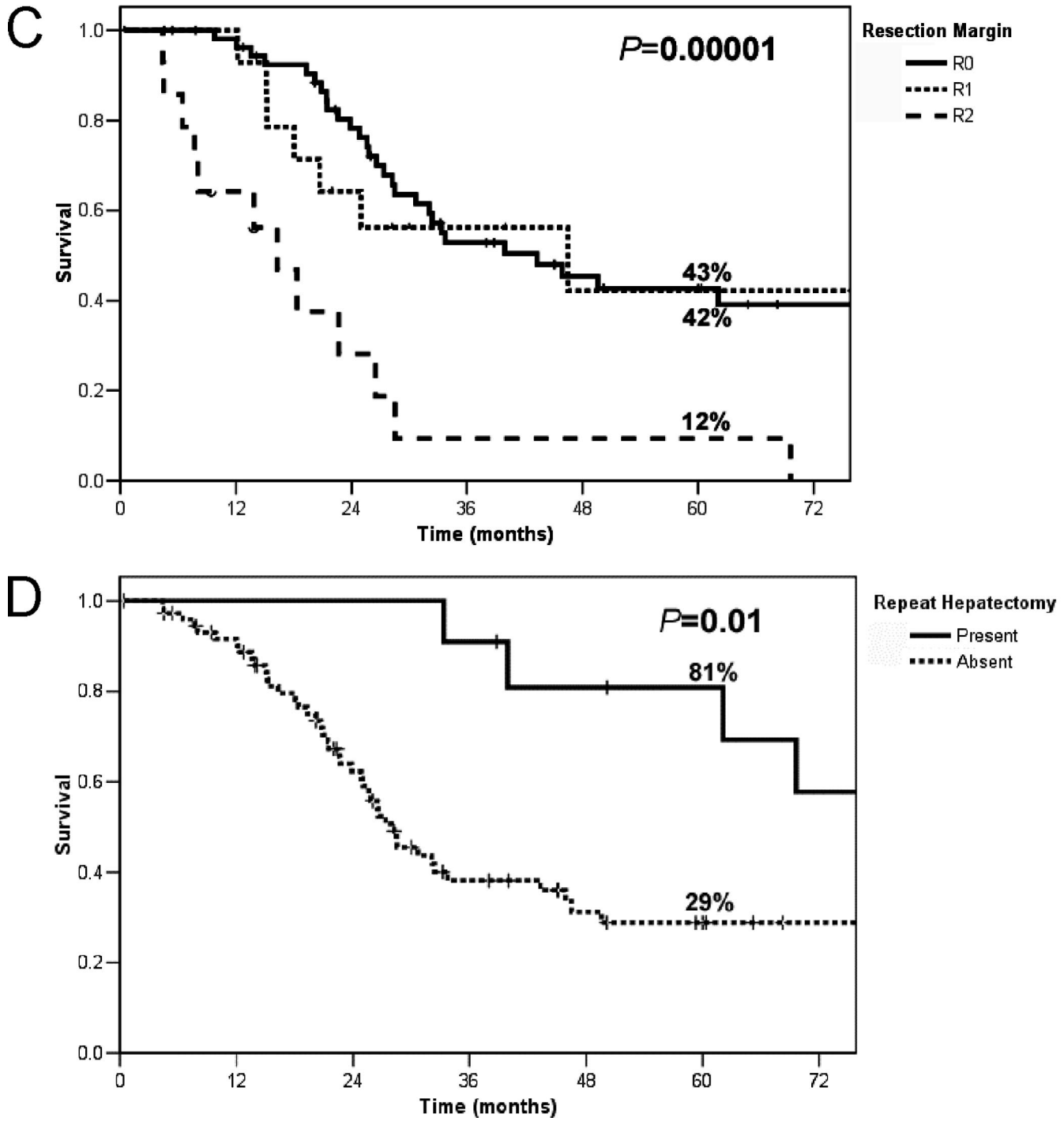

FIGURE 3. Continued.

Disease-Free Survival

At the conclusion of HR, 16 patients had residual metastatic disease, including 2 patients who came to the operation with extra-abdominal (bone) metastases, 11 patients with R2 resection, and 3 patients with both extra-abdominal disease and R2 resection. One patient with only intrahepatic disease, who initially underwent an R2 resection, was subsequently rendered disease free at rehepatectomy. Disease-free survivals were separately calculated from recurrence data for all 85 resected patients and for the 70 patients (82%) who had a postoperative disease free interval. Median and 5-year disease-free survivals for the cohort of 85 HR patients were 12 months and 17%, and median and 5-year disease-free survivals for the subset of

70 patients with a posthepatectomy disease-free interval were 20 months and 21%.

DISCUSSION

Patients with metastatic breast cancer are generally considered incurable. Treatment, therefore, frequently aims to minimize toxicity.[11] Although many oncologists will treat these patients with cytotoxic systemic therapy, most remain reluctant to refer patients for HR. Our group has taken an aggressive approach to these patients, offering them surgical therapy for resectable disease as part of a multimodality program. Using this approach, we have accumulated the largest reported cohort of patients with BCLM treated with HR. Analysis of our outcomes demonstrates that this strategy was associated with minimal toxicity, including a perioperative mortality rate of 0%.

The survivals experienced by our patients, including a 37% 5-year survival rate and a median survival of 32 months, compare favorably to the survivals reported for BCLM patients treated with systemic treatment alone. Untreated patients with BCLM have reported median survivals of approximately 3 to 6 months from the diagnosis of metastases.[7] Although systemic treatment can prolong survival, the peak median survivals reported for patients who respond to systemic therapy are only 15 months, and survival longer than 5 years is exceptional with medical therapy alone.[8,9] In addition, the survivals reported for patients treated with systemic therapy alone are typically measured from the diagnosis of BCLM. In contrast, surgical series measure survivals from the date of treatment. Indeed, when survivals were calculated in our patients from the date of diagnosis of BCLM, the median and 5-year overall survivals rose to 46 months and 41%, respectively.

The efficacy of HR in patients with BCLM is further supported by the benefit in survival provided by repeat hepatectomy. Patients who were treated with repeat hepatectomy had a higher 5-year overall survival rate (81%), compared with the patients with unresectable liver recurrences and patients without any hepatic recurrence following first HR (5-year OS, 29%). Given the low toxicity of HR, the superior survival rates reported for patients treated with curative surgical therapy, and the efficacy of repeat hepatectomy, inclusion of HR in the multimodality treatment plan for patients with resectable BCLM appears to be justified.

However, it could be argued that the favorable survivals observed in our patients may have been related to the selection of only patients with favorable prognostic features. Although it is certain that the patients included in our series are a "selected" group, representing a very small fraction of the total number of patients with stage IV breast cancer, the spectrum of disease represented in our study is significantly broader than in previously reported series.[12,14,20–22] As an example, in the last 10 years (1994–2004), we evaluated 248 patients with liver metastases from breast cancer. From this group, 60 patients (24%) underwent HR. The remaining 188 patients (76%) were excluded from surgical treatment based on poor performance status and/or the presence of uncontrolled extrahepatic disease.

Patients who were referred to our institution were considered for HR based solely on general performance status, resectability of intrahepatic disease, and control of extrahepatic metastases. Patients with limited extrahepatic disease were not excluded from consideration. One third of our patients had a history of extrahepatic disease prior to or at the time of HR. In addition, early in our experience, we did not use response to preoperative chemotherapy as a selection criterion for HR. By considering a wider array of disease presentation, our study group may be representative of a larger segment of patients with stage IV disease than has been examined previously; therefore, our results may be more applicable to current practice.

The lack of strict exclusion criteria used in our study also allowed determination of the prognostic significance of several previously unexamined study variables. The most important of these was the oncologic nature of the resection. R2 resections were associated with a poor prognosis, with only 10% of patients surviving 5 years, indicating that HR should only be attempted in patients with an intrahepatic disease pattern that appears to be completely resectable on preoperative imaging and intraoperative evaluation. In contrast, patients with R0 or R1 resection margins experienced markedly higher 5-year survival rates (43% and 42%, respectively). The minimal difference in observed outcomes between patients with R0 and R1 resections suggests that the microscopic margin of resection in BCLM is a less important prognostic factor. In summary, analysis of outcomes based on the oncologic nature of the resection indicates that HR should be offered in combination with systemic therapy only to those patients with macroscopically resectable BCLM.

Although our analysis determined that the presence of extrahepatic disease was not a significant prognostic factor, the inclusion of patients with various types of extrahepatic disease allowed identification of a subset of patients with extrahepatic disease who experience poor outcomes. Patients who harbored extrahepatic metastases at the time of hepatectomy (ie, bone metastases, perihepatic nodes, and/or small volume peritoneal disease) had a lower overall survival rate (5-year OS, 16%) than patients with either extrahepatic disease resected or in remission prior to hepatectomy (5-year OS, 25%) or those with no history of extrahepatic disease (5-year OS, 43%). Despite lower survival rates observed in patients with extrahepatic disease present at hepatectomy, long-term survivors were observed in this group; therefore, we do not recommend that patients with stable extra-abdominal metastases or patients with low-volume resectable intra-abdominal disease be excluded from consideration of HR.

One previous study that analyzed outcomes for patients with BCLM identified the disease-free interval from treatment of the primary breast cancer to the diagnosis of liver metastases (<48 months) as a significant prognostic factor.[12] In contrast, our analysis, which compared patients based on a more clinically relevant breakpoint (disease-free interval ≤ 1 year vs. >1 year), determined that disease-free interval was not an independent prognostic factor. Given the long median disease-free interval in both the Pocard et al study[12] and in our own analysis, it is unlikely that treatment decisions can

reliably be based on this factor alone. Certainly, no data currently exist that support the exclusion of BCLM patients from HR based on the timing of liver metastasis diagnosis.

Finally, by making a detailed evaluation of presystemic and postsystemic treatment imaging, we were able to identify the response to prehepatectomy systemic therapy as a major prognostic factor. Patients with intrahepatic tumors that progressed while on preoperative chemotherapy had a 0% 5-year survival rate. When prehepatectomy chemotherapy was able to stabilize tumoral disease 5-year survivals after HR increased to 11% and, importantly, the 5-year survival rose to 41% and became statistically significant in patients who had an objective response. An association between prehepatectomy chemotherapy response and survivals has been identified in patients with colorectal liver metastases.[23] However, the influence of preoperative chemotherapy response on outcome in patients with BCLM is a novel finding.

In addition, there appears to be a different relationship between response and survival in patients with BCLM and colorectal metastases. In contrast to the favorable prognosis observed for patients whose colorectal liver metastases remain stable during prehepatectomy chemotherapy, the prognosis for patients with stable BCLM during prehepatectomy chemotherapy are relatively worse (5-year OS, 12%), resembling that of BCLM patients with progression of disease during preoperative therapy (5-year OS, 0%). Given these results, we recommend that response to prehepatectomy chemotherapy be closely examined when selecting patients with BCLM for HR.

During the study period, a number of advances have been made in multiple areas of breast cancer treatment. Certainly, systemic therapies have improved, including the addition of anthracyclines and taxanes to chemotherapy regimens, aromatase inhibitors to antihormonal treatment, and the targeted biologic agent trastuzumab to the treatment of patients with Her2-neu-positive tumors. Surgical treatments for primary, nodal, and metastatic disease have also improved, becoming both safer and more effective. As well, radiographic staging modalities have become more sensitive. Combined, these advances have resulted in better breast cancer patient survivals.

When patient outcomes were compared in our study, the median survivals were longer in the group of patients treated from 1994 to 2004 versus 1983 to 1993, but this difference did not reach statistical significance. This may be due to the fact that more than 70% of the patients included in our study were treated in the more recent period. In addition, a majority of the advances in breast cancer treatments have been realized in patients with early-stage disease. For patients diagnosed with visceral metastatic disease, life expectancies have been fairly constant over time, suggesting that there is significant room for improvement in the global treatment strategy for these patients and that the addition of HR to effective systemic therapies may be one means to achieve this improvement.

The dogma that surgical therapy has no role in the treatment of cancer patients with apparent systemic disease spread (ie, metastatic breast cancer) is no longer valid. When included in the multimodality treatment plan, HR can be performed with low risk and can improve long-term outcomes, provided that the metastatic disease is responding to preoperative chemotherapy and that resection is macroscopically complete. In these cases, surgical therapy can act as an effective adjuvant treatment to systemic therapies, providing selected patients with a survival benefit as well as the hope for cure.

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Discussions

Dr. Daniel Jaeck: Thank you very much. Congratulations on this very elegant study. I enjoyed your presentation very much and I have 2 questions. The first one is concerning the predictive factors of survival. You did not mention hormonal receptors and, in fact, several papers in the literature insist on the fact that these are most important predictive factors. For instance, the last paper of Dominique Elias, published in 2003 (*Am J Surg*. 2003;185:158–164), and which you did not mention in your presentation, showed a significant difference between the patients with or without hormonal receptors because the median survival was of 44 months with and of 19 months without; the difference was significant. So, please could you comment on that? I have observed that in your series nearly half of the patients did not have the results of the hormonal receptors. By the way, thank you for sending the manuscript so I could look at the results in greater detail.

The second question is concerning the radiofrequency ablations that you did not mention here but that you mention in your paper. In 7 patients, you performed radiofrequency ablation: do you consider them as R0 resections? In your experience, when you had performed a radiofrequency ablation, did you have the same result as with a resection?

Thank you for your comments.

Dr. René Adam: Thank you, Professor Jaeck, for these very interesting questions. Hormonal receptors are indeed a critical factor to consider. However, because of the retrospective pattern of our study, it has been difficult to retrieve the hormonal status of the primary tumors for patients treated early in our series. We were able to obtain this information for around half of the patients and we did not find an important effect on survival. We are currently in the process of analyzing hormonal receptors and c-erbB2 in all of the hepatic tumors and this analysis will be included in our manuscript.

With regard to radiofrequency ablation, we have reserved this for patients with unresectable metastases, allowing us to make a complete treatment. No difference at all appears in terms of survival rate in this small group of patients compared with the group treated by surgery alone. So, my feeling is that it has allowed more patients to be treated completely and, apparently, without a negative effect on the survival.

Dr. Markus Büchler: Thank you. I enjoyed your paper. It's another paper from your institution that opens new perspectives for liver surgeons. We would be under heavy criticism by our oncologists if we moved forward to liver resection in breast cancer patients. In a way, they do not permit this because they say that this is systemic disease and cannot be influenced by surgery. In a way, you show that it can be influenced. However, the major question remains that of selection. You start with 108 patients, but can you tell us a bit more about what kind of selection there has been in these 108 patients? Let's see . . . in these 20 years, how many patients were there? You operated on 108. So, is that 10% of all the patients, or 20%? We require more insight into the selection process.

Another question is the underlying type of histology. You know that breast cancer has different histologies as against colorectal cancer, for example, ductular cancer and the other types. Is there any influence of the underlying histology on the outcome?

And the third issue is that you find that the patients responding to chemotherapy are the ones that have the best outcome after surgery. Do you have any insight into a database where the oncologists have such patients that reacted to chemotherapy? How do they do without surgery of the liver? Thank you.

Dr. René Adam: Thank you, Professor Büchler, for stressing these very critical points.

First, the selection process. It is a little bit difficult for us, as a tertiary center, to know the overall population from which our referrals came. Our strategy was to propose liver surgery in all referred patients, even those with limited extrahepatic disease but for whom it was possible to enter into a strategy of, I would say, a "complete" approach. I am not speaking about a "curative" approach, a "complete" approach. So, our feeling is that we have not been very selective in the process for these patients. Of course, we do not have the number of patients managed by medical oncologists that may not have been entered into the selection

process. I totally agree with you that most of medical oncologists are reluctant to offer liver surgery, even to very selected patients.

I think we should change our thinking on this problem. Why? Because the survival at 5 years of patients treated only by chemotherapy, even those responding to chemotherapy, is very low. It is only 3%. If you compare the outcomes for patients with solitary liver-only metastases treated by chemotherapy, a select group that is similar to most surgically treated patients reported in the literature, the median survivals are, respectively, 10 and 32 months. Adding surgery to chemotherapy, even if we admit that surgery may be an adjuvant treatment to chemotherapy, we have 30% to 40% of patients alive at 5 years. So, we should do our best to convince medical oncologists that surgery may play a role in the overall strategy of these patients.

With regards to histology, I should say that it is impossible in our series to make any study of the effect of histology because nearly all the patients had ductal adenocarcinoma.

With regard to the response of chemotherapy and the way that medical oncologists manage these patients, I come back to the first point. You may have medical oncologists, even with a patient responding very favorably, that do not refer her to a surgeon. However, some medical oncologists view this situation as similar to colorectal liver metastases, and will refer patients with breast cancer metastases for surgery. We have even operated on patients with complete clinical response, and we have discovered residual tumor in the specimen. We don't know what the benefit of surgery may be in the long term for this type of patient. It is part of the puzzle that allows selected patients or relatively selected patients to be offered long-term survivals.

Dr. Joan Figueras: As a hepatic surgeon, I am asked more and more frequently to operate on patients with hepatic metastases from breast cancer. I think that your observations would be very important in their management, but my question is regarding extrahepatic disease. Many of these patients have lymph nodes in the porta hepatis. What do you do? Can you differentiate the prognosis of the different kinds of extra hepatic disease? I mean, do lymph nodes in the porta hepatis or metastases do as well or badly as local recurrence at level of the axilla, for instance?

Dr. René Adam: Thanks for your question. Because of the small number of patients with extrahepatic disease, we were not able to distinguish outcomes between local recurrence and porta hepatis lymph node invasion. As described more fully in the paper, patients with extrahepatic disease at the time of hepatectomy (including those with portal node involvement) experienced poorer survivals. However, there were some long-term survivors in this group, so it may not be an absolute contraindication to resection. Based on our results, our current policy is to consider hepatectomy only in patients who respond to systemic therapy, but sometimes we discover extrahepatic disease during the operation. If lymphadenectomy of the pedicle is possible, we do this. If the disease is widespread and portal lymphadenectomy will not be curative, then we do not perform the resection. This explains why some patients in our series were considered nonresectable.

Dr. Henri Bismuth: Only a very short remark. The mortality is very low, and this is an argument if we are in doubt about undertaking the operation so as to convince the oncologists that we should offer a chance to the patient.