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CLINICAL INVESTIGATION

CT-Guided Radiofrequency Ablation in Patients with Hepatic Metastases from Breast Cancer

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Abstract The purpose of this study was to evaluate technical success, technique effectiveness, and survival following radiofrequency ablation for breast cancer liver metastases and to determine prognostic factors. Forty-three patients with 111 breast cancer liver metastases underwent CT-guided percutaneous radiofrequency (RF) ablation. Technical success and technique effectiveness was evaluated by performing serial CT scans. We assessed the prognostic value of hormone receptor status, overexpression of human epidermal growth factor receptor 2 (HER2), and presence of extrahepatic tumor spread. Survival rates were calculated using the Kaplan–Meier method. Technical success was achieved in 107 metastases (96%). Primary technique effectiveness was 96%. During follow-up local tumor progression was observed in 15 metastases, representing a secondary technique effectiveness of 86.5%. The overall time to progression to the liver was 10.5 months. The estimated overall median survival was 58.6 months. There was no significant difference in terms of survival probability with respect to hormone receptor status, HER2 overexpression, and presence of isolated bone metastases. Survival was significantly lower among patients with extrahepatic disease, with the exception of skeletal metastases. We conclude that CT-guided RF ablation of liver metastases from breast cancer can be performed with a high degree of technical success and technique effectiveness, providing promising survival rates in patients with no visceral extrahepatic disease. Solitary bone metastases did not negatively affect survival probability after RF ablation.

Keywords Interventional radiology · Radiofrequency ablation · Breast cancer · Liver metastases

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Introduction

Nearly half of all women diagnosed with metastatic breast cancer will eventually develop liver metastases [1]. Chemotherapy and hormone therapy are currently the mainstays of treatment for metastatic breast cancer, but recurrence after each response to chemotherapy is virtually inevitable, and the chance of a response is reduced with each subsequent course of chemotherapy [2]. Thus, chemotherapy in the setting of breast cancer hepatic metastases delays progression and prolongs survival (median survival duration, 18 to 24 months) but is rarely curative [3, 4].

Although the majority of patients with metastatic breast cancer have evidence of widespread metastatic disease involving additional sites, 5% to 20% will present with metastatic disease confined to the liver [5, 6]. This highly selected group of patients may benefit from a more aggressive treatment approach [7]. Recent studies suggest a role for hepatic resection in these patients with isolated metastatic spread to the liver. Single-institutional series have reported 5-year surgery-related survival rates of 18% to 51% [7–11]. Vlastos et al. demonstrated 2- and 5-year survival rates of 86% and 61%, respectively, when patients were treated with major liver resection or minor resection with or without radiofrequency (RF) ablation [12].

Many patients have nonresectable disease, and thus the prognosis of this tumor is dismal. The development of ablative techniques such as RF ablation has revolutionized the management of patients with liver metastases. Furthermore, RF ablation can be combined with liver resection when complete resection of the tumor is not feasible.

Hormone receptor status, expression of human epidermal growth factor receptor 2 (HER2), and extrahepatic disease are important prognostic factors for response to adjuvant and neoadjuvant treatments of breast cancer [13, 14]. In this study, we evaluated the technical success, technique effectiveness, and survival following RF ablation and the prognostic significance of estrogen-receptor (ER) and progesterone-receptor (PR) status, expression of HER2 (and treatment with trastuzumab), and presence of extrahepatic disease.

Materials and Methods

Patients and Tumor Characteristics

Prior to its initiation, our study protocol was approved by the institutional review board and informed patient consent was obtained from each patient.

Between 1999 and 2006, RF ablation was performed in 43 women with 111 unresectable breast cancer liver metastases that were treated in 72 sessions. A mean 1.7 treatment sessions was performed per patient. Treatment of new metastases, which were identified during follow-up, was described as new treatment round. A mean 2.6 tumors was treated per patient. Seven (16.3%) patients presented with local tumor progression at first follow-up (3 months) and were retreated.

At the time of RF ablation 10 patients (23.3%) presented with controlled, isolated bone metastases that were not considered to be determinants of life expectancy. Three patients (7%) had known lymph node metastases, one patient (2.3%) had concomitant pulmonary and lymph node metastases, and two patients (4.6%) had few pulmonary metastases, with no evidence of further spread into other organs. One patient (2.3%) presented with concomitant osseous and lymph node metastases. In another patient (2.3%) a single cerebral metastasis was successfully treated by cyberknife 6 months prior to RF ablation. There was no evidence of extrahepatic metastases in 25 patients (58.1%).

Inclusion Criteria

The following inclusion criteria were used:

- progressing metastatic liver disease from breast cancer (biopsy-proven in all patients);
- failure of established chemotherapies and/or hormone therapy regimen or cessation of therapy due to toxic side effects or patient refusal;
- consensus to include a patient by members of a multidisciplinary tumor board, including oncologists, gynaecologists, surgeons, radiation oncologists, and interventional radiologists;
- no more than five hepatic metastases and no metastasis larger than 5 cm in diameter;
- no significant extrahepatic tumor disease (bone metastases that were under control as a result of appropriate systemic treatment and/or radiation therapy were not considered a contraindication for RF ablation; in patients with tumor spread beyond the liver, inclusion depended on the individual performance status);
- platelet count $\geq 50 \times 10^9$/L;
- no treatment-refractory coagulopathy; and
- no clinically apparent infection.

The indications for RF ablation were locally nonresectable tumors in 30 patients (69.8%), general contraindication for surgery in 7 patients (16.3%), refusal of surgical resection in 2 patients (4.6%), and bilobar tumor involvement with combined hepatic resection of one lobe and RF ablation for the metastases in the remaining lobe in 4 patients (9.3%).

Previous Treatment

Adjuvant Hormonal Treatment Schedules

Nineteen of the 43 women (44.2%) in our study received initial tamoxifen after breast-preserving surgery. In 10 of them (23.3%), treatment was continued with letrozole after tamoxifen was stopped 5 years after primary breast surgery. Three patients (7%) received up-front letrozole only and 11 patients refused treatment with these drugs.

Treatment Schedule for Metastatic Disease

After detection of liver metastases, patients were candidates for cytotoxic chemotherapy: 26 patients (60.5%)

received an anthracycline-containing regimen (EC[epirubicin/cyclophosphamide]-, AC[doxorubicin/cyclophosphamide]-, EC-CMF[cyclophosphamide/methotrexate/fluorouracil]-scheme), whereas 13 patients (30.2%) received an anthracycline-free regimen which consisted of a taxane-based regimen in two patients (4.7%). Four patients (9.3%) refused systemic chemotherapy.

In our cohort 11 patients (26%) presented with hepatic breast cancer metastases and an overexpression of HER2 and were therefore candidates for trastuzumab.

Radiofrequency Ablation Procedure

After contrast-enhanced computed tomography (CT) was performed, the optimal electrode pathway to the metastasis was determined. All RF ablation procedures were performed using multitined expandable electrodes (RITA Starburst XL; RITA Medical Systems, Mountain View, CA, USA) that were placed under CT-fluoroscopy guidance. With this electrode design, an array of multiple, stiff, curved wires was deployed from a single 14-gauge cannula in the metastasis and progressively distended to its maximum diameter of up to 5 cm, during ablation. The exact positioning of the electrode and the complete coverage of the lesion with the hooks fully distended were warranted by CT-fluoroscopy guidance or, when there was doubt, with additional contrast-enhanced CT scans. After attaching to the high-power RF generator (RITA Medical Systems), the RF current was emitted from the active, noninsulated curved electrodes. The delivered power was increased till the target temperature of 95–100°C was reached. Subsequently, the energy was maintained for as long as 25 to 45 min. To control the achieved coagulation zone instantaneously after completing the procedure, a postprocedural contrast-enhanced CT scan with the electrode still in place was performed to depict incomplete ablation with the option of an immediate additional ablation as well as to detect potential periprocedural complications. For metastases <3 cm in size, a single session of ablation with a maximum electrode diameter of 5 cm was used to provide a sufficient safety margin. In lesions up to 5 cm in size, the electrode was repositioned several times in a single session to achieve a volume large enough to cover the entire metastasis including a safety margin. To reduce the risk of puncture-related bleeding, electrode-track ablation was performed after completion of the procedure at a lower power level (ca. 25 W). Our standard approach for RF ablation was to perform the procedure under moderate sedation and local anesthesia. The majority of ablations were performed with administration of a combination of midazolam maleate, parecoxib-sodium, and piritramid. Blood pressure, heart rate, and oxygen saturation were monitored continuously. In patients who presented with low tolerance to pain, or lesions that were difficult to target, the procedure was performed under general anesthesia. Preinterventional antibiotics were used for all patients.

Post-Radiofrequency Ablation Treatment

Seventeen patients (40%) received no further cytotoxic treatment after RF ablation. Twenty-one patients (49%) did receive various chemotherapeutic regimes: 11 received a monochemotherapy (vinorelbin tartrate) and the remaining 10 received a polychemotherapy concept including CMF ($n = 2$), EC ($n = 2$), fluorouracil/epirubicin/cyclophosphamide (FEC; $n = 1$), capecitabine, gemcitabine, doxorubicin, cisplatin, and mitomycin. In addition, four patients received trastuzumab and one patient received bevacizumab after ablation. Two patients were treated with aromatase inhibitors (anastrozole, letrozole), and four with antimicrotubule agents (e.g., paclitaxel or docetaxel). One patient received radioembolization utilizing yttrium-90 microspheres 5 years after initial RF ablation due to multiple, large hepatic metastases.

Assessment of Technical Success and Technique Effectiveness

To evaluate technical success and technique effectiveness of the RF ablation procedure, contrast-enhanced CT was performed (utilizing the same parameters chosen for pretreatment imaging) on the day following treatment, 6–8 weeks after the procedure, and every 3–4 months thereafter. The primary and secondary effectiveness rates (defined as the percentage of tumors that were successfully eradicated following the initial procedure) were evaluated for all metastases treated with RF ablation and that had been followed for at least 3 months ($n = 111$). A tumor that is treated according to protocol and covered completely, as determined at the time of the procedure, is "technically successful." Local tumor progression at the area of induced coagulation was defined by the following criteria:

- if the size of the metastasis increased from the size noted on the CT scan the day after treatment and
- if contrast enhancement showed that parts of the tumor/area of induced coagulation had a bulge consisting of solid material.

RF ablation was considered complete when no focal, nodular enhancement was seen within the area of induced coagulation or at its periphery on CT scans obtained at least 3 months after treatment (Fig. 1A–E) [15, 16]. Time to tumor progression (TTP) was determined as either progression in size of formerly treated metastases or detection of new hepatic lesions.

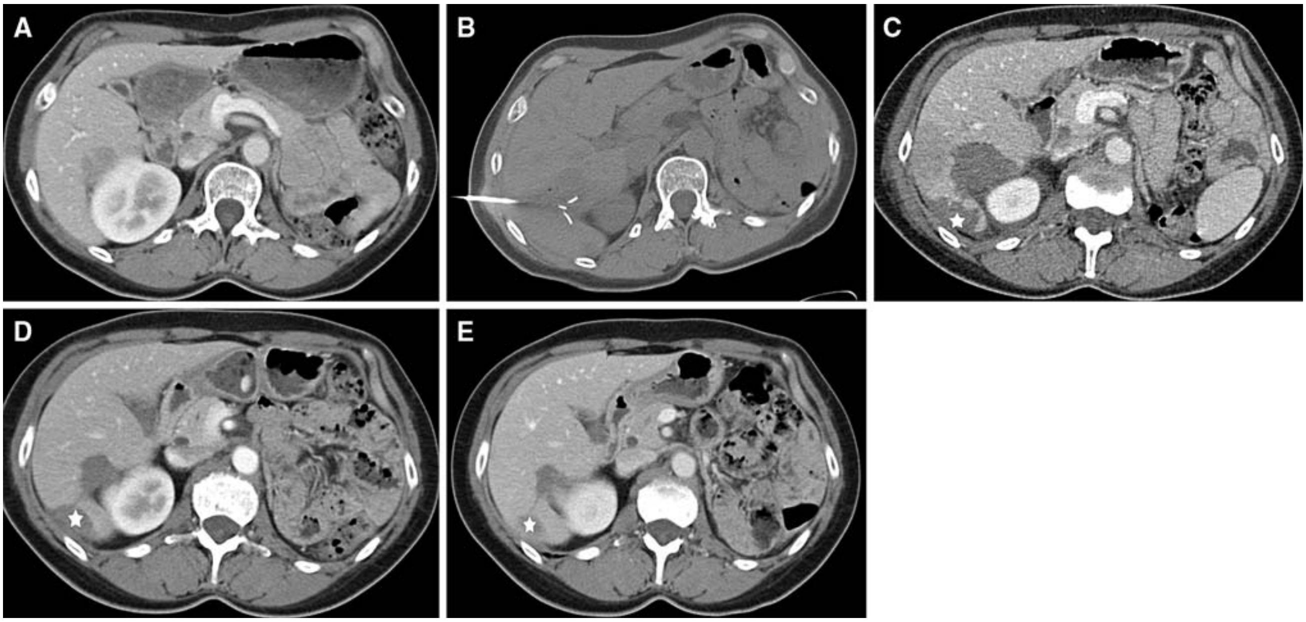

Fig. 1 A subcapsular metastasis with a maximum diameter of 2.5 cm is displayed in segment VI (**A**). A multitined expandable electrode was placed under CT-fluoroscopy guidance and progressively distended to a diameter of 4 cm (**B**). In order to avoid heat damage of the adjacent right kidney, a 5% glucose solution was administered in the perirenal tissue. The 24-h control scan showed complete coverage of the metastasis by the induced coagulation area (**C**). Note: the second hypodense lesion (*) represents the cranial aspect of another ablation area of a lesion below this slice. Follow-up scans at 3 months (**D**) and 6 months (**E**) display involution of the ablation area, with no evidence of tumor recurrence

Survival Analysis

Survival rates were calculated for all patients ($n = 43$) by Kaplan–Meier method using ER status and PR status, HER2 expression, and presence of extrahepatic disease. The log-rank test was calculated for comparison between the survival curves, and to test the probability that there was a trend in survival scores across the groups. If the p-value associated with the chi-square statistic was <0.05, it was concluded that, statistically, survival curves differed significantly or that the variable had a significant influence on survival time. Furthermore, survival curves were compared by calculating the hazard ratio with its 95% confidence interval (CI). Because the computation of the hazard ratio assumes that the ratio is consistent over time, the hazard ratio statistic had been ignored when survival curves crossed.

The estimated survival times are biased owing to a number of censored cases ($n = 30$). In these cases, the event in question had not been noted by the end of the period of observation. For the purposes of calculating the median survival time, these cases were treated as if the event had been noted at the end of the observation period. Statistical analyses were performed using MedCalc for Windows, version 7.3.0.1 (MedCalc Software, Mariakerke, Belgium).

Results

The median duration of follow-up after RF ablation was 37 months (range, 2 to 69 months). The mean patient age was 57 years (range, 35 to 81 years). The mean diameter of the treated lesions was 20.9 mm (±13 mm standard deviation [SD]; range, 5 to 85 mm). The metastasis that was 85 mm in size was treated for tumor debulking. At the time of this analysis 13 patients had died.

Technical Success and Technique Effectiveness

The technical success and technique effectiveness rates were determined using contrast-enhanced CT scans obtained 24 h, 6–8 weeks, and 3, 6, 9, and 12 months after RF ablation. During follow-up, no local tumor progression was detected later than 9 months after RF ablation.

Technical success (success of the treatment according to protocol, with the tumor completely covered) was achieved in 107 of 111 metastases (96%). In three patients with four metastases the RF ablation could not be executed completely since the patients described severe pain, not controllable with appropriate medication.

In 12 metastases (9 patients), incomplete ablation of the tumor was detected in the 24-h control scan. Therefore these patients were referred to a second session in which the treatment was finally completed in all but four cases. Therefore the overall primary technique effectiveness rate was 96%. Complete coverage of the tumor by the induced coagulation area was not achievable in the patient with the 8.5-cm tumor. The remaining three patients had metastases in close proximity to large blood vessels (e.g., vena cava). The heat sink effect therefore prevented the metastases from being completely covered by the induced coagulation area.

Because of the number of metastases and a somewhat limited tolerance for the time-consuming procedure, the treatment was delivered in two separate sessions in six patients (14%) in order to achieve complete coverage of the tumor by the induced coagulation area.

Local tumor progression was observed in 15 of 111 metastases (13.5%; seven patients) at 3 months follow-up, therefore, the tumor-based secondary therapeutic effectiveness rate was 86.5%. Local tumor progression was identified as a nodular and irregular area of enhancement at the rim of the ablation zone. In five of these seven patients RF ablation was repeated.

The median TTP within the liver was 10.5 months (mean, 10.7 months; range, 2.4 to 27.3 months).

Overall Survival

Survival curves were evaluated using the Kaplan–Meier method. The median survival rate for all patients, with calculation started on the date of RF ablation, was 58.6 months (Fig. 2).

Prognostic Value of Hormone Receptor Status

There were no statistically significant differences in the survival probability of patients with positive ($n = 18$) and negative ($n = 25$) hormone receptor status (log-rank test, $p = 0.5819$; $\chi^2 = 0.3032$) (Fig. 3A). The calculation of the hazard ratio did not apply. The median survival duration was 48.2 months for those patients with a positive hormone receptor status. Because less than 50% of the patients with a negative hormone receptor status died, the median survival duration was not calculated for this subset of patients.

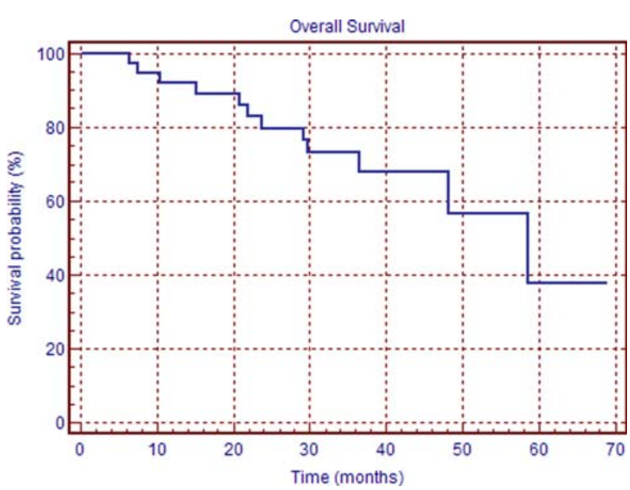

Fig. 2 This graph illustrates the overall survival probability calculated with the Kaplan–Meier method for 43 patients with 111 liver metastases. The estimated median survival duration was 58.6 months

Prognostic Value of HER2 Overexpression

There was no statistically significant difference in survival between patients without ($n = 32$) and with ($n = 11$) an overexpression of HER2 and treatment with trastuzumab (log-rank test, $p = 0.5798$; $\chi^2 = 0.3065$) (Fig. 3B). The median survival duration was 48.2 months for those patients with no overexpression of HER2. For the subgroup negative for overexpression of the HER2 protein, neither median survival nor hazard ratio was calculated, since prerequisites were not met.

Prognostic Value of the Presence of Extrahepatic Tumor Disease

A separate Kaplan–Meier evaluation of patients with ($n = 8$) or without ($n = 35$) extrahepatic breast cancer metastases (Fig. 3C) resulted in a statistically significant difference in the survival rate (log-rank test, $p = 0.0421$; $\chi^2 = 3.2353$). The median survival duration for patients with and without extrahepatic tumor spread was 36.4 and 58.6 months (hazard ratio = 2.83, 95% CI = 0.87 to 21.62), respectively. Patients with isolated bone metastases were excluded from this analysis. In addition, there was no statistically significant difference in survival probability between patients with tumor spread confined to the bones ($n = 10$; Fig. 3D) and patients with no extrahepatic tumor manifestations ($n = 33$) (log-rank test, $p = 0.5137$; $\chi^2 = 0.4193$; hazard ratio = 1.53, 95% CI = 0.37 to 7.30).

Treatment Side Effects and Complications

The Society of Interventional Radiology (SIR) reporting criteria were used to describe minor and major complications. Sixty-two of 72 RF ablation sessions (86%) were well tolerated by the patients in whom moderate sedation and local anesthesia were used. Seven patients (eight sessions; 11%) described moderate to severe discomfort during the procedure, which was manageable with appropriate medication. Due to low tolerance to pain in three sessions (7%; three patients), the procedure was abandoned and repeated in general anaesthesia.

The minor complications were discrete to moderate subcapsular hematoma in two patients (4.6%), hematoma of the abdominal wall in one patient (2.3%), and pleural effusion in five patients (11.6%). None of these conditions required further treatment, and they resolved uneventful.

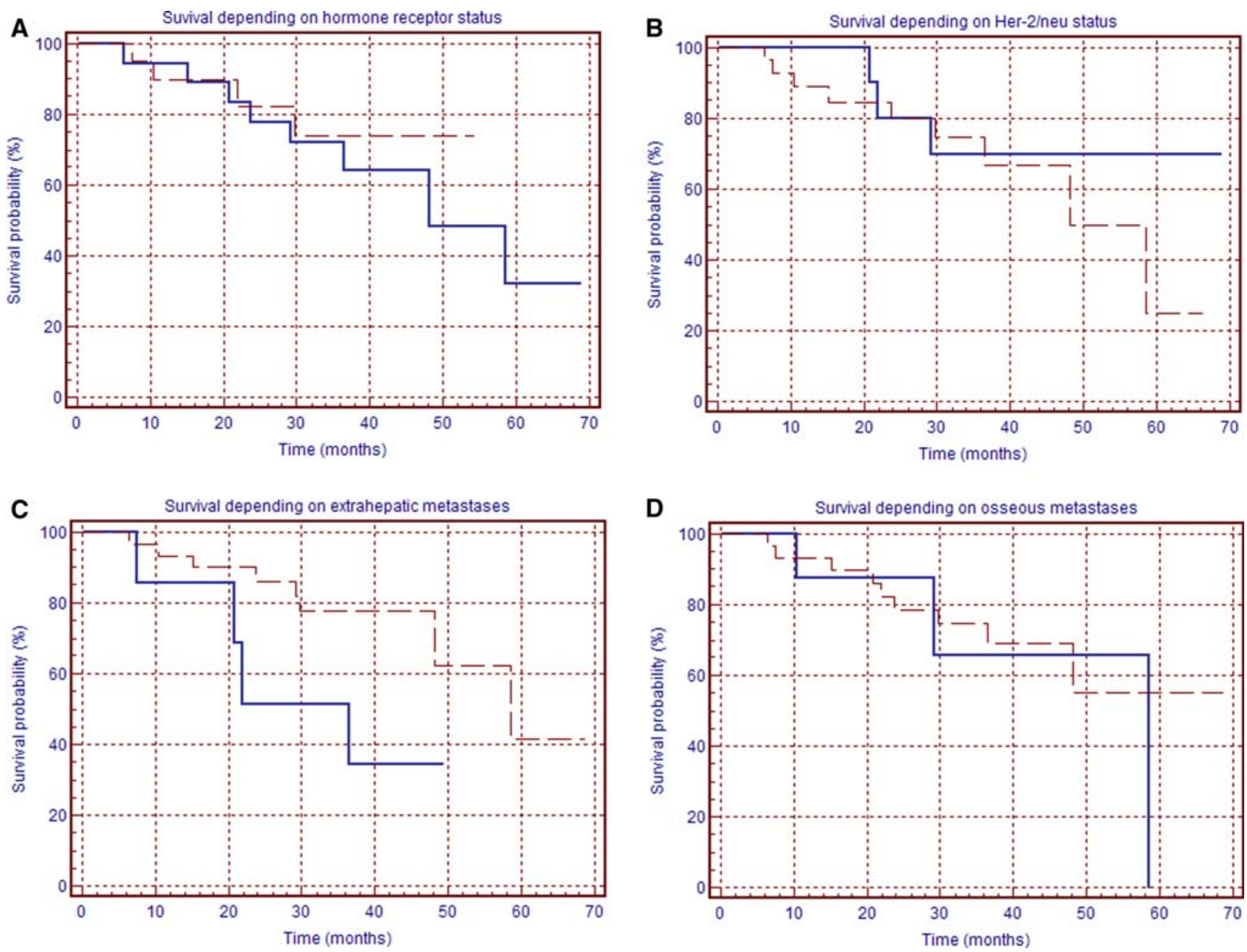

Fig. 3 This graph illustrates the survival probability calculated with the Kaplan–Meier method. The calculation was based on the following. (**A**) The presence (continuous line) or absence (interrupted line) of hormone-receptor positivity: the estimated median survival duration (hormone receptor positive) was 48.2 months. The difference was not statistically significant ($p > 0.05$). (**B**) The presence (continuous line) or absence (interrupted line) of HER2 protein overexpression: the estimated median survival duration (no overexpression of HER2) was 48.2 months. The difference was not statistically significant ($p > 0.05$). (**C**) The presence (solid line) or absence (dashed line) of extrahepatic metastatic disease: the estimated median survival for patients with and without extrahepatic spread was 36.4 and 58.6 months, respectively. The difference was statistically significant ($p < 0.05$). (**D**) The presence (solid line) or absence (dashed line) of metastasis confined to the bones: the difference concerning survival probability was not statistically significant ($p > 0.05$)

The major complications were severe intrahepatic bleeding in two patients (4.6%) and injury to the bile duct in one patient (2.3%). Both arterial bleedings were coiled successfully under angiography guidance immediately after the RF ablation procedure. The bile duct injury required external, percutaneous drainage. No liver abscess or pneumothorax was noted. Neither seeding of metastases along the cannulation tract nor 30-day mortality occurred in our study population.

Discussion

Most patients with metastatic breast cancer ultimately die from their disease, with a median survival of 18 to 24 months and a 5-year survival rate of 22% [3, 4]. Therefore, treatment is palliative in intent, and its goals include improving quality of life and prolonging survival. Although transient responses are possible with conventional treatment modalities (chemotherapy, hormonal therapy, or local radiotherapy), most patients develop progressive disease within 1–2 years of initiating therapy [17–19]. However, a small number of patients benefit from treatment for long periods of time.

Available data suggest that the liver is not a common initial site of distant metastases, observed in 5% to 20% of patients; however, more than half of the patients develop liver metastases at some point in their clinical course [5]. Despite the fact that the management of breast cancer patients with liver metastases represents a difficult situation, only a few studies have investigated the clinical outcome of this subset of patients, in whom reports of a median survival have ranged from 3 to 24 months [5, 6, 20].

On the basis of the results obtained with laser ablation and RF ablation in the treatment of hepatocellular carcinoma and hepatic metastases from colorectal cancer [21–28], we treated patients suffering from hepatic breast cancer metastases.

There are limited data on the use of RF ablation in treating hepatic metastases from breast cancer. In this study, primary technique effectiveness was 96%, which is comparable with the 92%, 88%, and 87% reported by Livraghi et al. [29], Gunabushanam et al. [30], and Lencioni et al. [31], respectively. In a multicenter trial of RF ablation in 102 patients with 153 hepatic metastases from breast cancer [31], Lencioni reported primary and secondary technique effectiveness rates of 87% and 95%, respectively, which are slightly different from the 96% and 86.5%, respectively, found in the current study. This variation between the primary and the secondary technique effectiveness of these patients might be due to the different follow-up protocol, which included ultrasound examination and the first imaging follow-up 3 months after the RF ablation procedure.

Differences in survival rates could be related to differences in patient selection, tumor staging, tumor biology, or a combination of these factors. The optimal therapeutic management of an individual with metastatic disease is largely dependent on the prognostic and/or predictive models that have been established through evaluation of multiple patient-, tumor-, and disease-related factors [32]. A short disease-free interval, a young age, a negative hormone-receptor status, lack of response to prior therapy, presence of visceral involvement, multiple sites of disease, and HER2 positivity are among the prognostic factors indicating an unfavourable disease course. It has long been reported that the development of visceral metastases, particularly in the liver, is an ominous sign indicating a poor outcome and a poor response to chemotherapy, endocrine therapy, or both [33–35]. Moreover, even with high-dose and intensive chemotherapy supported by stem cell support, liver metastases have been shown to retain their poor prognosis [36, 37]. Furthermore, it can be inferred that the biological aggressiveness of metastatic disease often reflects that of the primary tumor. In other instances, likely due to occasional or adjuvant treatment-induced mutations in metastatic cells, some prognostic factors, such as grading, receptor status, and cellular kinetic parameters, differ in primary and metastatic disease. Therefore, fast fatal outcome or relatively prolonged survival may occur in patients with distant metastases from primary tumors with a favorable or an unfavorable prognosis, respectively. Finally, the number of patients included in our study was relatively small.

A study published by Mack et al., however, which included 232 patients with 578 liver metastases from breast cancer who were treated with laser interstitial tumor therapy (LITT), failed to show significant differences in terms of survival probability depending on the number of metastases, the indication for LITT, a synchronous or metachronous pattern, disease-free interval (<4 or >4 years), or whether bone metastases were present. The authors described a tendency toward improved survival in patients with a N0- or N1-stage primary lymph node disease compared with patients with N2- and N3-stage disease. However, the difference was not statistically significant. Furthermore, patients with no evidence of bone metastases demonstrated a slightly improved mean survival (not statistically significant) compared to patients with controlled osseous involvement [38]. This finding is partially supported by the data presented here. Neither hormone-receptor status nor overexpression of the HER2 protein significantly impacted survival probability in our relatively small study population. In addition, corresponding to the results presented by Mack et al. [38], the presence or absence of controlled osseous metastases at the time of RF ablation did not demonstrate a significant difference in terms of survival probability. However, if extrahepatic disease beyond osseous involvement was noted, our data indicate a significant difference regarding the survival time.

In the study published by Gunabushanam et al. [30], the 1-year survival rate in the group with liver and bone metastases was higher than in the group with liver metastases only. Due to the very small number of patients and the described patient selection bias (patients with bone metastases already had biologically stable disease; absence of disease progression for at least 6 months was an essential inclusion criterion for those with bone metastases but not for patients with liver-only disease), this result proved not to be statistically significant. The authors stated that the presence of extrahepatic disease in itself did not appear to be a contraindication to RF ablation because liver metastases may have a more significant impact on a patient's long-term well-being than the limited bone metastases. However, our data suggest that especially those patients with tumor spread beyond the liver and bones have a reduced survival probability compared with all other groups. This result is confirmed by early data published by Zinser et al. [6]. They reported that survival in breast cancer patients with liver-only metastases (19 months) or those with liver and bone metastases (17 months) was longer than that of patients with metastases to other sites (12 months). The authors therefore concluded that the presence of isolated liver metastases may not indicate as poor a prognosis as previously believed.

In addition, surgical resection of limited hepatic metastases from breast cancer seems to provide a survival benefit compared with historical controls in numerous retrospective studies. Maksan et al. [9] evaluated 90 patients and reported an estimated 5-year survival rate in 51% of the hepatic resection group. Node-negative primary breast cancer and a long interval between treatment of the primary and liver metastases appeared to be associated with long survival after liver resection. Adam et al. [39] published data from a study of 85 patients with breast cancer liver metastases. Extrahepatic metastases had been treated prior to hepatic resection or were synchronously present in 27 patients (32%). Liver metastases were solitary in 32 patients (38%) and numbered more than 3 in 26 patients (31%). 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%, respectively: 28 patients (33%) developed isolated hepatic recurrences. However, perioperative complications occurred in 26% of the patients, with a median hospital stay of 9 days. Response to preoperative chemotherapy, resection margin, and rehepatectomy for intrahepatic recurrence were key prognostic factors. Raab et al. [10] also found that the resection margin is a key prognostic factor. They reported better survival with R0 (complete) resection than with R1 or R2 (incomplete) resections. Vlastos et al. demonstrated 2- and 5-year survival rates of 86% and 61%, respectively, when patients underwent major liver resection or minor resection with or without RF ablation [12]. However, these reports describe only relatively small patient cohorts, and all investigators noted considerable heterogeneity in the presentation and progression of metastatic disease. Thus, and despite initially promising results, most patients with metastatic breast cancer continue to be treated with systemic chemotherapy alone.

Compared with surgery, RF ablation offers the advantage of being less expensive and considerably less invasive. Due to minor loss of liver parenchyma after RF ablation, liver toxicities are less likely and simultaneous or subsequent use of other therapies, such as hormone therapy, chemotherapy, or both, remains feasible. Adam et al. described a procedure-related morbidity and subsequently prolonged hospital stay in 26% of all patients treated with hepatic resection [7]. Moreover, death has been reported after partial hepatectomy in breast cancer patients [11]. These complication rates are substantially higher than those in our own study group and rise above all complication rates reported in the RF ablation literature. This is an important drawback of surgery, especially because it is still not known whether the use of any local therapy can be justified in patients with metastatic breast cancer.

Conclusions

In summary, the results of our study indicate that RFA of hepatic breast cancer metastases is a safe and effective treatment option in highly selected patients. In addition to chemotherapy, less invasive thermal ablation techniques like RF ablation demonstrate their potential role in the management of liver metastases from breast cancer. Due to the excellent technical success and technique effectiveness, RF ablation might prolong the interval between two systemic chemotherapies. However, data are based solely on reports from small, heterogeneous single-institution series, and the lack of prospective randomized trials demonstrating that this regional treatment modality might add further benefit to conventional treatment hampers its integration into routine clinical practice. Moreover, there is ample room to improve the survival of breast cancer patients with liver metastases alone, who may indeed represent the population deserving a more aggressive therapeutic approach, including local ablation techniques like RF ablation. This hypothesis needs to be tested prospectively through well-designed clinical trials. However, given the small percentage of patients with isolated liver metastases and the paucity of centers experienced in the local ablation of liver metastases from breast cancer, a large, multicenter, international collaboration seems mandatory to accomplish this ambitious task.

References

1. Jardines L, Callans LS, Torosian MH (1993) Recurrent breast cancer: presentation, diagnosis, and treatment. Semin Oncol 20(5):538–547
2. Gregory WM, Smith P, Richards MA et al (1993) Chemotherapy of advanced breast cancer: outcome and prognostic factors. Br J Cancer 68(5):988–995
3. Miller KD, Sledge GW Jr (1999) The role of chemotherapy for metastatic breast cancer. Hematol Oncol Clin North Am 13(2):415–434
4. Stockler M, Wilcken NR, Ghersi D et al (2000) Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. Cancer Treat Rev 26(3):151–168
5. Hoe AL, Royle GT, Taylor I (1991) Breast liver metastases—incidence, diagnosis and outcome. J R Soc Med 84(12):714–716
6. Zinser JW, Hortobagyi GN, Buzdar AU et al (1987) Clinical course of breast cancer patients with liver metastases. J Clin Oncol 5(5):773–782
7. Adam R, Aloia T, Krissat J et al (2006) Is liver resection justified for patients with hepatic metastases from breast cancer? Ann Surg 244(6):897–907
8. Carlini M, Lonardo MT, Carboni F et al (2002) Liver metastases from breast cancer. Results of surgical resection. Hepatogastroenterology 49(48):1597–1601
9. Maksan SM, Lehnert T, Bastert G et al (2000) Curative liver resection for metastatic breast cancer. Eur J Surg Oncol 26(3):209–212
10. Raab R, Nussbaum KT, Behrend M et al (1998) Liver metastases of breast cancer: results of liver resection. Anticancer Res 18(3C):2231–2233

11. Selzner M, Morse MA, Vredenburgh JJ et al (2000) Liver metastases from breast cancer: long-term survival after curative resection. Surgery 127(4):383–389
12. Vlastos G, Smith DL, Singletary SE et al (2004) Long-term survival after an aggressive surgical approach in patients with breast cancer hepatic metastases. Ann Surg Oncol 11(9):869–874
13. Konecny GE, Thomssen C, Luck HJ et al (2004) Her-2/neu gene amplification and response to paclitaxel in patients with metastatic breast cancer. J Natl Cancer Inst 96(15):1141–1151
14. Imkampe A, Bendall S, Bates T (2007) The significance of the site of recurrence to subsequent breast cancer survival. Eur J Surg Oncol 33(4):420–423
15. Goldberg SN, Gazelle GS, Compton CC et al (2000) Treatment of intrahepatic malignancy with radiofrequency ablation: radiologic-pathologic correlation. Cancer 88(11):2452–2463
16. Paulet E, Aube C, Pessaux P et al (2008) Factors limiting complete tumor ablation by radiofrequency ablation. CardioVasc Interv Radiol 31(1):107–115
17. Rahman ZU, Frye DK, Smith TL et al (1999) Results and long term follow-up for 1581 patients with metastatic breast carcinoma treated with standard dose doxorubicin-containing chemotherapy: a reference. Cancer 85(1):104–111
18. Bergh J, Jonsson PE, Glimelius B et al (2001) A systematic overview of chemotherapy effects in breast cancer. Acta Oncol 40(2–3):253–281
19. Cristofanilli M, Hortobagyi GN (2001) New horizons in treating metastatic disease. Clin Breast Cancer 1(4):276–287
20. O'Reilly SM, Richards MA, Rubens RD (1990) Liver metastases from breast cancer: the relationship between clinical, biochemical and pathological features and survival. Eur J Cancer 26(5):574–577
21. Jakobs TF, Hoffmann RT, Trumm C et al (2006) Radiofrequency ablation of colorectal liver metastases: mid-term results in 68 patients. Anticancer Res 26(1B):671–680
22. Lencioni R, Crocetti L, Cioni D et al (2004) Percutaneous radiofrequency ablation of hepatic colorectal metastases: technique, indications, results, and new promises. Invest Radiol 39(11):689–697
23. Lencioni R, Cioni D, Crocetti L et al (2005) Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology 234(3):961–967
24. Livraghi T, Goldberg SN, Lazzaroni S et al (1999) Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. Radiology 210(3):655–661
25. Livraghi T, Goldberg SN, Lazzaroni S et al (2000) Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. Radiology 214(3):761–768
26. Livraghi T, Solbiati L, Meloni F et al (2003) Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". Cancer 97(12):3027–3035
27. Parkin DM, Bray FI, Devesa SS (2001) Cancer burden in the year 2000. The global picture. Eur J Cancer 37(Suppl 8):S4–S66
28. Lawes D, Chopada A, Gillams A et al (2006) Radiofrequency ablation (RFA) as a cytoreductive strategy for hepatic metastasis from breast cancer. Ann R Coll Surg Engl 88(7):639–642
29. Livraghi T, Goldberg SN, Solbiati L et al (2001) Percutaneous radio-frequency ablation of liver metastases from breast cancer: initial experience in 24 patients. Radiology 220(1):145–149
30. Gunabushanam G, Sharma S, Thulkar S et al (2007) Radiofrequency ablation of liver metastases from breast cancer: results in 14 patients. J Vasc Interv Radiol 18(1; Pt 1):67–72
31. Lencioni R (2004) Tumor Radiofrequency Ablation Italian Network (TRAIN): survival analysis in breast cancer patients with isolated hepatic metastases. 2004 Assembly of the Radiological Society of North America, Chicago, IL
32. Hortobagyi GN, Smith TL, Legha SS et al (1983) Multivariate analysis of prognostic factors in metastatic breast cancer. J Clin Oncol 1(12):776–786
33. Perez JE, Machiavelli M, Leone BA et al (1990) Bone-only versus visceral-only metastatic pattern in breast cancer: analysis of 150 patients. A GOCS study. Grupo Oncologico Cooperativo del Sur. Am J Clin Oncol 13(4):294–298
34. Leone BA, Romero A, Rabinovich MG et al (1988) Stage IV breast cancer: clinical course and survival of patients with osseous versus extraosseous metastases at initial diagnosis. The GOCS (Grupo Oncologico Cooperativo del Sur) experience. Am J Clin Oncol 11(6):618–622
35. Muss HB (1992) Endocrine therapy for advanced breast cancer: a review. Breast Cancer Res Treat 21(1):15–26
36. Rowlings PA, Williams SF, Antman KH et al (1999) Factors correlated with progression-free survival after high-dose chemotherapy and hematopoietic stem cell transplantation for metastatic breast cancer. JAMA 282(14):1335–1343
37. Rizzieri DA, Vredenburgh JJ, Jones R et al (1999) Prognostic and predictive factors for patients with metastatic breast cancer undergoing aggressive induction therapy followed by high-dose chemotherapy with autologous stem-cell support. J Clin Oncol 17(10):3064–3074
38. Mack MG, Straub R, Eichler K et al (2004) Breast cancer metastases in liver: laser-induced interstitial thermotherapy—local tumor control rate and survival data. Radiology 233:400
39. Adam R, Aloia T, Krissat J et al (2006) Is liver resection justified for patients with hepatic metastases from breast cancer? Ann Surg 244(6):897–908