Radiation segmentectomy for curative intent of unresectable very early to early stage hepatocellular carcinoma (RASER): a single-centre, single-arm study

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Summary

Background Unresectable solitary very early to early stage hepatocellular carcinoma is managed with ablation for curative intent. Radiation segmentectomy is a treatment option that delivers radioactive ^{90}yttrium (^{90}Y)-bound microspheres transarterially to a segment of liver. The aim of this study was to assess the safety and efficacy of radiation segmentectomy in patients with unresectable hepatocellular carcinoma deemed unfavourable for ablation.

Methods RASER was a single-centre, single-arm study that included adults (>18 years) with solitary hepatocellular carcinoma with unfavourable location for ablation, without metastasis or macrovascular invasion. Eligibility criteria included measurable disease 3 cm or less in diameter, Child-Pugh score A–B7, an Eastern Cooperative Oncology Group score of 0, and adequate haematological and organ function. The primary endpoint was target tumour response measured by mRECIST. Patients were followed up with imaging and office visits for up to 24 months. The trial is registered with ClinicalTrials.gov (NCT03248375), and is completed.

Findings Individuals were enrolled between Aug 3, 2016, and April 4, 2019, and the last patient follow-up occurred on March 31, 2021. Of the 44 individuals assessed for eligibility, 29 patients were included in the study. Initial target lesion complete response was observed in 24 (83%) of 29 patients, and partial response was observed in five (17%) of patients. All patients had an initial objective response and 26 (90%) individuals had a sustained complete response. Four (14%) patients had grade 3 leukopenia and two (7%) had grade 3 thrombocytopenia. There were two (7%) non-laboratory-related grade 3 adverse events (one arterial injury and one ascites). The most frequent (>10% patients) grade 1 or 2 adverse events were fatigue (nine [31%]); nausea, vomiting, or anorexia (seven [24%]); abdominal discomfort (six [21%]), leukopenia (nine [31%]), thrombocytopenia (four [14%]), increased alkaline phosphatase (four [14%]), increased alanine or aspartate aminotransferase (four [14%]), increased bilirubin (four [14%]), and decreased albumin (six [21%]). There was one death that was not treatment related.

Interpretation Radiation segmentectomy was efficacious, with a low proportion of high-grade adverse events in patients with unresectable very early to early stage hepatocellular carcinoma with suboptimal location for ablation. These results suggest that radiation segmentectomy should be further investigated as a potential curative treatment option for well selected patients.

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See Online for appendix

Introduction

Unresectable solitary very early to early stage hepatocellular carcinoma is treated with ablation for lesions 3 cm or smaller, with the goal of curative intent.[1] However, tumours might not be amendable to ablation for a variety of reasons, such as unfavourable locations (appendix p 4). In these situations, ablation might underperform, with high rates of incomplete necrosis and local recurrence.[2,3] Radiation segmentectomy, defined as selective administration of an ablative dose with ^{90}yttrium (^{90}Y) microspheres to two couinaud hepatic segments or less, is another treatment option showing promising results. Radiation segmentectomy uses the preferential blood flow to the tumour to deliver radioactive microspheres to a volume of tissue while minimising damage to the non-tumoural parenchyma. Unlike ablation, radiation segmentectomy avoids a percutaneous approach and thus limits the risk of seeding, bleeding, or injury to key structures.[4] Compared with transarterial chemoembolisation, radiation segmentectomy can provide better tumour control and complete response.[5–7] In addition, radioembolisation can increase progression-free survival and achieve similar responses to transarterial chemoembolisation followed by ablation for lesions 3 cm or less.[8] Radiological–pathological correlation has also shown complete pathological response for tumours less than 5 cm treated with radiation segmentectomy.[9,10] The LEGACY study[11] showed that radiation segmentectomy can provide good local tumour control and overall survival for solitary tumours up to 8 cm, adding to the body of

Research in context

Evidence before this study

We searched PubMed for articles published from Jan 1, 1991, to Jan 1, 2016, in English, focusing on publications of randomised studies and systematic reviews, but also including larger retrospective studies, for the treatment of unresectable hepatocellular carcinoma. In particular, we focused our review on very early to early stage hepatocellular carcinoma. We used search terms "hepatocellular carcinoma" and "selective internal radiation therapy" or "radioembolization" or "chemoembolization" or "ablation." We identified no prospective studies involving radioembolisation for very early to early hepatocellular carcinoma. Several retrospective studies were found, the results of which suggested that radioembolisation can achieve good response rates as well as result in complete histopathological necrosis. We also found many articles discussing suboptimal outcomes after thermal ablation in patients with unfavourable tumour locations.

Added value of this study

To our knowledge, this is the first prospective study to assess outcomes after radiation segmentectomy in patients with very early to early stage hepatocellular carcinoma. The study showed that radiation segmentectomy, which delivers an ablative radiation dose via a transarterial route, can achieve good sustained complete response rates for tumours deemed suboptimal for ablation. Our findings support the inclusion of radioembolisation in the Barcelona Clinic Liver Cancer guidelines for early stage hepatocellular carcinoma.

Implications of all the available evidence

This study provides a strong rationale for new randomised trials comparing radiation segmentectomy to ablation. Given complete pathological necrosis of the explanted tumours, larger investigative studies on the curative potential of radiation segmentectomy are warranted.

evidence in support of the US Food and Drug Administration approval and Barcelona Clinic Liver Cancer guideline inclusion of ^{90}Y glass microspheres for hepatocellular carcinoma.[12] Despite favourable results, no prospective study has validated the safety and efficacy of radiation segmentectomy used in very early to early stage, unresectable hepatocellular carcinoma. This is important, as retrospective studies involving radiation segmentectomy are often limited by selection bias and non-standardised imaging and adverse event follow-up protocols. We aimed to assess outcomes and adverse events of radiation segmentectomy, when used as a treatment for unresectable, solitary very early to early stage hepatocellular carcinoma deemed unfavourable for ablation.

Methods

Study design and participants

We conducted RASER, a prospective, open-label, single centre, single-arm study. Patients diagnosed with hepatocellular carcinoma as per the American Association for the Study of Liver Diseases guidelines and determined by a multidisciplinary tumour board to be ineligible for resection and suboptimal for ablation were included. Unfavourable location for ablation was defined as a maximum distance of 5 mm from the portal vein, hepatic vein, inferior vena cava, diaphragm, heart, stomach, bowel, liver capsule, gallbladder, or bile duct. Eligible patients had not previously received any treatment for liver cancer and had measurable disease 3 cm or smaller, a performance status score of 0 on the Eastern Cooperative Oncology Group (ECOG) scale, Child–Pugh score A–B7, and adequate haematological and organ function. Patients with metastatic disease or macrovascular invasion were excluded. Full inclusion and exclusion criteria are listed in the appendix (p 2). All patients provided written informed consent before enrolment. The study was reviewed and approved by the institutional review board and complied with the Declaration of Helsinki and Good Clinical Practice guideline. Enrolment was determined by the multidisciplinary tumour board, with imaging within 28 days of presentation.

Patients were followed up with visits within 6 weeks of treatment, 12 weeks after treatment, and 3 months thereafter for a period of 2 years. Follow-up visits evaluated tumour response, lung metastasis via CT scan of the chest (at 12 months and 24 months), ECOG performance status, laboratory values (complete blood count), differential, electrolytes, blood urea nitrogen, glucose, liver function test, coagulation panel, and α-fetoprotein biomarker), and adverse events. The end of study occurred after 24 months or earlier if the patient was lost to follow-up, died, or had a liver transplant.

Procedures

Patients had selective hepatic angiography with technetium-99m-labelled macroaggregated albumin (^{99m}Tc-MAA) with cone beam CT to determine the vascular supply to the tumour and perfused volumes. Nuclear scans were used to assess lung shunt fraction and splanchnic shunting. Patients were deemed ineligible for ^{90}Y glass microsphere infusion if the potential radiation dose to the lungs exceeded 30 Gy or if there was potential non-target microspheres deposition.

Based on the MRI before treatment, angiography, and cone beam CT, the volume of the perfused liver was measured. The amount of radioactivity required to deliver the desired dose was calculated using the formula:

$$(\text{GBq}) = \frac{\text{desired dose (Gy)} \times \text{liver mass (kg)}}{50}$$

The calculated dose was calculated as a segmental delivery with the goal of more than 205 Gy to the perfused area using the Committee on Medical Internal Radiation Dose model based on tumour response and survival data.[13,14] The Medical Internal Radiation Dose model assumes uniform distribution and complete ^{90}Y decay in situ and accounts for the fraction of activity remaining in the vial (R), mass of the tissue perfused by the microspheres in kilograms (M), lung shunt fraction (LSF) obtained by ^{99m}Tc-MAA single photon emission (SPE) CT, and administered activity in gigabecquerels (A), using the formula for the dose delivered:

$$\text{dose} = \frac{50\ (\text{A}) \times (1-\text{LSF}) \times (1-\text{R})}{\text{M}}$$

Radiation segmentectomy was done with ^{90}Y microspheres infused through selective branches off the hepatic artery. The delivery device used was glass-based (TheraSphere; Boston Scientific, Ottawa, ON, Canada), in which ^{90}Y is an integral constituent of the biocompatible glass matrix. Procedural steps and postprocedural protocol have been previously described and are detailed in the study protocol.[15] All procedures were done by interventional radiologists with more than 10 years of experience each.

After therapy, patients were taken for PET CT imaging. The commercially available software package, MIM 7.0.1 (MIM Software, Cleveland, OH, USA) was used to calculate ^{90}Y dose delivered to the tumour from the PET images (appendix p 5). Technical details regarding PET acquisition and reconstruction parameters are provided in the appendix (p 6).

Outcomes

The primary endpoint was target tumour response according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).[16] Imaging response assessment was done at each follow-up visit. Assessment of gadoxetate-enhanced MRI was done by an independent board-certified radiologist with 18 years of experience. Sustained complete response was defined as target lesion complete response without recurrence at the end of follow-up. Secondary endpoints were time to progression of the target lesion and overall disease, and adverse events using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[17] Adverse events were recorded for the duration of the study, up to 2 years. Major adverse events were considered as those grade 3 or higher, as defined by CTCAE. Overall progression was defined as having target lesion mRECIST defined progression, development of new intrahepatic or extrahepatic disease, or ECOG performance status 2 or higher.

Statistical analysis

To detect a 30% improvement in complete response rate with radiation segmentectomy compared with an assumed response rate of 50% with the standard of care (ie, TACE), with a power of 91% and an alpha of 0·05, we calculated we would need to enrol 30 patients. All patients were included in the outcome and safety analysis. Time to progression of the target lesion and overall disease was assessed using Kaplan-Meier analysis. Cumulative incidence of overall progression and target lesion progression were estimated using survival analysis methods for competing risks, with transplantation being treated as a competing risk.[18] An incidence curve for transplant was created using the product limit failure curve function.

Exploratory endpoints included duration of response (time interval from achieving objective response to progression by mRECIST, death, or the end of the study) and explanted liver histopathology of transplanted patients were used to assess pathological response. Actuarial overall survival was calculated for years 1 and 2.

All data were collected and monitored centrally. All statistical tests were done using SAS software (version 9.4). The trial is registered with ClinicalTrials.gov, NCT03248375, and is completed. There was a delay in registration due to administrative transition.

Role of the funding source

The funder of this study was not involved in any steps of the study, including study design, data collection, data analysis or interpretation, or reviewing the manuscript.

Results

Individuals were enrolled between Aug 3, 2016, and April 4, 2019, and the last patient follow-up occurred on March 31, 2021. Of the 44 patients screened, 29 were included in the study (figure 1). 15 patients were excluded: ten did not meet the inclusion criteria, and five declined to participate. No patients were excluded for excessive shunting or inability to treat selected vessels. No patients ended the study early due to additional locoregional treatment to the target area. Patient and tumour

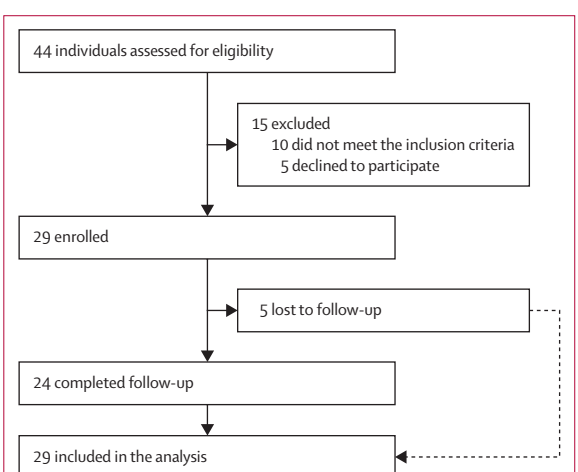

Figure 1: **Trial profile**

characteristics, according to the American Association for the Study of Liver Disease consensus guidelines, are listed in table 1.[19] Five (17%) of 29 patients were lost to follow-up before trial completion. Median follow-up was 691 days (IQR 379–719). Two (7%) patients had a second planned treatment within 10 days because of dose availability.

	Participants (N=29)
Age, years	63·4 (8·4)
Sex	
Male	23 (79%)
Female	6 (21%)
Cause of liver disease	
Hepatitis B virus	3 (10%)
Hepatitis C virus	13 (45%)
Non-alcoholic steatohepatitis	5 (17%)
Alcohol	7 (24%)
Sarcoidosis	1 (4%)
Haemochromatosis	1 (4%)
Child-Pugh score	
A5	14 (48%)
A6	12 (41%)
B7	3 (10%)
Median α-fetoprotein, ng/mL	5 (0–409·5)
Albumin-bilirubin grade 1	7 (24%)
Albumin-bilirubin grade 2	22 (76%)
Ascites	1 (3%)
Mean tumour diameter, cm	2·1 (0·4)
Liver segment tumour distribution	
1	0 (0%)
2	5 (17%)
3	0 (0%)
4	8 (28%)
5	2 (7%)
6	5 (17%)
7	3 (10%)
8	11 (38%)
Location	
Peripheral	28 (97%)
Central	1 (3%)
Number of injection locations	
1	24 (83%)
2	5 (17%)
Median lobar volume	
Right	896·7 (406·7–1523·8)
Left	439·0 (316·6–832·0)
Mean perfused liver volume, mL	153·6 (99·2)
<100	9 (31%)
100–200	12 (41%)
>200	8 (28%)
Median lung shunt fraction	4% (1·9–10·7)
Median calculated dose to the perfused segment, Gy	584 (181·0–3340·0)
Median tumoural dose delivered, Gy	1004·6 (190·8–3730·0)

Data are n (%), mean (SD), or mean (95% CI).

Table 1: **Patient characteristics**

Initial target lesion complete response was observed in 24 (83%) of 29 patients and partial response was observed in five (17%) patients for an objective response of 100%. For the duration of the study, 26 (90%) patients had a sustained complete response after a single treatment. Median time to complete response was 43 days (95% CI 40–47). Duration of response was evaluated for 28 (97%) patients with an initial response (complete or partial) and who had at least two follow-up images (one patient was lost to follow-up after one imaging assessment of a complete response). Median duration of response was 635 days (IQR 380–676); mean duration was 516 days (95% CI 439–593). Three (10%) patients had target lesion progression at 227, 496, and 668 days, respectively. Median time to target lesion progression was not reached. Cumulative incidence of target lesion progression at 1 year was 4% (95% CI 0–16) and at 2 years was 12% (3–28; figure 2). Actuarial overall survival at years 1 and 2 was 96%.

Nine (31%) patients had overall progression at a range of 181–699 days with three local progressions and seven new intrahepatic hepatocellular carcinomas. One (3%) patient had a new hepatocellular carcinoma followed by local recurrence on subsequent imaging. Median time to overall progression was not reached. Five (17%) patients had additional therapy during the study interval: three with ^{90}Y to the local recurrence as well as new tumours and two with transarterial chemoembolisation and ablation of new tumours. Cumulative incidence of overall progression at 1 year was 14% (95% CI 4–30) and at 2 years was 27% (11–45; figure 2). Eight (27%) patients received a liver transplant at a median of 341 days (range 228–521). Pathology results show all eight target lesions had 100% necrosis. Three of eight patients had additional hepatocellular carcinomas within the explanted liver. One patient had a 0·8 cm non-treated, moderately differentiated hepatocellular carcinoma, another had a 2·2 cm hepatocellular carcinoma with 90% necrosis (that was treated with thermal ablation), and one patient had several microscopic nodules with vascular invasion.

Treatment-related adverse events were evaluated in all 29 patients and common (ie, occurring in >10% patients) adverse events included fatigue (nine [31%]); nausea, vomiting, or anorexia (seven [24%]); abdominal discomfort (six [21%]); and laboratory changes such as transient leukopenia (13 [45%]; four [14%] were grade 3), thrombocytopenia (six [21%]; two [7%] were grade 3), increased alkaline phosphatase (four [14%]), increased aspartate or alanine aminotransferase (four [14%]), bilirubin (four [14%]), and decreased albumin (six [21%]). Five (17%) patients experienced access-site-related complications; one patient had a femoral artery injury requiring revascularisation (grade 3). Two patients developed portal vein thrombus (grade 2; both deemed unrelated to treatment) during follow-up: one in a right

portal vein branch adjacent to a new infiltrative hepatocellular carcinoma and the other a non-occlusive thrombus at the portomesenteric confluence determined as unlikely to be related to treatment. One patient had worsening ascites requiring paracentesis (grade 3). All grade 3 laboratory related adverse events were in patients with baseline haematological lab abnormalities, which is not accounted for in the CTCAE. No patients experienced radioembolisation-induced liver disease. There was one death, secondary to multiple organ failure at 296 days in a patient with aggressive tumour biology. Table 2 includes the grading of all treatment-related adverse events. Adverse events not related to treatment are provided in the appendix (p 3).

Dose delivered to the tumour was calculated for 26 (90%) patients with ^{90}Y PET CT imaging (appendix p 5). Three (7%) patients were excluded due to technical issues. The median dose delivered to the tumour was 1004·6 Gy (95% CI 844·7–1400·8) based on PET CT imaging calculation. The mean dose to the perfused segment for the eight patients with confirmed complete pathological response was 776·5 Gy (532·4–1020·6) with a mean PET CT calculated tumour dose of 1462·6 Gy (759·9–2165·3). All 29 patients had a lung dose of less than 30 Gy.

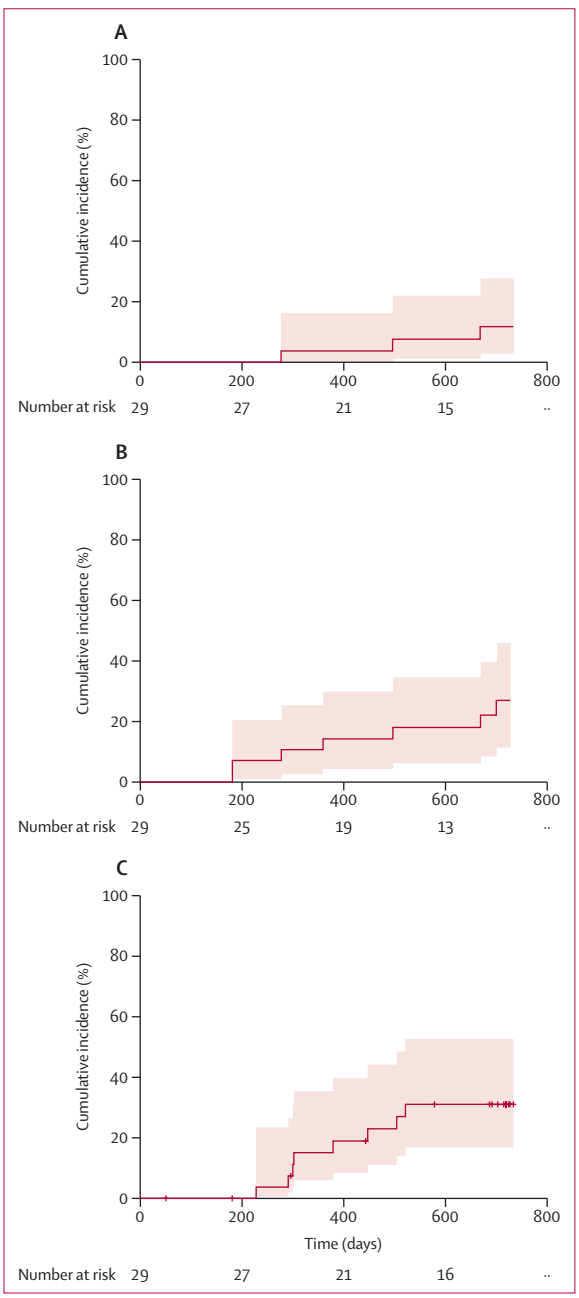

Figure 2: **Cumulative incidence analysis**
(A) Local progression, (B) overall progression, (C) and transplant.

Discussion

In this single centre, single-arm study, we prospectively evaluated the use of radiation segmentectomy in patients with unresectable very early to early stage hepatocellular carcinoma who were suboptimal ablation candidates. The results showed that radiation segmentectomy can achieve sustained complete response with low incidence of high-grade adverse events. Several prospective studies involving ^{90}Y radioembolisation have been published comparing radioembolisation to chemoembolisation, systemic therapy, and one with a personalised dose strategy using a higher radiation dose.[6,14,20–24] However, none have focused exclusively on early stage hepatocellular carcinoma. Our study showed a 90% sustained complete response rate with a median duration of response of

	Grade 1–2	Grade 3
Access-site-related adverse events	4 (14%)	1 (3%)
Arterial injury	0	1 (3%)
Haematoma	4 (14%)	0
Treatment-related adverse events	15 (52%)*	1 (3%)
Fatigue	9 (31%)	0
Nausea, vomiting, or anorexia	7 (24%)	0
Abdominal discomfort	6 (21%)	0
Ascites	0	1 (3%)
Treatment-related laboratory adverse events	19 (66%)†	5 (17%)‡
Leukopenia	9 (31%)	4 (14%)
Thrombocytopenia	4 (14%)	2 (7%)
Anaemia	3 (10%)	0
AST or ALT increased	4 (14%)	0
ALP increased	4 (14%)	0
Total blood bilirubin increased	4 (14%)	0
Albumin decreased	6 (21%)	0
Creatinine increased	3 (10%)	0
International normalised ratio increased	1 (3%)	0

Data are number of patients (%). No grade 4 events were experienced. AST=aspartate aminotransferase. ALT=alanine aminotransferase. ALP=alkaline phosphatase. *22 events. †38 events. ‡Six events.

Table 2: **Adverse events**

635 days. Complete response on initial imaging was 83%. Although most patients had complete response on the initial 6-week follow-up, radiation-based therapies are well described to have delayed imaging responses, which might explain the increase from 83% initial complete response to 90% sustained complete response. Compared with retrospective data for ^{90}Y radioembolisation in early stage hepatocellular carcinoma, our results were similar: two large retrospective studies showed complete response rates ranging from 83–92%, progression-free survival of 560 days, and a cumulative incidence of target progression of 8% at year 1 and 15% at year 2.[5,10] The multicentre LEGACY study[11] reviewed data from solitary tumours 8 cm or smaller and reported an 88% best objective response rate.

Several prospective trials have investigated thermal ablation for early hepatocellular carcinoma, showing complete response rates up to 97% for tumours smaller than 3 cm after one or more ablation procedures.[25] One propensity-matched study compared radiation segmentectomy to transarterial chemoembolisation plus ablation for lesions 3 cm or smaller and showed an 88% complete response rate in both groups after one treatment, which was similar to our sustained complete response rate of 90%.[8] Moreover, the histopathological analysis of eight tumours in this study after a single radioembolisation treatment showed 100% complete pathological necrosis. This is in comparison to 63% complete pathological necrosis of tumours 3 cm or smaller after a single session ablation reported by Mazzaferro and colleageus[26] and 74% in the data reported by Lu and colleagues.[2] Mazzaferro and colleagues[26] speculate that this low rate might be explained by many lesions requiring additional ablations. Others suggest perivascular location and subsequent heat sink might have a role.[2] Previously reported rates of complete pathological necrosis after ^{90}Y radioembolisation were 52% and 67%, with all lesions showing 90–100% necrosis.[9,27] The authors of those studies showed an association between higher doses and complete necrosis.[9,27] Our findings might be secondary to all patients receiving a high segmental dose. Achieving complete pathological necrosis of all explanted lesions is encouraging for radioembolisation as a curative treatment; however, this study did not standardise pathology review and our explanted sample only includes eight patients. The results of our study are meaningful, especially in the context of long transplant wait times which can at times exceed 2 years, and thus, durable bridging locoregional therapies are needed.

Ablation has been argued to be inferior to surgical resection because 2-year local recurrence can be as high as 26%.[28] Higher recurrence rates have been reported for tumours with suboptimal locations, with one study[3] showing 35% local recurrence at 2 years and 51% at 3 years.[3] Additionally, ablation might underperform for perivascular tumours, as evidenced by high rates of incomplete necrosis.[2] A meta-analysis of ablation with a mean follow-up of 22·8 months found an overall local progression rate of 14%.[29] Although most of these studies included patients with favourable tumour locations and not strictly 3 cm or smaller, like this study, our local progression rate of 10% was within this range. This is notable as tumours included in this study were all considered suboptimal for ablation. There were no reports of local progression in the LEGACY study,[11] perhaps due to differences in imaging protocols after treatment. There can be several explanations for local progressions after radioembolisation: (1) inadequate radiation of adjacent satellite lesions, (2) tumour biology, and (3) technical failure (inadequate dose or targeting). Of our three local progressions, two were determined to be technical due to a distal injection without a proper perfused margin and the third was due to aggressive tumour biology. Nevertheless, there is evidence that suggests failure after ablation might be due to suboptimal location.[2,3] Therefore, this study can serve as preliminary evidence that ^{90}Y radioembolisation can be a useful treatment in this population.

External radiation therapy, such as stereotactic body radiation therapy, is an alternative way to deliver a targeted radiation dose and has been described for the treatment of hepatocellular carcinoma with variable outcomes. External radiation therapies are limited in the amount of radiation dose that can be delivered because of potential collateral damage to surrounding structures, whereas radioembolisation is an internal radiation without such limits, resulting in higher target doses, which was shown in our study. Assessment of explanted livers with median tumour size of 3·7 cm treated with stereotactic body radiation therapy showed that 13% had complete pathological necrosis, 40% had 50–99% necrosis, 37% had less than 50% necrosis, and 10% had no necrosis, which is lower than what has been reported after of radiation segmentectomy.[30] Overall, the literature of external radiation has showed encouraging local control rates; however, data showing complete radiographical and pathological response are scarce compared with radiation segmentectomy.

The incidence of adverse events in this study is likely to be higher than that of previous retrospective studies of radiation segmentectomy because this was a prospective study that included additional follow-up visits, laboratory tests, and imaging. Clinical side-effects were transient and mostly mild, with two (7%) patients having non-laboratory related grade 3 adverse events. The most common side-effects were fatigue and abdominal discomfort, as well as laboratory markers of local liver injury (asparate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin). Similar to previously reported toxicities, we also noted transient haematological cell abnormalities such as leukopenia and thrombocytopenia. Haematological abnormalities are also seen in radiotherapy of non-bone-marrow bearing organs (including the liver) and are thought to be secondary to the abundance of

lymphocytes and platelets, which are extremely radiosensitive, that circulate in the liver. Clinical and laboratory abnormalities were less frequently observed than previously described after radioembolisation to larger regions,[14,20] further supporting a more targeted delivery. Only one death occurred in our study, secondary to progression to advanced hepatocellular carcinoma with portal invasion.

Retrospective studies[13,14] have shown complete pathological and radiographical response with estimated radiation doses of more than 205 Gy to the perfused segment using the Medical Internal Radiation Dose model and mapping cone beam CT. Other studies[27] suggest a segmental dose equal to or greater than 400 Gy as the threshold to achieve complete pathological necrosis. Of the eight patients with complete pathological necrosis, the mean dose to the perfused segment was 776·5 Gy and thus our findings add to the data, showing that appropriate segmental dosing can achieve complete pathological necrosis. The mean ablative dose to the tumour, as expected, was higher than the expected dose to the perfused segment. This difference is likely due to preferential blood flow to the tumour, which supports transarterial administration.

The study has several limitations, including no masked independent reviewers and no comparison group. In addition, procedures were done by experienced interventional radiologists with more than 10 years of experience with radioembolisation. The inclusion criteria in this study were strict, therefore limiting the generalisability of the results to a large proportion of patients diagnosed with hepatocellular carcinoma. Additionally, radioembolisation requires an established infrastructure, which might limit its use in places without nuclear medicine capabilities or a supportive reimbursement landscape.

In summary, radiation segmentectomy was effective with low numbers of high-grade adverse events in patients with unresectable very early to early-stage hepatocellular carcinoma in unfavourable locations for ablation. Sustained complete response rates and local progression of the target lesion were similar to the previously reported rates after thermal ablation. Moreover, complete pathological necrosis of all explanted tumours is encouraging. Larger investigative studies can be pursued for curative potential. These results support the inclusion of radiation segmentectomy in the Barcelona Clinic Liver Cancer guidelines for very early to early-stage hepatocellular carcinoma.

Contributors

EK, MS, MF, KK, RP, SN, BT, and AF, and RL were involved in the conception and design. EK, AS, KK, RL, AF, and GA and were involved in analysis and interpretation. EK provided data from patients included in the study, and contributed to manuscript development including writing the manuscript. BT, SN, RP, RL, AF, MS, MF, and PT contributed to providing data from patients included in the study. AF, KK, GA, RL, and AS contributed to manuscript development. AS, KK, and GA contributed to data collection. All authors contributed to manuscript revision. EK, AS, GA, and BT had access to the raw data. The corresponding author (EK) had final responsibility for the decision to submit for publication. All authors had access to the data and accept responsibility to submit for publication.

Declaration of interests

EK receives grant support, consulting fees, and is on the medical advisory board of Boston Scientific. RL is on the medical advisory board of Boston Scientific. AF receives royalties from Merit Medical; stock in Adient Medical; and consulting fees from Boston Scientific, Terumo, and Embolx. JL recieves grant support from Bayer Healthcare Pharmaceuticals, Eisai Inc, Boehringer-Ingelheim, and Ipsen; and consulting fees from Eli Lilly, Bayer, Merck, Bristol-Myers Squibb, Ipsen, Glycotest, Genentech, Roche, and AstraZeneca. PT received an honorarium from Bayer. All other authors declare no competing interests.

Data sharing

The study protocol can be seen in the supplemental data. Informed consent form can be obtained by contacting the corresponding author (EK). Individual participant data will not be made available.

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