MRI-guided stereotactic ablative body radiotherapy versus CT-guided percutaneous irreversible electroporation for locally advanced pancreatic cancer (CROSSFIRE): a single-centre, open-label, randomised phase 2 trial

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Summary

Background Pancreatic ductal adenocarcinoma is an aggressive disease with a dismal prognosis. Stage III locally advanced pancreatic cancer is considered unresectable and current palliative chemotherapy regimens only modestly improve survival. Guidelines suggest chemoradiation or stereotactic ablative body radiotherapy (SABR) could be beneficial in certain circumstances. Other local treatments such as irreversible electroporation could enhance patient outcomes by extending survival while preserving quality of life. We aimed to compare the efficacy and safety of MRI-guided SABR versus CT-guided percutaneous irreversible electroporation following standard FOLFIRINOX chemotherapy.

Methods CROSSFIRE was an open-label, randomised phase 2 superiority trial conducted at the Amsterdam University Medical Centre (Amsterdam, Netherlands). Eligible patients were aged 18 years or older with confirmed histological and radiological stage III locally advanced pancreatic cancer. The maximum tumour diameter was 5 cm and patients had to be pretreated with three to eight cycles of FOLFIRINOX. Patients were randomly assigned (1:1) to MRI-guided SABR (five fractions of 8 Gy delivered on non-consecutive days) or CT-guided percutaneous irreversible electroporation using a computer-generated variable block randomisation model. The primary endpoint was overall survival from randomisation, assessed in the intention-to-treat population. Safety was assessed in the per-protocol population. A prespecified interim futility analysis was done after inclusion of half the original sample size, with a conditional probability of less than 0·2 resulting in halting of the study. The trial was registered at ClinicalTrials.gov, NCT02791503.

Findings Between May 1, 2016, and March 31, 2022, 68 patients were enrolled and randomly assigned to SABR (n=34) or irreversible electroporation (n=34), of whom 64 were treated according to protocol. Of the 68 participants, 36 (53%) were male and 32 (47%) were female, with a median age of 65 years (IQR 57–70). Median overall survival from randomisation was 16·1 months (95% CI 12·1–19·4) in the SABR group versus 12·5 months (10·9–17·0) in the irreversible electroporation group (hazard ratio [HR] 1·39 [95% CI 0·84–2·30]; p=0·21). The conditional probability to demonstrate superiority of either technique was 0·13; patient accrual was therefore stopped early for futility. 20 (63%) of 32 patients in the SABR group versus 19 (59%) of 32 patients in the irreversible electroporation group had adverse events (p=0·8) and five (16%) patients in the SABR group versus eight (25%) in the irreversible electroporation group had grade 3–5 adverse events (p=0·35). The most common grade 3–4 adverse events were cholangitis (two [6%] in the SABR group *vs* one [3%] in the irreversible electroporation group), abdominal pain (one [3%] *vs* two [6%]), and pancreatitis (none *vs* two [6%]). One (3%) patient in the SABR group and one (3%) in the irreversible electroporation group died from a treatment-related adverse event.

Interpretation CROSSFIRE did not identify a difference in overall survival or incidence of adverse events between MRI-guided SABR and CT-guided percutaneous irreversible electroporation after FOLFIRINOX. Future studies should further assess the added value of local ablative treatment over chemotherapy alone.

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Introduction

Pancreatic ductal adenocarcinoma is an aggressive and lethal cancer. Prognosis is poor, with 5-year survival rates of around 10%.[1] Approximately 30% of patients present with locally advanced pancreatic cancer. Due to extensive vascular ingrowth, locally advanced pancreatic cancer is considered unresectable. Standard of care in the USA and Europe (including the Netherlands) for patients with locally advanced pancreatic cancer commonly consists of palliative chemotherapy comprising

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Research in context

Evidence before this study

We searched PubMed from database inception to Nov 30, 2023, for clinical trials published in English on the assessment of stereotactic ablative body radiotherapy (SABR) or irreversible electroporation in patients with locally advanced pancreatic cancer. The following search terms were used: ("locally advanced pancreatic cancer" OR "LAPC") AND (("stereotactic ablative body radiotherapy" OR "stereotactic body radiation therapy" OR "SABR" OR "SBRT") OR ("irreversible electroporation" OR "IRE")). Although a few prospective studies have been published with a single-arm design using either irreversible electroporation or MRI-guided SABR, to our knowledge, no randomised trials have been published comparing these two techniques in patients with locally advanced pancreatic cancer.

Added value of this study

In our study, no significant differences were identified between CT-guided irreversible electroporation and MRI-guided SABR in terms of overall survival, progression-free survival, or the number of complications. Quality of life in terms of overall health and mean pain scores were stable up to 6 months after ablative treatment. Both SABR and irreversible electroporation seem to have the potential to induce a systemic immune response.

Implications of all the available evidence

SABR and irreversible electroporation might both be considered for temporary disease control in certain circumstances after FOLFIRINOX. Future randomised studies on the additive effects of ablation when combined with FOLFIRINOX are warranted.

FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) or gemcitabine with or without nab-paclitaxel, which might moderately improve survival.[2–5] National Comprehensive Cancer Network guidelines[4] state that, following chemotherapy, chemoradiation or stereotactic ablative body radiotherapy (SABR) might be useful in certain circumstances. Despite encouraging results from single-arm studies,[6–9] irreversible electroporation is currently not recommended outside clinical trials due to paucity of comparative data. Novel ablative therapies could enhance patient outcomes by extending survival while preserving quality of life.

SABR, also known as stereotactic body radiotherapy, is a form of external beam radiotherapy that accurately delivers a limited number of fractions of high radiation doses using multiple precisely aimed radiotherapy beams. As a result of this technique, it is possible to escalate the biologically effective dose, offering the potential for increased tumour control, while the rapid dose fall-off outside the target volume reduces toxicity to the nearby organs at risk. The use of MR-guidance provides real-time imaging, thus allowing for more precise targeting of the tumour, without the need to place fiducial markers.[10] Additionally, SABR offers shorter treatment time, since it is usually delivered in 1–2 weeks, compared with 5–6 weeks required for conventionally fractionated radiotherapy. Irreversible electroporation is another focal ablative therapy that employs high-voltage electrical pulses to eradicate cancerous tissue.[11] These pulses disrupt the membrane potential of cells, causing membrane permeabilisation and subsequent loss of cellular homeostasis, followed by an initiation of cell death through apoptosis and delayed necrosis. By contrast with thermal ablation methods, irreversible electroporation preserves the extracellular tissue scaffold of critical luminal structures such as major blood vessels, bile ducts, and the intestines. Additionally, the electrical energy is not restrained by the heat-sink effect. These features of SABR and irreversible electroporation render these techniques especially suitable for tumours with adjacent vulnerable structures, as is the case with locally advanced pancreatic cancer. Multiple prospective studies have confirmed the feasibility and relative safety of SABR[12–16] and irreversible electroporation[6–9] for use in patients with locally advanced pancreatic cancer, with encouraging survival outcomes. However, it is currently unknown whether one of these ablation techniques is superior in terms of overall and progression-free survival. Considering the clinical potential of these local therapies, it would be beneficial to determine if future research should focus on one treatment for use in randomised trials, specifically those assessing the additive value of ablation when combined with chemotherapy over chemotherapy alone. The aim of this study was to compare the efficacy and safety of SABR with irreversible electroporation in patients with unresectable, non-metastatic locally advanced pancreatic cancer pretreated with FOLFIRINOX.

Methods

Study design and participants

CROSSFIRE was a single-centre, open-label, randomised phase 2 superiority trial conducted at the Amsterdam University Medical Centre (Amsterdam, the Netherlands). CROSSFIRE was originally designed as a phase 2/3 trial to reflect the adoption of SABR and irreversible electroporation as standard of care following FOLFIRINOX in a growing number of centres. Since the trial stopped early for futility and consequently did not meet the original sample size, and because both techniques are not yet universally considered standard of care, the study was downgraded to a randomised phase 2 trial.

Participants were discussed in multidisciplinary tumour board meetings involving experts from pancreaticobiliary surgery, diagnostic and interventional radiology, medical oncology, radiation oncology, gastroenterology, and pathology. Included patients had histological and radiological

confirmation of unresectable stage III locally advanced pancreatic cancer as defined by the American Joint Committee on Cancer (primary tumour stage T4 [involvement of the coeliac axis or superior mesenteric artery] with any N stage) and National Comprehensive Cancer Network criteria (head or uncinate process tumours with >180° involvement of the coeliac axis or superior mesenteric artery; corpus or tail tumours with >180° involvement of the coeliac axis or superior mesenteric artery; or ≤180° coeliac axis and aortic involvement; otherwise, any tumour with >180° venous involvement or with contour irregularity or thrombosis, or if venous resection and reconstruction are considered impossible).[17,18] Other inclusion criteria were receiving at least three cycles of pretreatment FOLFIRINOX; a maximum axial tumour diameter of 5 cm; age 18 years or older; WHO performance status 0–1; and adequate biliary drainage in case of biliary obstruction. Exclusion criteria were tumours downstaged from locally advanced pancreatic cancer to resectable tumours; transmucosal tumour invasion into the surrounding duodenum or stomach; history of epilepsy; history of cardiac disease, specifically congestive heart failure (>New York Heart Association class 2), active coronary artery disease (defined as myocardial infarction within the 6 months before screening) or ventricular cardiac arrhythmias; having an implanted stimulation device; uncontrolled hypertension (>160/95 mm Hg); compromised liver function; uncontrolled infections; previous immunotherapy, radiotherapy, or surgical treatments; second primary malignancy (5-year overall survival <95%); contraindication for MRI; and any other condition that was unstable or could jeopardise the safety of the participant. Local disease progression of the tumour up to 5 cm after neoadjuvant chemotherapy was not an exclusion criterion, nor were metal biliary stents. MRI, PET-CT, or staging laparoscopies were not routinely performed in the work-up of these patients.

This trial was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol and amendments were approved by the Amsterdam University Medical Centre ethics committee and institutional review board. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to SABR or irreversible electroporation treatment without subgroup stratification using a computer-generated variable block randomisation model (block sizes 4, 6, and 8). The randomisation was done by one of the trained researchers of the CROSSFIRE trial group. This was an open-label trial and hence participants, investigators, clinicians, and trial staff were not masked to group allocation.

Procedures

Before study participation, pretreatment with three to eight cycles of FOLFIRINOX was mandatory. An interval period of at least 4 weeks was required between the last chemotherapy dose and start of study treatment.

All SABR procedures were performed using MRI-guided radiotherapy by two radiation oncologists (AMEB and FJL), both with 7 years of experience. In the preprocedural phase, a simulation included a planning 0·35 T inspiration breath hold, balanced fast imaging with steady-state free precession (TRueFISP) MRI scan (17 s), which was acquired on the MRIdian linear accelerator (ViewRay, Oakwood Village, OH, USA), followed by a planning CT scan in breath hold, both performed in supine position. No immobilisation device was used. The gross tumour volume (ie, pancreatic tumour) equated to the clinical target volume (ie, no elective lymph node regions were targeted). The planning target volume was generated using an isotropic margin of 3 mm around the gross tumour volume, excluding any overlap with the organs at risk, to avoid undue high radiation doses to surrounding organs such as the stomach and duodenum. No intravenous contrast was administered because the tumour and the organs at risk surrounding the tumour were well visualised on the simulation scans and if necessary, diagnostic imaging was used to define the target volume. All patients were instructed to fast for 2 h before each treatment. Treatment plans delivered with the MRIdian linear accelerator were based on intensity modulated radiation therapy step-and-shoot technique. Treatment was delivered in five fractions of 8 Gy on non-consecutive days using gated breath hold delivery, as per our routine institutional practice. Adaptive re-optimisation was performed for each SABR fraction, and our on-table adaptive workflow and gated delivery has been previously described including the high dose constraints used for the organs at risk.[10,19] Overall treatment time generally did not exceed 14 days; however, if necessary and at the discretion of the treating radiation oncologist, treatment scheme or overall treatment time could be adjusted.

All irreversible electroporation procedures were performed using a percutaneous approach (NanoKnife System; AngioDynamics, Latham, NY USA) by interventional radiologists with 12 years (MRM) and 8 years (JJJdV) of experience in the field of tumour ablation. Patients received intravenously administered prophylactic antibiotics (cefuroxime 1500 mg and metronidazole 500 mg) 1 h before the procedure. All irreversible electroporation procedures were conducted under general anaesthesia in a supine position. Muscle relaxants were administered to prevent muscle spasms during pulse delivery. An electrocardiography device was used to prevent pulse-induced arrhythmias by synchronising pulse delivery with the refractory period (R-wave) of the cardiac cycle. To enhance intraprocedural tumoral and vascular visibility, CT arteriography was used, as previously described.[20] In summary, before the irreversible electroporation procedure, a flush catheter was placed in the supracoeliac aorta transfemorally, through which small doses of contrast (20 mL) were

delivered during needle advancement under fluoroscopy, which allows real-time visualisation of the tumour and surrounding vasculature. Catheter-based arterial and portal venous phase CT were used to assess the required number of needles and their configuration as determined by the tumour location, size, and surrounding vasculature. Needle electrodes were inserted using catheter-based contrast enhanced CT fluoroscopy guidance, aiming for at least a 5 mm tumour-free margin and an interelectrode distance of 15–24 mm. The active tip length was set to 15 mm. Initially, ten test pulses of 1500 V per cm and 90 µs were delivered between selected electrode pairs, targeting a current between 20 A and 40 A. Voltage was altered manually in case of undercurrent (<20 A) or overcurrent (>40 A). Thereafter, 90 pulses per selected electrode pair were administered, totalling 100 pulses. For deep seated tumours (>15 mm) overlapping ablations could be achieved by an electrode pullback. Directly after the procedure the ablation zone was assessed using contrast enhanced CT to verify sufficient tumour coverage and to identify possible early complications.

After local ablative treatment with either SABR or irreversible electroporation, it was advised that patients continue adjuvant chemotherapy to complete a total of 12 cycles. Although continuation of chemotherapy was stated in the protocol, the final decision to resume chemotherapy post-ablation and choice of regimen (FOLFIRINOX preferred) was at the discretion of the patient and treating oncologist.

Patient assessments consisted of radiological, laboratory, and quality of life (QoL) and pain evaluations every 3 months. Treatment response was also assessed every 3 months using a contrast enhanced CT scan. Clinical blood samples verified haematological values, tumour marker CA19.9, electrolytes, kidney function, liver function, and liver enzymes. Peripheral blood samples were collected at baseline, at 2 weeks, and at 3 months after ablative treatment and peripheral blood mononuclear cells were isolated for flowcytometric analysis to track changes in various immune cell subsets including activated, proliferating effector $CD8^{+}Ki67^{+}$ T cells and $CD4^{+}PD\text{-}1^{+}$ T cells, and activated regulatory T cells (Tregs; $CD3^{+}CD4^{+}CD127^{-}CD25^{+}CD45RA^{-}FoxP3^{hi}$), as previously described.[21] If patients had an isolated local recurrence but met the other inclusion criteria, re-ablation was considered. After previous treatment with irreversible electroporation, both irreversible electroporation and SABR were considered. However, after initial treatment with SABR, only re-ablation with irreversible electroporation was permitted.

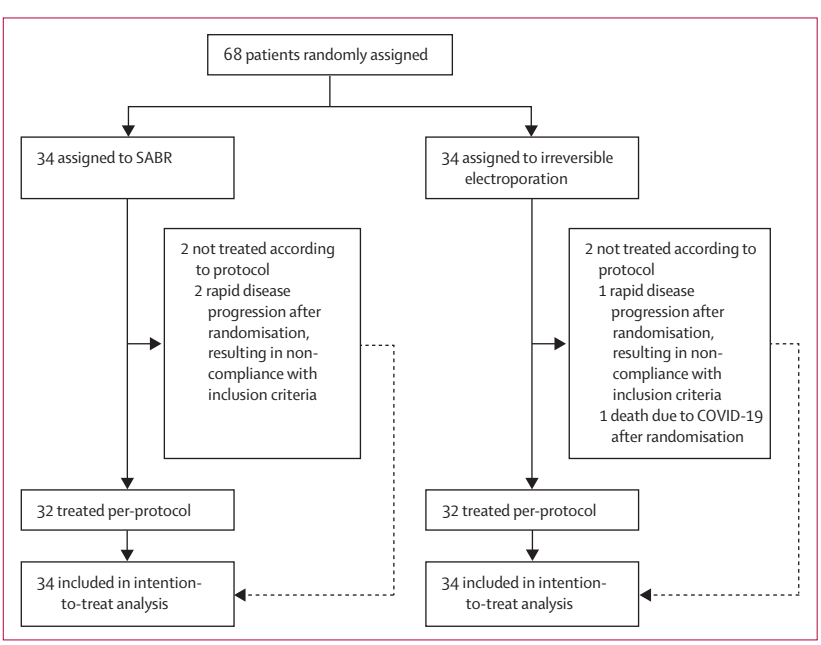

Figure 1: **Trial profile**
SABR=stereotactic ablative body radiotherapy.

Outcomes

Outcomes and definitions were specified using the consensus guidelines for image-guided tumour ablation.[22] The primary endpoint was overall survival from randomisation (defined as the time from randomisation to death from any cause). Secondary endpoints were: progression-free survival (defined as the time from randomisation to unequivocal disease progression), which was radiologically assessed using contrast enhanced CT scans as per the Response Evaluation Criteria in Solid Tumours (RECIST) criteria (version 1.1);[23] treatment safety and side-effects, assessed by documenting adverse events as per Common Terminology Criteria of Adverse Events (CTCAE) criteria (version 5.0);[24] QoL, assessed through validated QoL and pain questionnaires (EuroQoL-5D overall health score [scale 0–100] and the visual analogue scale (VAS) pain rating [scale 0–10]); and immunological responses, assessed using flow cytometry. The prespecified secondary endpoint of untreatable progression-free survival was not analysed since there were no crossover treatments and a limited number of repeat treatments, thus this endpoint is not reported. The cost-effectiveness analysis for both techniques will be reported elsewhere. Post-hoc endpoints were overall survival from diagnosis (defined as the time from diagnosis to death from any cause), local tumour progression-free survival (defined as the time from randomisation to unequivocal local progression), and distant progression-free survival (defined as the time from randomisation to unequivocal distant progression), radiologically assessed using contrast enhanced CT scans as per RECIST criteria (version 1.1).[23] The technical success of irreversible electroporation was defined as complete ablation coverage of the tumour based on contrast enhanced CT directly after the procedure. The objectives for target coverage during SABR were a V95% (ie, volume receiving 95% of the prescribed dose) of the gross tumour volume of at least 90% and a

maximum dose of up to 125% of the prescribed dose (equalling 40 Gy in five fractions). A patient was deemed to have received adjuvant chemotherapy if they had received at least two cycles within 6 months of ablative treatment and before any signs of progression (analysed in the per-protocol cohort), while receipt of palliative chemotherapy was defined having received chemotherapy 6 months after ablative treatment or after any sign of disease progression (analysed in the intention-to-treat cohort).

	Stereotactic ablative body radiotherapy (n=34)	Irreversible electroporation (n=34)
Age, years	66 (56–70)	65 (57–70)
BMI, kg/m^2	22·3 (20·2–26·8)	22·2 (20·5–23·5)
Sex		
Male	15 (44%)	21 (62%)
Female	19 (56%)	13 (38%)
American Society of Anaesthesiologists score		
1	0	0
2	27 (79%)	25 (74%)
3	7 (21%)	9 (26%)
Tumour localisation		
Head or uncinate process	27 (79%)	28 (82%)
Corpus or tail	7 (21%)	6 (18%)
Tumour diameter (mm)	38 (32–46)	34 (28–40)
T stage		
1	0	0
2	0	0
3	0	0
4	34 (100%)	34 (100%)
N stage		
0	27 (79%)	30 (88%)
1	7 (21%)	4 (12%)
Vascular encasement (>180˚)		
Superior mesenteric artery	16 (47%)	22 (65%)
Coeliac axis	10 (29%)	11 (32%)
Hepatic artery	11 (32%)	14 (41%)
Portal vein or superior mesenteric vein	23 (68%)	18 (53%)
Number of neoadjuvant FOLFIRINOX cycles	4 (4–5)	5 (4–8)
Disease response after neoadjuvant FOLFIRINOX*		
Partial response	1 (3%)	1 (3%)
Stable disease	30 (88%)	28 (82%)
Progressive disease (local)	3 (9%)	5 (15%)
Median CA19·9 tumour marker serum concentration, U/mL		
≤69	19 (56%)	16 (47%)
>69	15 (44%)	18 (53%)

Data are median (IQR) or n (%). 32 patients in each group were included in the per-protocol population. RECIST=Response Evaluation Criteria in Solid Tumours. *As per RECIST (version 1.1) criteria.

Table 1: **Baseline characteristics of participants (intention-to-treat population)**

Statistical analysis

Based on a 5% significance level (α) and 80% power, a sample size of 130 patients was calculated on the basis of an assumed median overall survival of 14·0 months for SABR and of 23·0 months for irreversible electroporation as per overall survival reported in the literature.[6,25–28] at the time of designing this trial, assuming 24 months of patient recruitment and 12 months of subsequent follow-up. 138 patients were required to account for an expected loss to follow-up of 5%. Under the assumption that 20% of patients would not be eligible following the screening phase (ie, before enrollment), a total of 173 patients were required. SABR was used as the reference group, but a two-sided superiority design was used to prove superiority of either technique. An interim analysis for futility was conducted after inclusion of approximately half of the calculated sample size. If the two-sided conditional probability for superiority was below 0·2 (20%), study continuation would be deemed futile. The conditional probability was calculated using PASS (version 22.0) by entering the target number of events (n=102), observed number of events, and the observed hazard ratio (HR) and log-rank test statistic at the time of the interim analysis. We used SPSS (version 28.0), R (version 4.3.1), and PASS for statistical analyses.

	Stereotactic ablative body radiotherapy	Irreversible electroporation	p value
40 Gy total radiation dose, n	32	NA	..
Technical success	NA	100%	..
Needle electrodes			
Number	NA	4 (4–6)	..
Pairs	NA	6 (5–8)	..
Duration of hospital stay, days	NA	3 (2–5)	..
Adjuvant chemotherapy*	..	..	0·07
No	28	22	..
Yes (FOLFIRINOX†)	4	10	..
Number of cycles	4 (2–5)	5 (4–6)	..
Palliative chemotherapy‡	..	..	0·62
No	21	19	..
Yes	13	15	..
Repeat local treatment			
With irreversible electroporation	0	4	..
With stereotactic ablative body radiotherapy	1§	0	..

Data are n, %, or median (IQR). NA=not applicable. *Adjuvant chemotherapy was defined as having received at least two cycles within 6 months of ablative treatment and before any signs of disease progression. †All patients who received adjuvant chemotherapy had FOLFIRINOX. ‡Palliative chemotherapy was defined as chemotherapy received after 6 months of ablative treatment or after any sign of disease progression. §For a second metastatic tumour in the pancreas.

Table 2: **Procedural characteristics and adjuvant treatment**

A Cox proportional hazards model was used to obtain HRs and their associated 95% CIs for the survival endpoints. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. The primary outcome was assessed in the intention-to-treat cohort, which included all randomly assigned participants. A subgroup analysis for overall survival from randomisation was conducted to obtain HRs using outcomes of a univariable Cox regression model (p=0·1). Safety was analysed in the per-protocol population. Adverse events were reported on a per-patient level and compared using the Pearson's χ^2 test. The QoL and pain scores were assessed using a two-sided *t* test. Changes in frequency and activation status of the immune cell subsets were compared within each treatment group at the different timepoints with a one-way repeated measures ANOVA and a post-hoc Dunnett's multiple comparisons test. The trial was registered at ClinicalTrials.gov, NCT02791503.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 1, 2016, and March 31, 2022, 68 patients were enrolled; 34 were randomly assigned to receive SABR and 34 to receive irreversible electroporation (figure 1). Of these, two patients in the SABR group and two patients in the irreversible electroporation group were not treated according to protocol; one of the patients in the irreversible electroporation group died due to COVID-19 before treatment, while the other three patients had rapid disease progression (tumour >5 cm or metastatic disease) after which they no longer complied with the inclusion criteria. Hence, the per-protocol cohort consisted of 32 patients in the SABR group and 32 patients in the irreversible electroporation group. According to protocol, immune monitoring was performed in the first 40 patients (20 patients in each group). No patients were lost to follow up.

See Online for appendix

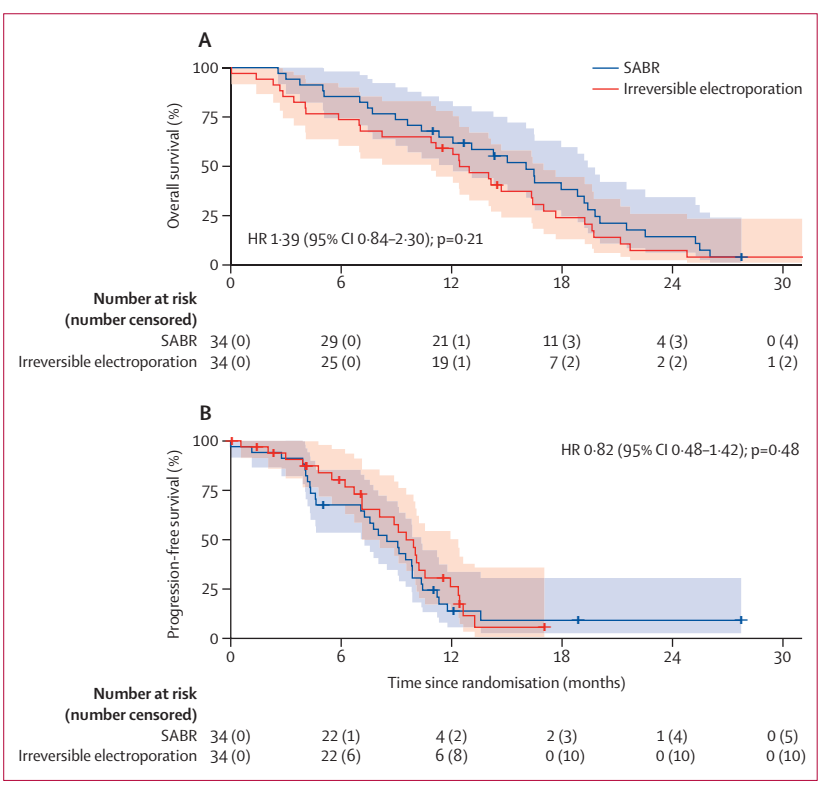

Figure 2: **Kaplan-Meier curves for overall survival (A) and progression-free survival (B)**
SABR=stereotactic ablative body radiotherapy. HR=hazard ratio.

Patient baseline characteristics were similar between study groups (table 1). Of the 68 participants, 36 (53%) were male and 32 (47%) were female, with a median age of 65 years (IQR 57–70), and median BMI of 22·2 kg/m² (IQR 20·4–25·2). The median tumour diameter was 36 mm (IQR 29–42), and 55 (81%) of 68 patients had tumour localisation in the head or uncinate process and 13 (19%) in the corpus or tail. Median number of FOLFIRINOX cycles was four (IQR 4–6). According to RECIST, two (3%) of 68 patients had a partial response, 58 (85%) patients had stable disease, and eight (12%) patients had local disease progression after neoadjuvant FOLFIRINOX. Procedural characteristics and treatment details are summarised in table 2. All patients in the SABR group who were treated per-protocol received a total dosage of 40 Gy (five fractions of 8 Gy). A median of four needle electrodes (IQR 4–6) and six needle electrode pairs (5–8) were used in irreversible electroporation procedures. Median duration of hospital stay after irreversible electroporation was 3 days (IQR 2–5). Technical success of irreversible electroporation was 100%.

At a median follow-up of 13·0 months (IQR 7·2 to 19·1), median overall survival was 16·1 months (95% CI 12·1 to 19·4) in the SABR group compared with 12·5 months (10·9 to 17·0) in the irreversible electroporation group (HR 1·39 [95% CI 0·84 to 2·30]; p=0·21; figure 2A). The two-sided conditional probability analysis for superiority using the primary outcome was 0·13, which was lower than the stopping limit of 0·2, rendering continuation of the trial futile. Inclusion was therefore stopped after 68 patients. Median progression-free survival was 8·5 months (95% CI 7·3 to 10·3) in the SABR group versus 9·5 months (7·1 to 12·4) in the irreversible electroporation group (HR 0·82 [95% CI 0·48 to 1·42]; p=0·48; figure 2B). Post-hoc survival analyses demonstrated that median overall survival from diagnosis was 21·4 months (95% CI 17·5 to 24·2) in the SABR group versus 18·2 months (14·8 to 22·9) in the irreversible electroporation group (HR 1·29 [95% CI 0·78 to 2·1]; p=0·33; appendix p 1), median local tumour progression-free survival was 17·9 months (95% CI 11·2 to not reached) in the SABR group versus 10·2 months (9·4 to not reached) in the irreversible

electroporation group (HR 1·83 [95% CI 0·87 to 3·9]; p=0·11; appendix p 1), and median distant progression-free survival was 8·5 months (95% CI 7·3 to 10·4) in the SABR group versus 13·2 months (95% CI 12·4 to not reached) in the irreversible electroporation group (HR 0·43 [0·23 to 0·81]; p=0·007; appendix p 1).

No significant differences were identified in overall rate of complication (ie, number of patients with adverse events of any grade) between the SABR and irreversible electroporation groups (20 [63%] of 32 patients ***vs*** 19 [59%] of 32 patients; p=0·8). Similarly, no significant differences in the number of patients who had grade 1–2 adverse events were identified between groups (15 [47%] of 32 patients in the SABR group *vs* 11 [34%] of 32 patients in the irreversible electroporation group; p=0·31) or in the number of patients who had grade 3–5 adverse events (five patients [16%] *vs* eight patients [25%]; p=0·35; table 3). Two (6%) of 32 patients in the SABR group and seven (22%) of 32 patients in the irreversible electroporation group had a grade 3–5 adverse event that was deemed possibly or likely treatment-related (p=0·07). Following SABR, four (13%) of 32 patients had grade 3 or 4 adverse events. Of these, one late toxicity in the form of haematemesis and haemobilia was deemed possibly related to treatment. In the irreversible electroporation group, seven (22%) of 32 patients had a grade 3 or 4 adverse event, of which six were deemed likely or possibly treatment related. One patient developed portal vein thrombosis, portobiliary fistula, abdominal angina (superior mesenteric artery stenosis), and a gastric outlet obstruction. Other possible treatment-related cases included pancreatitis (two patients), abdominal pain, cholangitis, and an ileus. None of the complications were related to the use of CT arteriography. Eight patients died within 90 days of local ablative treatment: three in the SABR group and five in the irreversible electroporation group. In each treatment group, one of these deaths was deemed a treatment-related grade 5 adverse event. In the SABR group, one (3%) patient had bleeding of the ampulla of Vater, resulting in haemodynamic instability followed by death, while in the irreversible electroporation group, one (3%) patient had a fatal duodenal perforation. Other deaths within 90 days were most likely the result of rapid disease progression. Three patients (one patient in the SABR group and two patients in the irreversible electroporation group) with possible treatment-related grade 3–5 adverse events also had a metal biliary stent in situ at the time of local ablative treatment.

In the irreversible electroporation group, baseline QoL scores were similar (mean overall health score 74 [SD 18]; mean VAS pain score 1·9 [SD 2·1]) to those at 3 months (overall health score 76 [19]; p=0·69]; VAS pain score 1·8 [1·7; p=0·92]), and 6 months after treatment (overall health score 77 [15; p=0·59]; VAS pain score 1·8 [1·7; p=0·95]; figure 3). Similarly, in the SABR group, baseline QoL scores (overall health score 80 [SD 12]; pain VAS 1·5 [SD 2·1]) were similar to those at 3 months (overall health score 76 [SD 12; p=0·35]; VAS pain score 2·1 [SD 2·4; p=0·3]) and 6 months (overall health score 82 [SD 10; p=0·56]; VAS pain score 1·4 [SD 2·2; p= 0·88]; figure 3). At 9 months, mean pain scores were higher than baseline for the irreversible electroporation group (VAS pain score [SD 2·5]; p=0·08]) and SABR group (VAS pain score [SD 2·5; p=0·06]), but overall health scores remained unchanged. At 12 months, mean overall health score decreased to 70 (SD 12; p=0·09) in the SABR group, indicating a reduction in QoL, whereas QoL

	Stereotactic ablative body radiotherapy (n=32)		Irreversible electroporation (n=32)	
	Any event	Treatment-related	Any event	Treatment-related
Cholangitis	2 (6%)	0	1 (3%)	1 (3%)
Pancreatitis	0	0	2 (6%)	2 (6%)
Abdominal pain	1 (3%)	0	2 (6%)	1 (3%)
Ileus	0	0	1 (3%)	1 (3%)
Duodenal perforation	0	0	1 (3%)	1 (3%)
Haematemesis and haemobilia	1 (3%)	1 (3%)	0	0
Bleeding ampulla of Vater	1 (3%)	1 (3%)	0	0
Portal vein thrombosis, porto-biliary fistula, abdominal angina (superior mesenteric artery stenosis), and gastric outlet obstruction	0	0	1 (3%)	1 (3%)

Stratified on the basis of whether events were deemed treatment-related.

Table 3: **Adverse events (grade 3–5)**

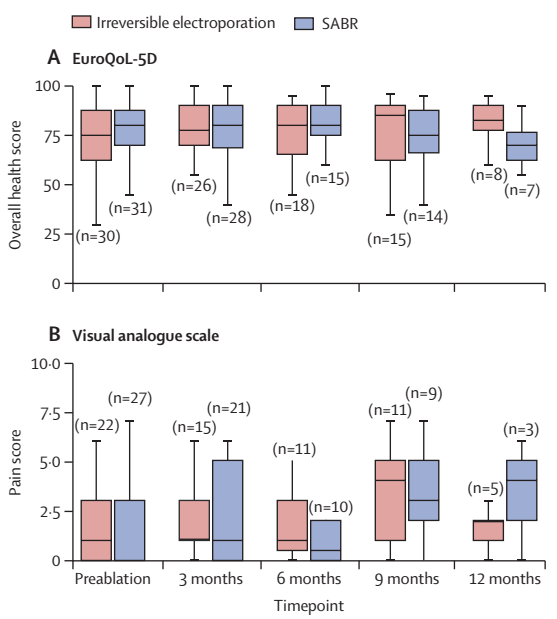

Figure 3: **Quality of life outcomes**
The EuroQoL-5D overall health score (A) and mean pain score (B) at each of the 3-monthly questionnaire timepoints. The EuroQoL-5D overall health score ranges from 0 to 100, whereby a higher score indicates better quality of life. The visual analogue scale pain score is scored on a scale of 0 to 10, whereby a higher score indicates higher pain intensity. Boxes show IQR, horizontal lines show median, and whiskers show minimum and maximum values.

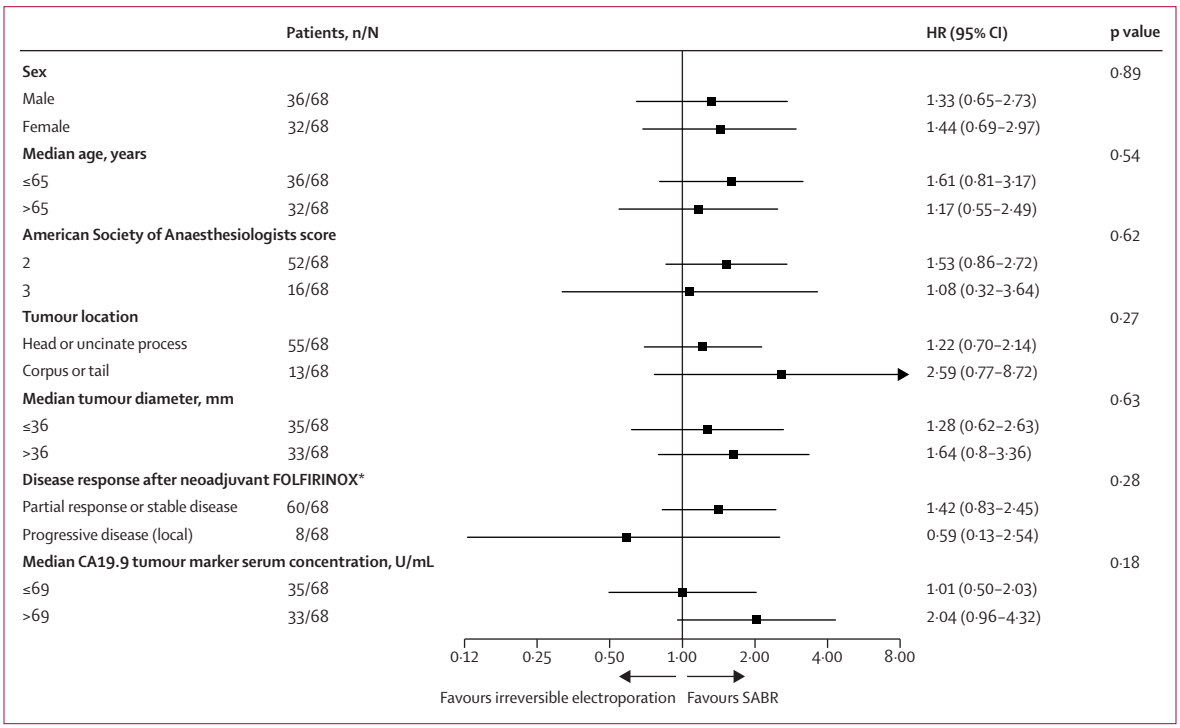

Figure 4: **Subgroup analysis of overall survival**
HRs higher than 1 favour SABR and HRs below 1 favour irreversible electroporation. HR=hazard ratio. SABR=stereotactic ablative body radiotherapy. RECIST=Response Evaluation Criteria in Solid Tumours. *As per RECIST (version 1.1) criteria.

in terms of mean overall health score remained stable for the irreversible electroporation group (81 [12; p=0·30).

Immune monitoring results indicated a favourable transient shift in systemic immune status with significantly increased ratios of activated and proliferative $CD8^+$ T cells to suppressive activated Tregs at 2 weeks, declining to baseline levels by 3 months after treatment in both groups (appendix p 2). Transient PD-1 upregulation on activated $CD4^+$ T cells 2 weeks after treatment was only observed in patients in the irreversible electroporation group (appendix p 2).

In the subgroup analysis for overall survival, no differences were identified between the treatment groups (figure 4). When patients were stratified according to their neoadjuvant chemotherapy response, irrespective of ablative treatment, a significant difference in overall survival from randomisation (p=0·03) and from diagnosis (p=0·03) was observed between patients with partial response or stable disease and those with local disease progression. Among individuals with a partial response (n=2) or stable disease (n=58), median overall survival was 15·1 months (95% CI 12·5 to 18·0) from randomisation and 20·7 months (17·6 to 23·2) from diagnosis. Among patients with local disease progression (n=8), median overall survival was 9·7 months (95% CI 7·5 to not reached) from randomisation and 13·2 months (11·1 to not reached) from diagnosis.

Four (13%) of 32 patients received adjuvant chemotherapy with FOLFIRINOX (median four cycles [IQR 1–6]) after SABR and ten (31%) of 32 patients (median five cycles [IQR 4–6]) after irreversible electroporation (p=0·07; table 2). A post-hoc univariable Cox regression excluding all patients who received adjuvant chemotherapy in both the SABR and irreversible electroporation groups demonstrated that overall survival (HR 1·38 [95% CI 0·76–2·50]; p=0·30), progression-free survival (0·77 [0·39–1·50]; p=0.4), local tumour progression-free survival (1·75 [0·72–4·23]; p=0·2), and distant progression-free survival (0·42 [0·19–0·94]; p=0·03) outcomes were similar to the survival outcomes of the entire cohort (ie, including patients who did and did not receive adjuvant chemotherapy), indicating that adjuvant chemotherapy was not a significant confounder for the survival endpoints. Palliative chemotherapy was administered to 13 (38%) of 34 patients in the SABR group and 15 (44%) of 34 patients in the irreversible electroporation group (p=0·62). Treatment with adjuvant and palliative chemotherapy was not mutually exclusive; one patient in the SABR group and three patients in the irreversible electroporation group received both adjuvant and palliative chemotherapy. Four (13%) of 32 patients with isolated local recurrent disease after initial irreversible electroporation received repeat local ablative treatment using irreversible electroporation. One (3%) of 32 patients in the SABR group developed a distant tumour recurrence within the pancreas, outside of the ablated region. This tumour was subsequently also treated with SABR.

Discussion

To the best of our knowledge, this is the first randomised trial comparing SABR with irreversible electroporation for patients with locally advanced pancreatic cancer after treatment with neoadjuvant FOLFIRINOX. The results demonstrated no significant differences in overall survival between groups. The trial was stopped early due to meeting prespecified stopping rules for futility. Progression-free survival and incidence of adverse events were not significantly different between the SABR and irreversible electroporation groups. Post-hoc analyses demonstrated that overall survival from diagnosis and local tumour progression-free survival were also not significantly different between the two treatment groups. Distant progression-free survival, another post-hoc analysis, was significantly longer after irreversible electroporation than after SABR. Although a higher number of patients in the irreversible electroporation group received adjuvant chemotherapy than did patients in the SABR group, an additional sensitivity analysis excluding the cohort treated with adjuvant chemotherapy found a similar significant difference in distant progression-free survival between groups. This finding indicates that the effect is potentially based on differences in the local ablative modality used.

For irreversible electroporation, the outcomes observed in this study are consistent with the results of the PANFIRE-1 and PANFIRE-2 trials, which demonstrated a median overall survival of 11 months from percutaneous irreversible electroporation in similar patient cohorts.[6,7] In other prospective trials, median overall survival after irreversible electroporation ranged between 7 months and 10·7 months.[8,9] In a systematic review, median overall survival of the retrospective series after irreversible electroporation ranged from 14 months to 27 months.[29] A randomised trial demonstrated the additive effect of irreversible electroporation with gemcitabine when compared with gemcitabine alone. Specifically, patients who received irreversible electroporation plus gemcitabine had superior overall survival (19·8 months *vs* 9·3 months; p<0·001) and progression-free survival (8·3 *vs* 4·7 months; p<0.001)[30] when compared with gemcitabine alone, denoting the efficacy of ablative treatment. Similarly, a post-hoc matched comparison of the PANFIRE-2 trial participants and a historical cohort of patients treated with FOLFIRINOX alone found a survival difference for FOLFIRINOX plus irreversible electroporation versus chemotherapy alone (17·0 months *vs* 12·4 months p=0·038).[31]

Published research on SABR for locally advanced pancreatic cancer reported overall survival ranging from 6·4 to 23 months.[12–16,32] In the LAPC-1 trial, patients had a median overall survival of 18 months from initiation of FOLFIRINOX.[14] Another prospective study that used a MRI-integrated SABR workflow in a similar patient cohort reported a median overall survival of 16 months.[15] Although no trials have been published comparing SABR plus chemotherapy with chemotherapy alone, ambiguous results have been reported of the additive effects of conventional radiotherapy. The randomised LAP-07 trial demonstrated no significant difference in overall survival when comparing chemotherapy with chemoradiotherapy.[33] Conversely, the randomised trial by the Eastern Cooperative Oncology Group showed that radiotherapy plus gemcitabine improved overall survival when compared with gemcitabine alone (11·1 months *vs* 9·2 months; p=0·017).[3] The Dutch LAPSTAR trial (NCT06272162), a phase 3 randomised trial comparing chemotherapy with SABR to chemotherapy alone in patients with locally advanced pancreatic cancer who are not eligible for tumour resection after initial systemic therapy, will hopefully provide information about whether SABR will yield additional survival benefits.

The substantial range of survival outcomes published for both techniques, and especially the differences between prospective and retrospective studies, are most likely attributable to selection bias, including diverse patient and disease characteristics, and response to neoadjuvant chemoradiotherapy regimens and additional surgical treatment after ablation. Widely varying treatment specifics, including the use of MRI-guidance, total dose, and number of fractions for SABR, and number of pulses, pulse duration, voltage settings, and the treatment approach (ie, open *vs* percutaneous) for irreversible electroporation, might also have been a contributing factor. Earlier mathematical series assessing the added value of MRI-guidance over conventional SABR showed improved delineation of soft tissue, allowing for more precise targeting of tumour contours while limiting exposure to surrounding organs at risk.[10]

Our results showed that patients with a partial response or stable disease after neoadjuvant chemotherapy had a significantly better overall survival (20·7 months from diagnosis) than those with local disease progression (13·2 months from diagnosis). Overall survival from diagnosis after FOLFIRINOX alone was 15·3 months among patients with a partial response or stable disease[34] in a similar patient cohort with locally advanced pancreatic cancer from the literature, which might suggest a potential survival benefit of ablative treatment in this subset of patients. The lower overall survival outcomes in patients with local disease progression implies a more aggressive tumour biology, supporting the importance of patient selection for local treatment. For these patients, potential modest clinical benefits should be carefully weighed against treatment-related risks.

The potential synergy between chemotherapy and ablation can be explained by their cytoreductive properties, but might also be partly explained by the notion that both cytotoxic drugs and ablative techniques enhance an anti-tumour response by stimulating immunogenic cell death, reducing tumour-induced immune suppression, and by improving T-cell functions.[35] Both irreversible electroporation[21] and stereotactic radiotherapy[36] have

demonstrated the ability to induce an immune response in patients with pancreatic cancer. One preclinical study found that irreversible electroporation might have a more robust immune potentiation and disease inhibiting ability than does ionising radiation.[37] The immune monitoring data presented in this study confirm earlier findings from the PANFIRE-2 trial,[21] indicating a transient systemic change in immune status with increased frequencies of activated, proliferating effector T cells and decreased rates of activated Tregs 2 weeks after irreversible electroporation, resulting in a more favourable ratio of $CD8^+Ki67^+$ T cells to activated Treg cells. A similar immune permissive shift at 2 weeks was also observed in patients in the SABR group. Simultaneous upregulation of PD-1 on T cells after irreversible electroporation highlights the potential of combining this form of ablation with PD-1 blockade. Although these immune potentiating effects after ablation seem temporary, they nevertheless offer a window of opportunity for multimodal treatments combining ablation with immunotherapy. Initial studies have shown promise,[38,39] and data from the PANFIRE-3 trial,[40] in which patients with metastatic pancreatic ductal adenocarcinoma were treated with irreversible electroporation combined with local (Toll-like receptor 9 agonist cytosine-phosphate-guanine oligodeoxynucleotides) and systemic (anti-PD-1) immunotherapy, is currently being analysed. A more detailed and comprehensive comparative analysis of the immune monitoring data from both treatment groups, including tumour antigen-specific T-cell rates, response kinetics, and their association with survival, will be published separately.

In the per-patient safety analysis, no significant difference was identified between SABR and irreversible electroporation in terms of incidence of adverse events of any grade (63% *vs* 59%) nor the grade 3–5 adverse events (16% *vs* 25%). However, when considering only potentially treatment-related grade 3–5 adverse events, SABR resulted in fewer complications than irreversible electroporation (two [6%] patients *vs* seven [22%] patients). A study using a similar MRI-integrated SABR protocol in patients with locally advanced pancreatic cancer concluded this workflow to be relatively safe with no acute treatment-related toxicity of grade 3 or worse.[12] In the LAPC-1 trial,[14] serious grade 3–5 adverse events were reported in 10% of treated patients (of which 5% were grade 5 events). For irreversible electroporation, the incidence of serious grade 3–5 adverse presented here were comparable to those presented in the PANFIRE-1 and PANFIRE-2 trials (21 serious complications in 50 patients).[6,7] The use of CT arteriography provided beneficial intraprocedural visibility of the tumour and vascular structures, enabling more precise electrode placement and supporting periprocedural safety.[20]

Since locally advanced pancreatic cancer is deemed incurable, potential improvements in survival should be cautiously weighed against changes in QoL. We demonstrated maintenance of QoL from baseline, as reflected by the stable overall health score and pain scores up to 6 months after ablative treatment. Between 9 and 12 months after ablative treatment, decreases in overall health scores and increasing pain scores are likely to reflect disease progression.

A limitation of this trial was that it stopped early for futility, preventing definitive conclusions on marginal differences in survival. Another limitation was the absence of a control group of patients treated with chemotherapy alone. The LAPSTAR trial will provide a definitive answer regarding this question. Furthermore, we acknowledge that the imbalance in adjuvant chemotherapy regimens between the two study groups could potentially affect overall and progression-free survival, which we accommodated for by performing an additional analysis excluding the cohort treated with adjuvant chemotherapy. Additionally, the overall survival from diagnosis, local tumour progression-free survival, and distant progression-free survival analyses were performed post-hoc and are therefore exploratory in nature. Furthermore, MRI, PET-CT, and diagnostic laparoscopies were not routinely performed, and size progression of the primary tumour under neoadjuvant FOLFIRINOX within the predefined limit (5 cm) was allowed. Although a maximum period of 4 weeks was permitted between the contrast enhanced CT during work-up and ablative treatment, it is likely that some patients had micrometastatic disease at the time of randomisation that was not yet apparent on imaging, particularly when considering that 12% of patients had local disease progression after neoadjuvant FOLFIRINOX.

In conclusion, no significant differences in overall survival, progression-free survival, or incidence of adverse events were identified between the two treatment groups. QoL was stable for up to 6 months after local treatment. Both ablative therapies seem to have the potential to induce a systemic immune response. Although disease control can be temporarily achieved with both MRI-guided SABR and CT-guided percutaneous irreversible electroporation, future studies should further assess their added value over chemotherapy alone. The choice of ablative treatment will depend on site-specific factors such as availability, expertise, and feasibility, in addition to patient preference, taking into account differences in treatment invasiveness, duration, and hospital stay.

Contributors

MM, AB, TdG, LV, and HS were involved in the study design and funding acquisition. LV, AR, BG, ES, and FT oversaw the quality of the trial, and were responsible for data curation and project administration. BG and FT extracted the data, analysed the results, prepared the figures, did the literature search, and wrote the initial manuscript. MM, AB, FT, and HS have accessed and verified all the data underlying the manuscript. AR, LV, ES, SvdL, DV, MD, HHS, JB, BvdB, PvdT, RP, BLW, TdG, and JdV were involved in the investigation, and writing and reviewing the manuscript. All authors had direct access to underlying data reported in the manuscript, and reviewed and approved the manuscript before submission.

Declaration of interests

MM, HS, BG, AR, LV, TdG, and FT received research funding from the Adessium Foundation for the conduct of the CROSSFIRE trial and

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Data sharing

For eligible studies, qualified researchers can request access to individual, de-identified, patient-level clinical data through a data request. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement, which describes the conditions for release and requirements for data transfer, storage, archiving, publication, and intellectual property. Requests are reviewed by the trial management group in terms of scientific merit and ethical considerations, including patients' consent. Data requests can be submitted to interventieradiologie@amsterdamumc.nl.

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