



Can local ablative techniques replace surgery for locally advanced pancreatic cancer?

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Abstract: In the treatment of pancreatic ductal adenocarcinoma (PDAC) the best chance at long term survival or cure has to date always included the complete surgical removal of the tumor. However, locally advanced pancreatic cancer (LAPC), about 25% of all newly diagnosed PDAC, is defined by its primary technical unresectability due to infiltration of visceral arteries and absence of metastasis. Induction therapies, especially FOLFIRINOX treatment, together with technical surgical advancement have increased the numbers for conversion to secondary resectability. Recent data on resections after induction therapy show promising, almost doubled survival compared to palliative treatment. Yet, around 70% of LAPC remain unresectable after induction therapy, often due to persistent local invasion. As locally ablative techniques are becoming more widely available this review examines their possible applicability to substitute for surgery in these cases which we propose to group under the new term “Inconvertible LAPC”. The need for defining this novel subgroup who might benefit from ablative treatment is based on the findings in our review that high-level evidence on ablative techniques for PDAC is largely lacking and the latest effective, harmonized treatment guidelines for LAPC are not often incorporated in these studies. The “inconvertible LAPC” label requires persistent unresectability after staging and induction therapy of LAPC according to current guidelines followed by liberal indication for aggressive surgical exploration at a center equipped for extended pancreatic resections. Ideally, this specification of a new, distinct patient group will also put it in the spotlight more, hopefully prompt more trials designed to generate robust evidence and optimize transferability of study results.

Keywords: Pancreatic cancer; locally advanced pancreatic cancer (LAPC); ablation techniques; irreversible electroporation (IRE); induction therapy

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Background

The claim “only steel can heal” describes not only traditional surgical self-confidence but also seems to sum up the clinical management of pancreatic cancer. While pancreatic surgery is risk-prone for perioperative morbidity and mortality complete removal of a pancreatic carcinoma remains the only chance at cure or longtime

survival. Today’s clinical pathways for pancreatic ductal adenocarcinoma (PDAC) distinguish resectable, borderline resectable (BRPC), locally advanced (LAPC) and disseminated stages (1,2). About half of all newly diagnosed patients present with metastases and 15–20% are resectable upon diagnosis, according to data from the SEER database (3). As the benefit of neoadjuvant therapy in resectable tumors is still a matter of debate in spite of

numerous trials and a few meta-analyses (4-7), international consensus guidelines recommend upfront resection for resectable PDAC outside of clinical trials. Five-year survival rates in the resectable group can reach around 20%, in favorable subgroups exceeding 50% (8). In stage IV pancreatic cancer palliative chemotherapy with FOLFIRINOX is the current standard of care (9). In locally advanced stages without dissemination, however, recommendations are not so straightforward: BRPC and LAPC together comprise about 30% of all new cases and, semantically, some authors term BRPC the resectable subtype of LAPC. The distinction between BRPC and LAPC differs between guidelines which set different limits regarding the degree of venous and arterial involvement and in part CA 19-9 levels and performance status (3,10-14). Generally, though, LAPC is considered technically not completely resectable, whereas BRPC can be surgically removed by simultaneous resection of adjacent vasculature and/or multi-organ resections with an increased risk of microscopically positive margins. In BRPC many cohort studies as well as randomized controlled trials (RCT) to date have investigated possible benefits of preoperative (radio-) chemotherapy reflecting the emerging practice of choosing pretreatment over an upfront surgical resection in patients with an inherent risk of unresectability or microscopic incomplete resection [reviewed in (15-17)]. Consensus guidelines in Europe as well as the US recommend neoadjuvant treatment (1,2) and a recent meta-analysis advocates for preoperative FOLFIRINOX specifically (16). LAPC in the unresectable sense is defined by the National Comprehensive Cancer Network (NCCN) as well as the International Study Group of Pancreatic Surgery (ISGPS) as: (I) no distant metastasis, (II) solid tumor contact with superior mesenteric artery (SMA) and/or celiac artery $>180^\circ$, (III) solid tumor contact with the first jejunal SMA branch and/or aortic involvement, (IV) unresectable superior mesenteric vein (SMV) and/or portal vein (PV) due to tumor involvement or occlusion, (V) contact with most proximal draining jejunal branch into SMV (2,11). By the AHPBA/SSAT/SSO, however, it is defined as: (I) no distant metastasis, (II) circumferential encasement of SMA and/or common hepatic artery (CHA), (III) abutment of CA due to tumor involvement, (IV) unreconstructable SMV and/or PV due to tumor involvement or occlusion [(12), reviewed in (18)]. Neoadjuvant chemotherapy, or rather more precisely: induction chemotherapy is a relatively novel concept for these tumors emerging from the encouraging results that were seen with FOLFIRINOX treatment in

the palliative and adjuvant setting (19-22). More centers around the world are thus embracing multimodal pathways in the situation of questionable local resectability—and in unresectable LAPC there is nothing to lose: first line palliative chemotherapy treatment recommendations are FOLFIRINOX or gemcitabine/nab-paclitaxel and are thus identical to the regimen which would retrospectively be termed “induction chemotherapy” in case of a response that renders the patient suitable for surgical exploration (1,23,24). In clinical reality this means that a patient with local involvement of visceral arteries but no signs of distant metastases who is judged unresectable by their surgeon will get sent for FOLFIRINOX treatment but also summoned for surgical reevaluation after at least 4-6, in some guidelines more cycles. In case of stable disease or better surgical exploration should be generously scheduled as data demonstrate secondary resectability in up to 60% of patients with imaging not accurately depicting local spread post chemotherapy (25,26). Surgical evaluation will also consider CA 19-9 dynamics which have been shown to correlate with resectability (27,28) and up to 12 preoperative cycles will usually be administered; in rare cases patients are resected after even more. Before and alongside FOLFIRINOX multiple (radio)chemotherapy regimens for LAPC have been proposed and evaluated in clinical trials (18). Some authors advocate for a cautious surgical approach as the importance of secondary resection in case of response or stable disease is still under debate to date, but other data have shown an advantage compared to continued chemotherapy (29-32).

Two 2016 meta-analyses on 365 and 355 patients, respectively (19,33), found a median survival of 24.2 months with a pooled proportion of 25.9%/28% of patients undergoing secondary resection after FOLFIRINOX and a range of 0-44%. Resection rates up to 60% have been reported, though (26). Thus, in overall more than 70% of patients after induction chemotherapy the tumor is not suited to be resected. Often, this is due to distant metastasis at restaging or exploratory laparotomy, but a large proportion remains unresectable due to local spread. These patients will usually keep on receiving chemotherapy, maybe switched to second line agents, and are labelled palliative. Depending on the local standards regarding restagings during palliative chemotherapy they might be reevaluated for surgery again down the line but only rarely will undergo resection; international guidelines are lacking for this situation. If other methods of local tumor control for LAPC equal to surgery or at least superior to palliative

chemotherapy were available this could open up new treatment pathways for LAPC patients.

Ablation techniques pancreatic experience

In contrast to other solid organ malignancies locally ablative strategies have not had much relevance for PDAC in the past as, in some series, major postinterventional morbidity and mortality have been reported due to anatomical features unique to the pancreas. Available data have not generated sufficient evidence to date to incorporate ablative techniques into any treatment guideline, yet, on an individual basis their application can be justified at specialized centers. Apart from possible benefits for oncological outcome, prevention of local complications of tumor growth and pain relief, some studies also point towards advantageous systemic immunological effects secondary to ablative treatment (34-37).

Although they encompass completely different therapeutic mechanisms, photodynamic therapy (PDT), brachytherapy, stereotactic body radiation (SBRT) and irreversible electroporation (IRE) are all non-thermal ablation techniques. This distinction is especially important for application on pancreatic lesions, as the surrounding anatomical structures, namely the duodenum, bile duct, mesentericoportal vessels and visceral arteries, are temperature sensitive and damage can lead to fatal complications. Techniques based on thermal tissue destruction include high-intensity focused ultrasound (HIFU), cryoablation, radiofrequency ablation (RFA), microwave ablation (MWA) and laser-induced thermotherapy (LITT). Whereas HIFU uses extracorporeal directed ultrasound waves focused on the target region and represents a non-invasive technique guided by ultrasound or magnetic resonance imaging (MRI), all other thermal ablative techniques involve placing a probe in the target tissue, either during laparotomy or percutaneously guided by cross-sectional imaging or ultrasound; alternatively, endoscopic application has been successfully performed, too (38). After HIFU PV thrombosis, jaundice, pancreatic fistula, pancreatitis, GI bleeding, bowel perforation and severe skin burns have been described with a morbidity rate ranging from 0% to 23.2% [reviewed in (39)], and the technique has mostly been evaluated for pain palliation in pancreatic cancer (40,41). Studies are often small, non-controlled, heterogeneous by population and protocols and no reliable survival advantages have been reported.

Cryoablation is a modality which can be applied during open surgery, by percutaneous needle insertion or endoscopically (42). The probe is rapidly cooled down

to $-160\text{ }^{\circ}\text{C}$ and reheated to $0\text{ }^{\circ}\text{C}$ causing necrosis as well as apoptosis of the target zone; different protocols exist, but several freeze-thaw cycles are repeated. While it is rarely studied in Western countries, Chinese doctors seem to be more routinely using it and a consensus statement on pancreatic cryotherapy was issued with mostly Asian participation (43). However, the evidence to support the technique is still weak: In two retrospective studies comparing palliative surgery with and without additional cryoablation in overall 260 patients no survival benefit was found (44,45). The risk profile was comparable to other thermal techniques on the pancreas with cases of pancreatic and biliary leakage, delayed gastric emptying and intestinal hemorrhage. Similar to the data for HIFU in LAPC, cryoablation can induce lasting pain control (46), but apart from the two studies mentioned above only case series are available for pancreatic indications. Addition of different cryo-adjuvants has been tested to achieve sufficient effects at the freeze zone margin (47) and postulated abscopal immunologic effects have led to combination treatment protocols including immunotherapies, especially in renal cell cancer and non-small cell lung cancer [reviewed in (48) but also PDAC (37,49)].

In RFA, a high frequency alternating current produces heat leading to protein denaturation and necrosis starting at $60\text{ }^{\circ}\text{C}$ and vaporization and carbonization of the tissue beyond $100\text{ }^{\circ}\text{C}$ (50). It is widely used on liver lesions and some other malignancies and thus available at more centers than other ablative techniques. Its limitations include a heat-sink effect, when thermal energy dissipates via the blood stream in the proximity of larger blood vessels, and a required safety distance of at least 5 mm to bile duct, vessels and the duodenum with some interventionalists preferring 10–15 mm. RFA is most effective in symmetric, well defined lesions, whereas LAPC is known for its blurred boundaries. Most published studies report pancreatic RFA during laparotomy, however, endosonographic and percutaneous application has been reported in mostly experimental or exploratory settings, too (38). A 2014 systematic review on its use in LAPC found five studies on 158 patients and a reported median overall survival (OS) after RFA of 3–33 months, a morbidity related to RFA of 4–37%, mortality of 0–19% and overall morbidity of 10–43% (51). In more recent publications, complication rates were improved: In several studies from Verona, Italy, (one percutaneous, six open surgery, one endoscopic) and one from Utrecht, Netherlands, OS ranged between 14.7 and 25.6 months [reviewed in (37,39)] with a severe

complication rate of 0 to 28% and 30-day mortality between 0 and 3%. Complications included hepatic failure, duodenal perforation, severe acute pancreatitis, duodenal hemorrhage, pancreatic fistula, portal vein thrombosis, duodenal/biliary injury, gastric ulcer or fistula, hemoperitoneum. No randomized controlled trials are available on RFA in LAPC yet; the Dutch randomized controlled PELICAN trial was designed to close this gap, but no results have been published to date (Dutch trial register number NTR5517). Best available evidence on RFA in LAPC comes from prospective cohort studies without oncological control groups thus far.

MWA is a regularly used technique on hepatic lesions but has rarely been evaluated for pancreatic tumors. Microwaves cause heat by oscillation of predominantly H₂O-molecules in an electromagnetic field (52). Compared to its main contestant in hepatic application, RFA, MWA is faster with larger ablation volumes and less interference by heat-sink effect, but also less predictable, pear-shaped ablation areas (53,54). In pancreatic cancer, a total of 30 patients from case series have been reported in the literature with either percutaneous or open MWA (55-58). Apart from one patient with severe pancreatitis/pseudocyst and one with pseudoaneurysm of the GDA (56) no major complications were described; reported survival data are patchy and do not allow any conclusions as to oncological effectiveness.

LITT has to date most often been used in hepatic (59), intracranial (60), thyroid (61,62) and prostate (63) tumors. LITT operates with very fine needles and optical fibers and has a theoretical advantage of being less invasive and more precise than other ablative techniques, though comparative studies are lacking. In the only clinical report to date, Di Matteo *et al.* presented a case series of nine patients with localized PDAC unresponsive to chemotherapy and treated with EUS-guided LITT (64). No complete tumor ablation was intended, and no side effects were observed, though pending further clinical studies these data represent hardly more than a proof of principle.

PDT is closely related to LITT as it uses light wave energy as well, but the ablative effect is achieved by the interaction of the light waves with a photosensitizer which needs to be administered before. The chemical reaction produces radical oxygen species (ROS) which destroy surrounding tissue making it a non-thermal technique; depending on the selectivity of the agent for cancerous cells healthy tissue is spared. As light wave penetration is very shallow PDT has so far mainly been applied to intraluminal early stage malignancies such as esophageal, gastric,

colorectal and bladder cancer [reviewed in (65)]. The dense peritumoral stroma in PDAC and its oxygen-deprived environment further limit light penetration and effectiveness of PDT. Since 2002, overall 44 patients receiving PDT for PDAC have been reported in the literature. Bown *et al.* treated 16 LAPC with meso-tetrahydroxyphenylchlorin and percutaneous, CT-guided PDT. Three duodenal obstructions and two gastroduodenal artery bleeds were observed; median OS was 9,5 months (66). Percutaneous PDT with verteporfin application resulted in a median OS of 8.8 months for 15 patients, no SAE were observed (67); and one patient is reported after use of Photolon[®] with PDT via EUS without SAE (68). In the most relevant study to date, DeWitt *et al.* gave 12 treatment-naïve LAPC patient porfimer sodium and PDT via EUS, followed by gemcitabine/nab-paclitaxel, with a median OS of 11.5 months. Notably, two patients underwent secondary resections with one complete pathological response; sunburns and hyperpigmentation were the reported side effects (69). Research in this field is focusing on the development of ideal photosensitizers; it is generally agreed that PDT is hardly a radical treatment but more of an adjunct in the strive for local control and palliation.

For brachytherapy radionuclides of phosphorus-32, iodine, gold, iridium, and yttrium have been studied for local PDAC treatment since the 1970ies with I-125 nuclides being the most frequently used agent (70). The radioactive seeds are implanted with specialized cannulas into the tumor under CT-, MRI- or EUS-guidance, but intraoperative use has been described, too (71). I-125 seeding has most often been studied in addition to other therapies and in case series, but a few contemporary, prospective comparative studies are available, too. One study comparing 66 unresectable patients receiving enteric bypass plus I-125 seeds or bypass alone for LAPC found significantly improved median OS of 11 *vs.* 7 months in the brachytherapy group; pain scores were significantly better as well (72). Risks include pancreatitis, infection, seed migration and intestinal perforation (73,74).

SBRT, also called stereotactic ablative body radiation (SABR), is a highly focused percutaneous radiation treatment with an intense dose of radiation on the target region, while limiting the dose to the surrounding organs, performed within few (usually 1-5) sessions at high doses (6-25 Gy). Cyberknife[®] is a specific technique of SBRT using real-time tracking of gold fiducial markers, real-time respiratory modelling and continuous monitoring to

correct for tumor movement and radiation administered via a robotic arm. Only these highly accurate technologies achieve a sufficient, ablative biologically effective dose. Limitations of ablative dose delivery to pancreatic tumors are mostly due to the proximity of tumors to the duodenum, jejunum, and stomach, and trials examining conventional radiotherapy have largely failed to show any advantages (3,75). Despite unconvincing data on conventional radiotherapy and limited evidence for SBRT current NCCN and ASCO guidelines recommend either for LAPC without distant progression after 6 months of chemotherapy (2,24). A 2016 systematic review on SBRT in LAPC (76) found 19 studies (6 prospective, 13 retrospective, no RCTs) with a median OS ranging from 5.7 to 47 months; a more recent review on a partly overlapping group of studies gave a median OS after SBRT of 6.2 to 12.5 months and secondary resectability of 0–20.3% (39). Local complications reported include gastroparesis, gastrointestinal (duodenal) bleeding, duodenal or gastric outlet obstruction, duodenal perforation, gastric ulcer, anorexia, nausea/vomiting, and SMV/inferior v. cava thrombosis (77) reported in few patients. Systemic radiation toxicity (cytopenias, nausea/diarrhea, infections) was reported in up to 28.5% of patients (39). RCTs are still lacking for SBRT in LAPC but some are currently ongoing: The US based RCT evaluating mFOLFIRINOX with and without SBRT, PANC0015, sponsored by Stanford University is not yet completed; so is the randomized controlled CROSSFIRE trial from the Netherlands, comparing IRE with SBRT. The CONKO-007 RCT from Germany, similar to PANC0015, evaluates the addition of radiation to induction therapy but no results have been published yet.

Since 2012, IRE, a non-thermal local tumor ablation technique, has been studied in LAPC (78). During IRE, tissue is destroyed by the application of a high-voltage direct current via electrodes inserted into the tumor, rendering cellular membranes porous and effectively breaking down the membrane barrier, thus killing the cell by predominantly inducing apoptosis (79). Notably, as there is only very little thermal effect, adjacent structures are spared. IRE can be applied on the pancreas via laparotomy or percutaneously by image-guided puncture; the most commonly used system is the NanoKnife® device. Several contraindications are usually applied: Tumor size >5 cm, combined severe stenosis of the CHA and PV given the 10% risk of an acute PV occlusion, as well as metal implants like bile duct stents/cardiac pacemakers and a history of cardiac arrhythmias are considered incompatible with IRE, though the risk of metal

implants is still being discussed (80). A 2017 systematic review (81) examined 10 studies of IRE in LAPC reporting on 446 patients and concluded that IRE is safe and feasible, but effects on survival were difficult to evaluate as the studies were heterogeneous in their designs and techniques. In an even more recent systematic review on 18 studies (all single-center, 8 retrospective, 7 prospective and 3 case series) the findings were similar; additionally, open IRE as compared to percutaneous had higher morbidity (35.6%) and mortality (4.6%) with 11 reported deaths attributed to GI bleeding, intraperitoneal hemorrhage, extensive bile duct and duodenal ischemia, liver failure, pulmonary embolism, multi-organ failure and unknown reasons (82). Overall, 5.3% of patients underwent secondary resection after downstaging post IRE, and median overall survival as reported from date of IRE ranged from 7–27 months. This systematic review included 498 patients overall even though it excluded IRE for margin accentuation during surgery and studies on IRE in combination therapies other than (radio-) chemotherapy. Another systematic review additionally found an overall complication rate of 30%, with up to 59% in the rarely studied laparoscopic application of IRE, and associated mortality of 3% (83). In a current retrospective comparison of FOLFIRINOX with and without addition of IRE van Veldhuisen *et al.* found significantly longer OS (17.2 *vs.* 12.4 months) after added IRE (84), and in a matched analysis of 32 pairs receiving IRE or conventional radiotherapy after induction therapy IRE showed doubled median OS of 21.6 *vs.* 10.6 months (85). However, the prospective IMPALA study did not find improved median OS by addition of open IRE (16 months) to palliative chemotherapy (15 months), while underlining the importance of resection after induction therapy (34 months) (86). The prospective cohort study PANFIRE-II reported a median OS of 9/11 months after FOLFIRINOX/other chemotherapy and percutaneous IRE in 40 patients (87). To date, no randomized controlled data are available on IRE in LAPC; the ongoing CROSSFIRE study randomizing for FOLFIRINOX followed by either SBRT or IRE has not been published yet (NCT02791503). A few reports exist on immunological effects of IRE in humans pointing to suitability for combination with immunotherapies (34,37,88,89).

Discussion

For all we know today, LAPC “only steel can heal”: the most robust available data comparing LAPC resected after induction (radio-)chemotherapy with unresected LAPC

demonstrate almost a doubling of median survival times [35.3 vs. 19.9 months in a matched analysis (29)] and a 5-year OS of 25.4% after secondary resection (32). In the light of these numbers, even if they are retrospective and include in part disseminated patients in the control groups, it seems highly unlikely that any future randomized controlled trials on resection versus continued (radio-) chemotherapy after response to induction therapy can be ethically justified and thus will probably never come. Only 20–30% of all LAPC patients in the aforementioned collectives ultimately were able to undergo resection after induction treatment, but the true rate of resectable versus locally unresectable versus disseminated LAPC at reassessment after induction therapy has not been established so far as reports have been focusing on other aspects. Furthermore, no biomarkers are currently available to distinguish any of these LAPC subgroups. Though molecular pathology might lead to improved surgical treatment stratification in the future (90,91), how can we best treat for the time being the remaining non-disseminated LAPC patients who, even under the most aggressive surgical approach, never get their tumor excised? Do we have local treatment options besides surgery to improve survival for this group? Reviewing the data the locally ablative techniques have yielded so far, possibly IRE currently has the highest potential to be included in future guidelines due to large patient series and the advantages of its non-thermal mode of action. Overall, though, the level of evidence generated by the studies on most ablative techniques is disappointing; controlled data are scarce, RCTs a rarity. As some trials with potentially high levels of evidence are still ongoing, the quality of data might improve in the near future, but currently there are modalities (MWA, LITT, PDT) that have been rarely studied and others (cryoablation, RFA, brachytherapy, HIFU, SBRT, IRE) with a sizeable number of publications, yet in both groups not a lot of evidence can be drawn. Clinically, this means that even though some techniques seem to be rather common they are performed on an exploratory/compassionate basis, and it will depend on local options if a patient is offered an ablative treatment and which, and under which protocol. Nevertheless, most data point towards acceptable safety and feasibility of the reviewed techniques with potential advantageous oncological effects. We therefore believe that high-quality trials are urgently needed to evaluate these modalities further. The first step, however, should be the definition of the patient subgroup who might benefit from non-surgical local treatment options. Considering the data on feasibility of extended resections and benefit of

survival after resection in LAPC we call for the definition of a new PDAC subgroup: “Inconvertible LAPC”. This concept should be used to characterize LAPC staged and treated with induction therapy according to consensus standards, followed by surgical (re-) exploration at centers equipped for extended resections which are judged locally unresectable by an experienced HPB surgeon. Alternatively, a multidisciplinary assessment after induction therapy that exploration is considered futile but dissemination is excluded is required.

The discussion about resectability of PDAC and the definition of BRPC and LAPC criteria has brought new standards to the reporting of surgical as well as oncological studies on pancreatic cancer and ensures comparability of measures and outcomes as well as standardized evaluation of new treatment pathways. However, for ablative therapies to date no precise definition of the target patient group exists and thus many publications report on a mix of stage II–IV cancers, which in the light of the latest data on powerful induction chemotherapies and outcomes of conversion surgery does not seem appropriate. Only now that effective, harmonized treatment pathways for LAPC are emerging can this specific subgroup even be defined. Furthermore, many publications on ablative therapies are unclear about the multidisciplinary assessment of the study participants; studies are often carried out by dedicated interventionalists, from radiology, radiation oncology, nuclear medicine or gastroenterology, who might not always be involved in the full scheme of oncological decision making. By defining the aforementioned requirements for LAPC patients to be grouped as “Inconvertible LAPC” and thus eligible for a locally ablative approach a multidisciplinary assessment according to current consensus guidelines on LAPC is ensured—the goal being that no patient should be unduly dismissed for surgical exploration as well as optimizing transferability of study results. Ideally, this specification of a distinct patient group will also put it in the spotlight more and hopefully prompt more trials designed to generate robust evidence. The first steps to apply the concept of “Inconvertible LAPC” should include large prospective cohort studies to establish its true incidence after state-of-the-art induction treatment and under an ambitious surgical approach at specialized centers. Ideally, molecular profiling would be performed in these patients as well, possibly pointing out markers with relevance to further treatment modalities other than just type of chemotherapy. To more quickly approximate these data, our group is currently designing a patient-level meta-analysis focusing on the

patient fraction already reported in the literature who fulfills these criteria. As reviewed here, published cohorts to date typically encompass a very heterogeneous population and tend to sum up different biological behaviour like local progression or dissemination as “unresectable”. If more granular data could be extracted we might be able to put our finger on the special subgroup of “inconvertible LAPC”. Future trials should then be designed in a way that outcomes of local ablation therapies can be directly compared to those of conversion surgery after induction as well as to palliative standards of care according to current guidelines. IRE and SBRT appear the most likely candidates here, as both come with the largest body of data for reference.

Even though some of the reviewed studies suggest the inherent superiority of an interventional, less-invasive approach over radical surgery, only if ablative strategies can convince under these standardized circumstances might it be time to compete against radical extended surgery in LAPC—the road for locally ablative techniques to replace surgery in LAPC is still very long.

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Footnote

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