



Review Article

The timing and design of stereotactic radiotherapy approaches as a part of neoadjuvant therapy in pancreatic cancer: Is it time for change?



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ARTICLE INFO

Article history:

Received 4 February 2021

Revised 6 April 2021

Accepted 7 April 2021

Keywords:

Pancreatic cancer

Stereotactic body radiotherapy

Total neoadjuvant therapy

ABSTRACT

Stereotactic Radiotherapy (SRT) over 5–15 days can be interdigitated without delaying chemotherapy. Bridging chemotherapy may allow for extended intervals to surgery, potentially improving sterilization of surgical margins and overall survival. SRT for pancreatic adenocarcinoma should not be limited to the tumor, and should consider hypofractionated approaches to regional nodes.

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The prognosis of pancreatic cancer

Pancreatic cancer has a poor prognosis, with a five-year overall survival (OS) of 3–14% in the non-metastatic setting [1]. Surgery has always played a vital role in treatment, potentially curing patients eligible to undergo complete resection of localized pancreatic cancer [2]. Unfortunately, over half of patients present with

metastases while only 10–20% have localized potentially resectable disease, leaving around 30% classified as borderline resectable (BR) or locally advanced pancreatic cancer (LAPC) [3,4]. Neoadjuvant therapy (NAT) has emerged as a standard approach for patients with BR and LAPC. Patients typically receive upfront combination chemotherapy for 2–4 months to treat micrometastatic disease, assess tumor biology, and increase the likelihood of margin-negative resection through margin sterilization and downstaging. Early systemic therapy is important, as approximately 30–50% of patients with LAPC will have evidence of metastatic disease within three months of diagnosis [4].

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Box 1 Chemotherapy for Pancreatic Cancer Modified FOLFIRINOX has recently emerged as the standard of care for adjuvant systemic therapy, demonstrating unprecedented median survival of nearly five years for patients undergoing upfront surgical resection and six months of postoperative mFOLFIRINOX. However, around half of patients without pre-operative therapy undergoing upfront surgery will have microscopically involved margins.

Box 2 The Pace of Development in Radiotherapy Conventional radiation regimens take 5-6 weeks to deliver and lead to delays in the receipt of systemic therapy. Abbreviated Stereotactic Radiotherapy (SRT) allows for the expedited administration of RT which may allow for earlier interdigitation without delaying highly effective systemic therapy.

The high rate of distant metastasis associated with pancreatic cancer underscores the importance of systemic therapy. Two recent trials of adjuvant chemotherapy (ESPAC-4, PRODIGE 24) in highly selected patients eligible for upfront surgical resection reported unprecedented median survival ranging from 30 to 54 months [5,6]. However, these trials also suggested an incidence of microscopically positive surgical margins (i.e., R1 resections) for upfront surgery ranging from 40 to 60% [5,7]. Negative (i.e., R0) resection margins are most challenging to obtain posteriorly, and appear to be strongly associated with isolated surgical bed recurrence [8]. Local failure is a known contributor to demise, as demonstrated by a classic autopsy series reporting 30% of patients died with locally destructive pancreatic cancer [9]. Pain from a lack of local control is known to affect quality of life adversely [10]. Moreover, ESPAC-4 and PRODIGE 24 demonstrated anywhere from one quarter [5] to one half [7] of first failures to be locoregional-only, suggesting a potential utility of additional local treatment before surgery.

Improving chances of successful surgery

Many complexities make the treatment of pancreatic cancer a challenge, including aggressive biology, early metastases, difficult anatomic location, intense non-surgical therapy, and cancer cachexia, making all of the above worse. Even in a trial setting, 30–40% of patients treated with upfront surgery will not receive all recommended adjuvant therapy due to surgical morbidity, poor performance, refusal, or early recurrence, thereby strengthening the rationale for a neoadjuvant approach [1].

Neoadjuvant chemotherapy (NAC) is associated with decreased rates of pancreatic fistulas and clinical sequella, such as delayed gastric emptying and surgical site infections, which commonly contribute prolonged post-surgical recovery and a delay in adjuvant therapy [11]. NAC facilitates early treatment of micrometastatic disease and allows for the identification of occult metastatic disease, facilitating appropriate patient selection for surgery. A recent meta-analysis comprised of 38 studies with 3,484 resectable or BR pancreatic cancer patients suggested NAT, i.e., NAC with or without radiotherapy (RT), appears to improve OS by intention to treat, despite lower overall resection rates in the patients who received NAT [12]. NAT was also associated with lower rates of pathologically positive lymph nodes and more R0 resections than upfront surgery alone [12].

However, preoperative chemotherapy alone may not be enough for some cases of BR and LAPC. A recent prospective study of 680 BR and LAPC patients suggested the receipt of complementary neoadjuvant radiation, in addition to chemotherapy, correlated with improved survival [13]. A large retrospective report of total neoadjuvant therapy (TNT) for LAPC demonstrated CA 19–9 response, ≥ 6 preoperative chemotherapy cycles, and major pathologic response to be independently associated with improved regression free survival and OS [14]. Of these three factors, major pathologic response was associated with the largest incremental benefit in OS [14].

Improving radiation techniques

Radiation therapy (RT) has failed to prove a consistent benefit in OS when utilizing traditional, protracted techniques. However, there is also an absence of large, well conducted trials to have tested this when giving protracted courses of CCRT in the neoadjuvant setting. Conventional fractionation schemes around six weeks in duration typically use concurrent fluoropyrimidine or gemcitabine at radiosensitizing doses, which are likely inadequate for the prevention of metastases. The pancreas is difficult to treat with RT due to the proximity of radiosensitive healthy tissues such as the stomach and duodenum. However, modern techniques have demonstrated hypofractionated pancreatic stereotactic RT (SRT) alone or concurrently with capecitabine [NCT03073785] [15] over 5–15 days is safe and effective, and less than 10% of patients will experience severe adverse effects [16]. Prior arguments against the use of RT in a protracted manner due to the resulting delay in necessary systemic treatment are no longer valid with SRT. Perhaps most importantly, SRT may be offered before surgery without taking the option of systemic therapy or surgical intervention off the table.

Dose painting techniques are incredibly technical and vary by institution. Many centers advocate for dose-painting to vascular areas of concern [17,18]. When utilizing a five-fraction regimen, a minimum of 33 [19–21] or 35 [22] to 40 [23] Gy to gross disease is recommended. Further increases in total dose and dose per fraction are possible, with two studies demonstrating dose escalation up to 60 Gy in 5 fractions is dosimetrically feasible with adequate Planning Target Volume coverage and respect of Organs at Risk dose constraints [24,25]. Patients or tumors which may not be candidates for surgery may be well served by more prolonged hypofractionated regimens (e.g., 67.5/15 or 75/25; BED10 98 Gy), especially for tumors less than 1 cm away from luminal structures [26]. Biologically equivalent dose ($\alpha/\beta = 10$) ranging from a minimum of 48 [27] Gy to 60 [22] to 72 [24,28] Gy have been associated with improved OS, in keeping with a minimum of 30–40/5, 35–48/10 or 38–53/15. Fiducials or real time Magnetic Resonance Imaging tracking serve to localize the tumor, and accuracy of treatments is within 2–3 mm. Near-misses are of concern with such steep gradients. Modern imaging appears to underestimate the true pathologic size of the tumor by at least 4 mm, which presents additional challenges in highly conformal irradiation of pancreatic tumors, warranting further investigation of optimal tumor volumes and dosing [29–31]. Areas of clinical microscopic risk, including nodal regions, around the celiac trunk and superior mesenteric artery should be included based on patterns of failure [22,32]. ESTRO guidelines support the consideration of elective nodal irradiation (ENI) for resectable tumors, as the importance of local control increases in the context of surgery [33]. Further, single institution data has suggested rare out of field failures with five fraction regimens mandating ENI [34].

An ongoing trial of NAC with or without consolidative SRT in BR pancreatic cancer recently closed at interim analysis due to futility [NCT02839343] [35]. There are several concerns with the introduction of SRT to the tumor only, in the pre-operative setting in this trial, clearly the early futility termination of this trial raises con-

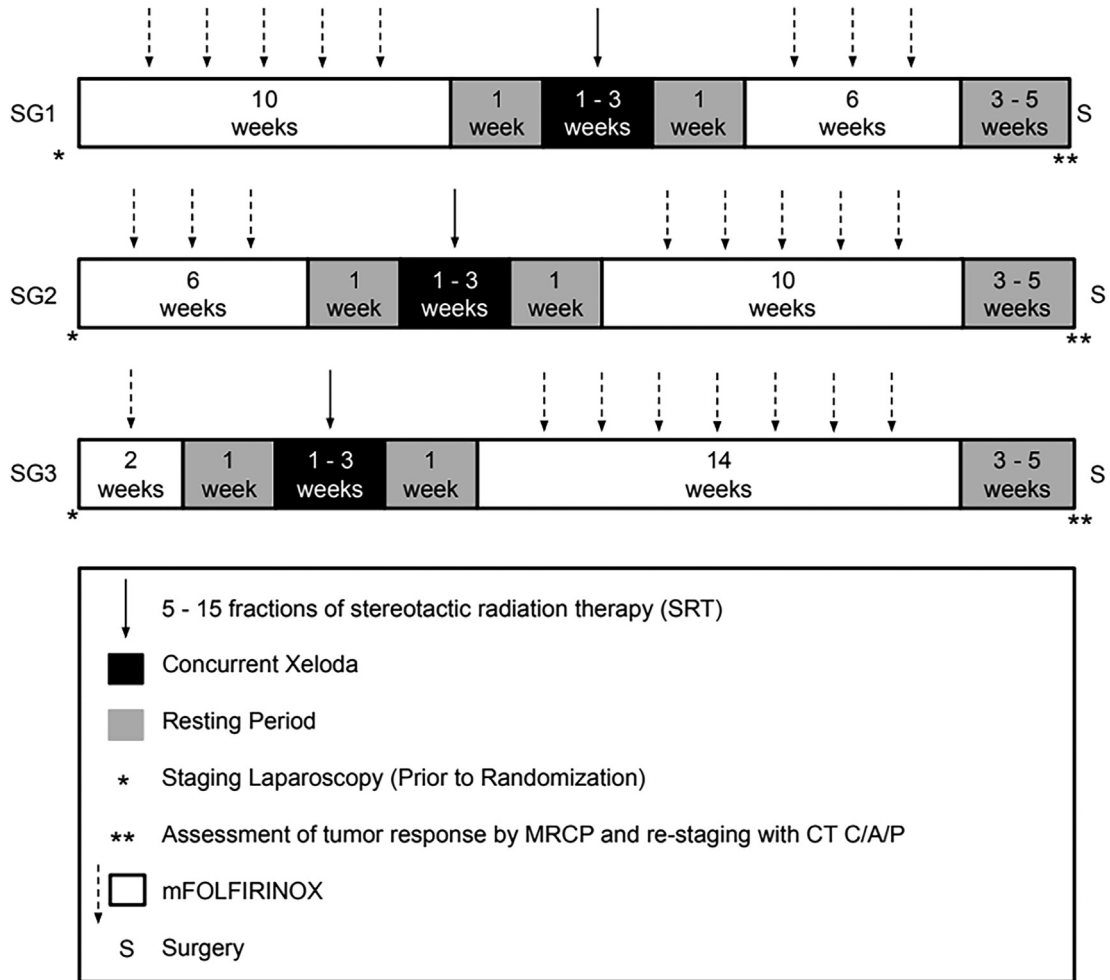


Fig. 1. Example of a Phase I Trial Schema Investigating Earlier Interdigitation of Preoperative Stereotactic Radiotherapy (SRT) Key: SG = Study Group. Example of a Phase I trial scheme investigating escalation of the interval to surgery after stereotactic radiotherapy (SRT) in the neoadjuvant treatment of pancreatic cancer.

cerns regarding the use of pre-operative SBRT outside of high volume centers for resecting BRPC [36]. Current paradigm for TNT in pancreatic cancer is to deliver induction chemotherapy and perform surgery within 4–8 weeks after completion of neoadjuvant RT (if performed). It is not surprising to see pathologic complete response (pCR) rates after TNT of around 10% to be among the most commonly reported, which is low even for adenocarcinomas [14,37-39].

Achieving maximum tumor regression prior to surgery

Surgeons often prefer to operate within 6–8 weeks after RT due to concerns for radiation fibrosis, which could lead to increased technical difficulty and complications including intraoperative and post-operative hemorrhage [40]. Recent studies have suggested that neoadjuvant therapy is not associated with increased morbidity or mortality [11,41].

The sequencing of preoperative chemotherapy and radiation in pancreatic cancer has not been evaluated in a randomized setting. We are aware of two trials which demonstrate the feasibility and safety of RT followed by consolidative chemotherapy for BR pancreatic cancer with promising rates of R0 resections [42,43]. Notably, both trials utilized prolonged fractionation concurrent chemoRT (CCRT) followed by consolidative gemcitabine for two [43] or three months [42], the latter performing surgery five

months after RT with reasonable rates of perioperative complications.

The evolving paradigm in sequencing of neoadjuvant therapy in rectal cancer provides some consideration for shifting the timing of radiation in pancreatic cancer; although differences in these two malignancies is recognized. Considerable data has investigated the impact of extending the interval between radiation and surgery with longer durations of consolidative chemotherapy. Such an approach may allow for maximal tumor regression after radiotherapy and surgery to be performed months later. The TIMING trial for rectal adenocarcinoma is a landmark phase II study that specifically investigated the impact on pCR by progressively extending the interval from CCRT to surgery with oxaliplatin-based chemotherapy. In this setting, pCR more than doubled from 18% to 38% when adding three months of oxaliplatin-based chemotherapy after CCRT as compared to the control arm, which received no preoperative oxaliplatin-based chemotherapy after radiotherapy. Pelvis fibrosis was increased, but consistently stable between experimental groups despite increasingly prolonged intervals to surgery. Importantly, there were no differences in technical difficulty of the operation or perioperative complications even though patients underwent surgery six weeks versus five months after radiotherapy in the control and experimental arms, respectively [44]. This concept was also investigated in the context of SRT with reasonable rates of perioperative complications [45,46]. Further, preliminary data from OPRA has suggested upfront CCRT followed

by consolidation chemotherapy results in maximum tumor regression as compared to induction chemotherapy followed by CCRT [47]. This paradigm of earlier interdigitation of radiotherapy warrants investigation in pancreatic cancer to understand its impact on improving survival. Only large, well designed, prospective trials, can address and answer these important questions in pancreatic cancer.

Considerations for a novel multidisciplinary treatment paradigm for pancreatic cancer

An upfront or earlier interdigitation of preoperative radiotherapy is a strategy that could be considered for pancreatic adenocarcinoma, so long as there is no resulting delay in systemic therapy or increase in perioperative complications. Fig. 1 presents a potential trial schema to test this hypothesis. Patients with BR and LAPC without evidence of liver metastases on MRI would be eligible. Routine staging laparoscopy before clinical trial registration would be utilized to improve patient selection, as best available data suggests that around 25% of patients will have radiographically occult peritoneal disease [48–50]. Randomization would begin after receipt of the induction portion of chemotherapy to avoid loss of power which may occur for patients who develop progressive disease while on chemotherapy. CA 19–9 would be assessed at study entry, prior to radiotherapy, prior to consideration of surgery, and post-operatively (if completed). Factors influencing the decision to resect are multifactorial, including no evidence of progression or development of new metastatic disease, evidence of biochemical response or stability as determined by serum tumor markers, performance status of 0 or 1, and absence of life-limiting comorbidities. As radiographic response does not appear to predict surgical resectability [14,51–54], the decision to proceed with exploration and possible resection would be determined by the operating surgeon after multidisciplinary review and discussion. A central review board may also be considered to assist with determination of surgical eligibility as is done in the ongoing LAPIS trial [NCT03941093].

If Study Group (SG) 1 and SG2 result in reasonable rates of perioperative complications and favorable R0 resection rates, radiotherapy may be delivered perhaps as soon as after the first or second cycle of chemotherapy (SG3, Fig. 1). Once the safest, longest interval between SRT and surgery has been determined, a Phase II trial could be conducted to investigate the efficacy of the proposed regimen. Co-primary endpoints could be resection rate and major pathologic response while secondary endpoints might investigate *peri*-operative complications, local control, overall survival, and quality of life, for example.

Elective nodal volumes (i.e., celiac trunk and superior mesenteric artery +/- hepatic artery, superior mesenteric vein, and portal vein) utilizing simultaneous integrated boost would be mandated to minimize marginal miss [15,17,34,55]. Five to fifteen fractions would be allowable on our sample schema while controlling for time to surgery from completion of radiotherapy, favoring the latter in the context of gross primary or nodal disease nearby to organs at risk [17].

Importantly, pancreatic cancer guidelines now support the upfront use of concurrent CCRT or SRT as a part of neoadjuvant therapy for some non-metastatic patients based on patient and physician preference [4,56]. The hypothesis of adjusting the timing of radiotherapy is within an acceptable standard of care and an ongoing study is investigating consolidative chemotherapy after SRT [NCT03460925]. The sample study design would supplement this hypothesis by investigating the timing to surgery with the goal of extending the duration of consolidative chemotherapy.

Preoperative radiotherapy is emerging as an approach to pancreatic cancer with several potential advantages. Earlier integration of radiotherapy followed by consolidative systemic therapy may be a promising management strategy. If shown to be safe and feasible, this novel multidisciplinary treatment paradigm has the potential to improve oncologic outcomes, including R0 resection, major pathologic response, and overall survival.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Hall's department receives research and travel support from Elekta AB, Stockholm, Sweden. All other authors declare no conflicts of interest.

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