Radiation Therapy for Pancreatic Cancer: Current and Evolving Paradigms

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Background

Ionizing radiation therapy (RT) uses high-energy rays or subatomic particles to impart DNA damage to decrease cell multiplicity and survival. RT is a component of treatment for 50% of all patients diagnosed with cancer and, together with surgery and systemic therapy, forms a pillar of cancer treatment [1]. External beam RT has been utilized for various indications in the treatment of pancreatic cancer, with evolving paradigms that potentiate both curative and palliative intent in both neoadjuvant and adjuvant settings. Across these disease states, RT may be beneficial as curative preoperative therapy, consolidative local therapy for locally advanced pancreatic cancer (LAPC), a palliative modality, and potentially even to consolidate oligometastatic disease in well-selected patients on clinical trials.

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While only 15% of patients with pancreatic cancer are deemed to have resectable disease at upfront staging, up to 50% of patients harbor localized disease that is not yet metastatic [2]. Even for the considerable proportion of patients with metastatic disease, patients often succumb to or suffer from complications of local progression [3]. Local progression from pancreatic tumors may lead to severe morbidity and compromises quality of life from pain, biliary obstruction, associated infection, or invasion of adjacent luminal tissues. In this regard, especially for non-metastatic disease, RT is commonly used to optimize local control and limits the morbidity and mortality from local disease recurrence or progression. Neoadjuvant RT offers improved clinical outcomes in patients eligible for surgery and is associated with higher rates of negative surgical margins. RT is also useful in patients presenting with tumors that are difficult to resect surgically, as local treatment with RT often downstages tumors enough to allow for surgical resection.

While RT is typically delivered in the neoadjuvant setting in combination with chemotherapy, choice of radiation modality, dose, and fractionation across clinical contexts remains challenging owing to lack of clear consensus within the pancreatic cancer radiation oncology community and diverse choice of doses and fractionation schemes in prospective trials. In this chapter, we offer an overview of the literature on radiation therapy across stages and states of pancreatic cancer (Fig. 3.1). We present technological considerations in RT delivery for pancreatic cancer, along with future directions as the role for RT continues to evolve.

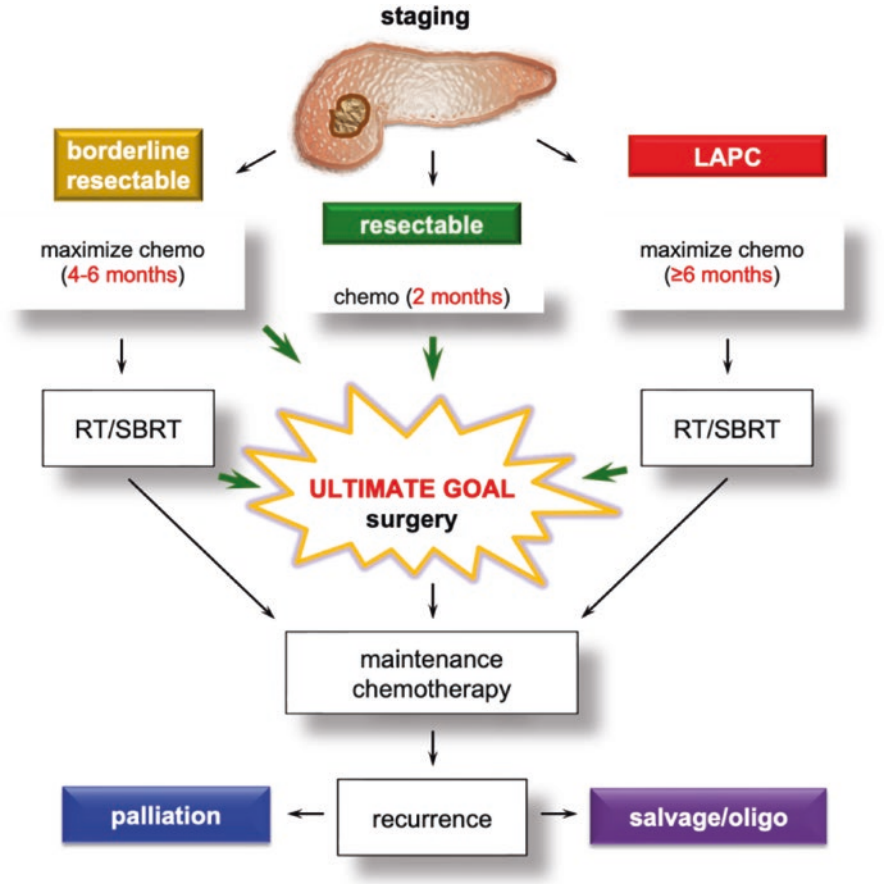

Fig. 3.1 Treatment paradigm incorporating multimodality management of pancreatic cancer across different stages of disease

Primer on Modern Radiotherapy

External beam radiation therapy is generated by a linear accelerator, which delivers ionizing beams of RT conformally shaped to target areas of disease and avoid normal tissues [4]. While some RT effects are due to direct DNA damage, most RT manifests DNA damage through indirect generation of free radicals in an oxygen-dependent process. These ionizing beams may consist of high energy photon rays more commonly, or mass-bearing particles. Within the arena of photon therapy, a primitive form is known as 3D radiation, which involves straight beams of radiation directed in various angles by the gantry, allowing for concentration of dose where the beams intersect at the target [5].

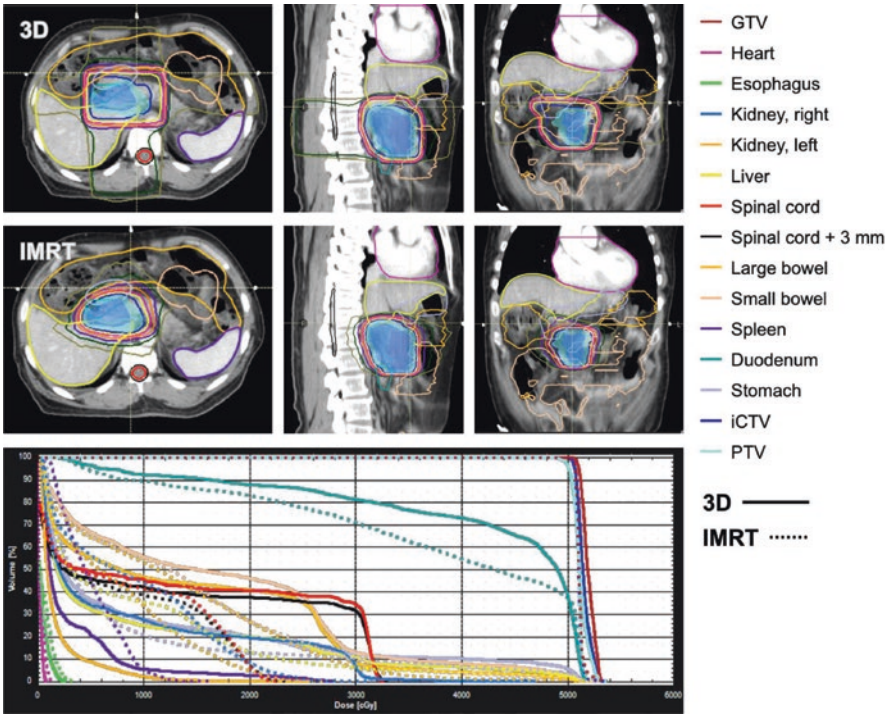

Fig. 3.2 Sample treatment plan comparison of 3D vs. IMRT for pancreatic cancer

Building on this, photon-based therapies that are more advanced include intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT). IMRT utilizes photon energy and delivers treatment using multiple radiation beams at varying intensities and discrete angles, with multi-leaf collimation at each angle to allow for change of the shape as the gantry turns [6]. This modality is particularly valuable when treating targets with complex shapes, rendering it suitable to treat pancreatic tumors (Fig. 3.2) [7].

VMAT is a state-of-the-art photon-based radiation modality that also utilizes photon energy but allows for continuous modulation of the multi-leaf collimation across a high number of radiation beams delivered across an uninterrupted arc in a relatively short period [8]. While data regarding VMAT is relatively limited, one dosimetric study comparing VMAT, IMRT, and 3D RT showed that VMAT could achieve adequate treatment planning, while having better sparing of organs at risk (OARs), particularly the duodenum and small bowel [9]. In this study, VMAT was also associated with fewer cases of grade 3+ gastrointestinal toxicity [9]. 3D RT, IMRT, or VMAT in conventional doses is typically given in 1.8–2 Gy equivalents per day, rendering fractionation schedules that can span up to 5.5 weeks of daily weekday treatment. On occasion, these fractions can be abbreviated with higher doses per fraction, a term called hypofractionation, which has been investigated with some promise in pancreatic cancer.

To this end, more exaggerated hypofractionation has its own classification as a unique therapeutic modality known as stereotactic body radiation therapy (SBRT). SBRT is an advanced radiation modality that delivers highly conformal radiation with significant dose escalation to ≥5 Gy per fraction, compared to conventional fractionation with ≤3 Gy per dose [10]. Owing to the higher doses per fraction, SBRT allows for treatment delivery in a shorter fractionation schedule, typically consisting of 1–5 fractions. However, the high doses per fraction with SBRT limit the role of this modality in patients for whom distance between disease and organs at risk is adequate to avoid severe radiation-induced toxicity. As such, treatment planning with SBRT is similar to that of IMRT, but necessitates smaller margins and higher fidelity, complex image-guidance while delivering treatment. As we will discuss below, studies in BR pancreatic cancer and LAPC show some promising signals with SBRT, but progress is needed to (1) clarify its impact on patient outcomes, (2) optimize patient selection, and (3) refine the indications for treatment with this modality.

Finally, a different form of ionizing radiation involves the use of particles, such as protons, neutrons, or carbon ions, which have a higher relative biological effectiveness compared to photons [11]. These beams manifest radiation with minimal or no exit dose due to targeted fall-off of radiation beams at precise distances, enabling dose escalation to the target while minimizing dose to normal tissue beyond the target [11]. Proton and carbon beams also create a "Bragg peak" with high dose at the distal end of the radiation beam. A disadvantage with these types of RT is uncertainty of the "hot" beam edge, which may be precarious in the setting of pancreatic cancer treatment due to the sensitivity of lumen in neighboring bowel.

Resectable and Borderline Resectable Pancreatic Cancer

One-fourth of all patients with pancreatic cancer present with resectable or borderline resectable (BR) disease (Fig. 3.3) [12].

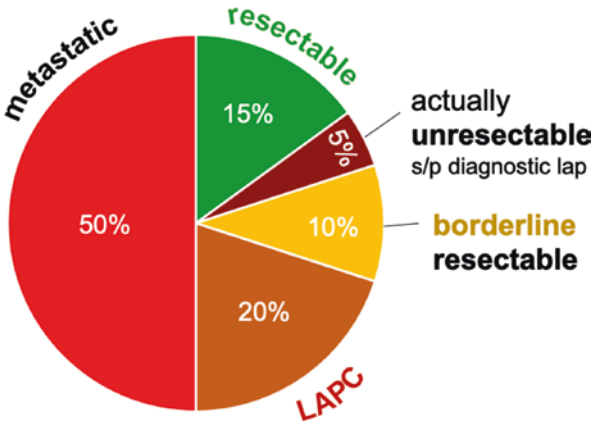

Fig. 3.3 Proportion of pancreatic cancer in staging categories at diagnosis

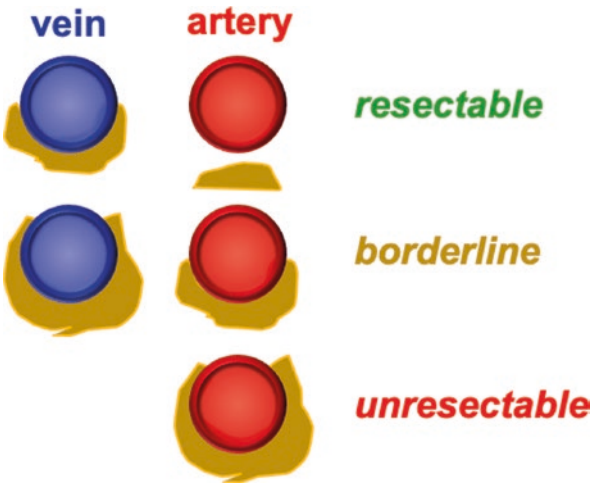

Fig. 3.4 Degree of vessel involvement by pancreatic cancer defines resectability

While TNM staging has been devised for pancreatic cancer, patient disposition to treatment is primarily guided by CT-guided delineation of resectability [13]. While definitions vary across regional sites of the oncology community, resectable disease generally denotes disease that does not involve surrounding arteries, with a tumor-vessel interface (TVI) that does not exceed 180° (Fig. 3.4). BR pancreatic cancer describes a tumor confined to the pancreas, with limited encirclement of adjacent vasculature (<180° encirclement of the SMA or celiac trunk), and in situations where vascular reconstruction is feasible. The concept of BR pancreatic cancer has emerged in the past decade to encompass a distinct spectrum of disease for which resection is relatively more likely to yield a microscopic positive margin (R1 resection), ascribed to the relationship between the pancreatic cancer and neighboring blood vessels [13].

Other key factors that influence the disposition of patients include features that signify a higher risk for the presence of occult metastatic disease. This includes patients with elevated CA 19-9 (>100 U/mL) levels or symptomatic patients with extreme pain or weight loss [14]. Advanced disease may also be noted on imaging with a tumor larger than 3 cm or the presence of suspicious lymph nodes. These factors may suggest optimal treatment with neoadjuvant systemic therapy prior to consideration of surgery to ensure that a surgical outcome is worthwhile.

Surgery is widely considered the sole potentially curative modality for patients with pancreatic cancer who can achieve a margin-negative resection [14]. The potential of positive surgical margins has consistently portended poorer overall survival (OS), as well as increased risk of tumor recurrence and progression [15]. In ESPAC-1, positive margins conferred a median OS of 11 months vs. 17 months in patients with negative margins [16]. Similarly, a single-institution report of 1175 patients with pancreatic cancer found a median OS of 14 months with margin-positive resection vs. 20 months with R0 resection [17]. Microscopic tumor at resection margins offered a detriment to survival to a similar extent as grossly positive

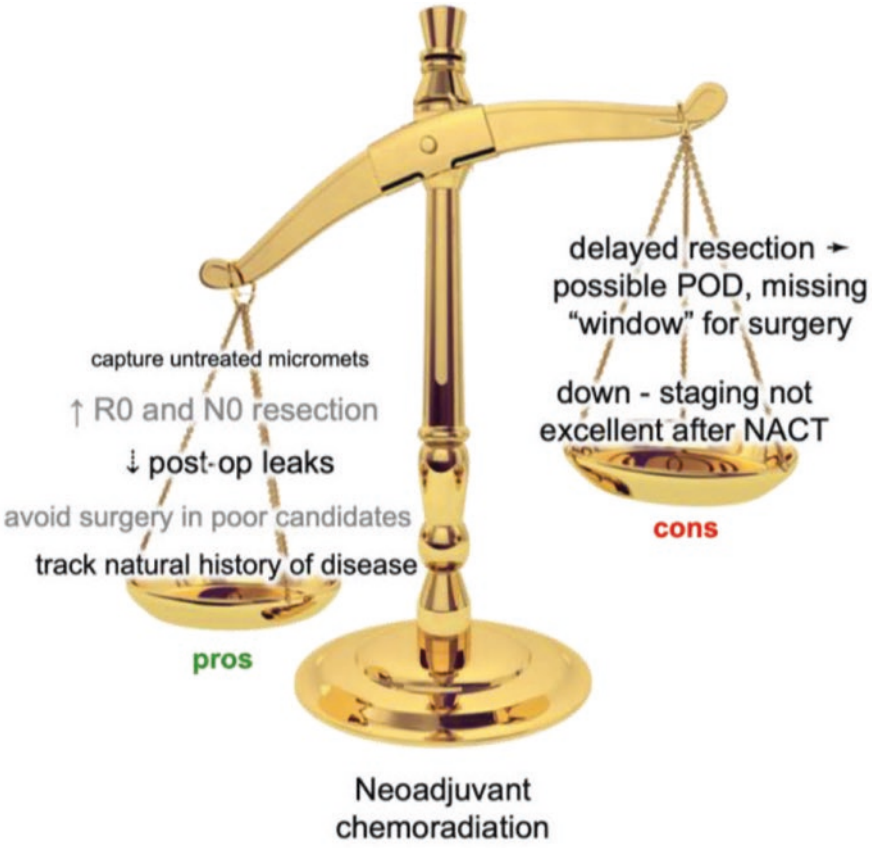

Fig. 3.5 Proposed and observed benefits with the neoadjuvant chemoradiation approach for the treatment of pancreatic cancer

margins [15]. The importance of negative margins in determining post-resection survival has spurred investigation of preoperative therapy, including RT, for patients with resectable and borderline resectable pancreatic cancer. The aims of this approach are to optimize the odds of margin-negative resection, decrease the risk of postoperative relapse, and improve the likelihood of longer-term disease control (Fig. 3.5).

The safety and feasibility of neoadjuvant RT was assessed in a 1997 prospective aggregate analysis comparing clinical outcomes and toxicity between preoperative and postoperative chemoradiation in patients with resectable disease. This trial demonstrated that preoperative RT was safe and associated with similar outcomes to postoperative treatment [18]. Another single center trial included patients with resectable pancreatic cancer treated with preoperative chemoradiation with 5-fluorouracil [19]. Patients who did not progress 1 month after treatment underwent surgical resection with intraoperative RT [19]. The trial showed that

Table 3.1 Summary of outcomes with modern neoadjuvant chemoradiation (CRT) optimizing the resectability and survival of patients with pancreatic cancer

PREOPANC	Surgery ($n = 127$)	Neoadjuvant CRT ($n = 119$)	p-value
Resection rate	72%	61%	0.065
R0 resection rate	40%	71%	<0.001
Serious adverse events	41%	62%	0.28
5-year OS	6.5% (95% CI: 3.1–13.7)	20.5% (95% CI: 14.2–29.8)	0.025
Hazard ratio	0.73 (95% CI: 0.56–0.96)		
Jang et al. [21]	Surgery ($n = 18$)	Neoadjuvant CRT ($n = 17$)	p-value
Resection rate	78.3%	63%	>0.05
R0 resection rate	26.1%	51.8%	0.01
Grade ≥3 adverse events	11.1%	7.7%	0.643
2-year OS	40.7%	26.1%	0.028
ESPAC-5F1	Surgery ($n = 32$)	Neoadjuvant CRT ($n = 56$)	p-value
Resection rate	62%	55%	0.668
R0 resection rate	15%	23%	0.721
Adverse events	–	17.6%	0.28
1-year OS	40% (95% CI: 26–62%)	77% (95% CI: 66–89%)	<0.001
Hazard atio	0.27 (95% CI: 0.13–0.55)		

neoadjuvant RT was safe and associated with minimal toxicity, with only 9% of patients experiencing grade 3 toxicity [19].

More recently, the PREOPANC trial was a phase III randomized controlled trial that included patients with resectable or BR pancreatic cancer [20], generating significant support for the neoadjuvant treatment approach (Table 3.1). In this well-balanced multicenter intention-to-treat trial, patients were randomized at diagnosis to either receive preoperative chemoradiotherapy followed by surgery and adjuvant gemcitabine or undergo upfront surgery followed by similar adjuvant therapy [20]. RT was delivered with 36 Gy in 15 fractions. Of note, resectability in this trial was defined according to the Dutch criteria, which are more stringent and thus may exclude patients that may be considered resectable or borderline resectable by conventional understanding in the United States. In the PREOPANC trial, resectable disease was defined as ≤90° involvement of the superior mesenteric vein (SMV) or portal vein (PV) and no contact of the superior mesenteric artery (SMA). Borderline resectable pancreatic cancer was defined as ≤270° involvement of the SMV or PV, and ≤90° involvement of the celiac axis, hepatic artery, or SMA. Other exclusion criteria included T1 tumors.

With the primary endpoint of OS in the long-term follow-up report, neoadjuvant chemoradiation followed by surgery demonstrated improvement compared to upfront surgery, with a 5-year OS of 20% vs. 6% ($p < 0.001$). In the initial report, the OS benefit was only seen in the per-protocol analysis as well as in patients with BR pancreatic cancer. Significantly, patients who received neoadjuvant chemoradiation had improved rates of R0 resections (71% vs. 40% for patients treated with upfront surgery, $p < 0.001$) [20]. Moreover, the addition of preoperative RT was also associated with improved local-regional control and disease-free survival [20].

These results favoring neoadjuvant RT were supported by a multicenter phase II/III randomized controlled trial published in 2018 by Jang et al. [21]. This study

randomized patients with BR pancreatic cancer to receive either neoadjuvant gemcitabine-based chemoradiation followed by surgery or upfront surgery [21]. The trial showed that patients receiving neoadjuvant therapy had improved 2-year survival rates, with a median survival of 21 months vs. 12 months in the upfront surgery arm, and higher 2-year survival at 40.7% vs. 26.1% [21]. Patients in the neoadjuvant chemoradiation arm also had double the rate of R0 resection compared to patients treated with upfront surgery at 52% vs. 26% [21].

The evidence discussed thus far highlights the compelling role for preoperative chemoradiation in treating patients with resectable or BR pancreatic cancer. However, the aforementioned trials did not compare neoadjuvant chemoradiation to chemotherapy alone. The Alliance A021501 trial included 126 patients with BR pancreatic cancer and randomized them to either neoadjuvant mFOLFIRINOX alone for 8 cycles, or neoadjuvant mFOLFIRINOX for 7 cycles followed by high-dose, specialized RT preceding surgery in patients without disease progression, followed by adjuvant mFOLFOX6. The RT used in this trial consisted of either SBRT to 33–40 Gy in 5 fractions or hypofractionated RT to a dose of 25 Gy in 5 fractions in other patients [22]. This supremely conformal, focused, and high-dose radiation treatment was used for its potential to achieve sharper dose fall-off gradients to normal tissue, deliver higher doses to areas at elevated risk for R1 resection, and decrease the time to resection.

This phase II trial paradoxically showed—considering the other work noted above—that patients receiving chemoradiation had worse 18-month OS and surgical outcomes compared to patients treated with chemotherapy alone [23]. The radiation treatment arm of this trial was closed prematurely at the interim futility analysis based on stopping rules rooted on a concerningly high margin-positive resection rate observed in the preoperative RT arm. As a result, statistical requirements to conclude efficacy were unable to be met, and there was inadequate power for comparison. Nevertheless, the trial included two patients that showed pathologic complete response, and both of those patients were in the radiation arm. The suggestion from the Alliance trial was that not all patients with BR pancreatic cancer would benefit from local treatment with neoadjuvant SBRT.

Notably, this Alliance trial randomized patients at the start of all preoperative therapy, not after the initial mFOLFIRNOX. Thus, there were imbalances between the two arms by the time these patients came to SBRT vs. undergoing one more cycle of mFOLFIRNOX. The design of this trial was counterintuitive to the treatment paradigm generally instituted, in which local therapy with curative intent, such as surgery, is offered only to thoughtfully selected patients who have no disease progression or signs of distant failure. Similar to how surgical resection is not typically a treatment that these mutable patients are blindly randomized to, highly conformal SBRT may not offer a favorable outcome if patients are not carefully chosen and thus poised to benefit from such a local treatment modality. In other words, "routine" disposition of patients to SBRT is not meant to be done, and patients undergoing such therapy must be carefully selected. Additionally, the participating trial institutions had varying comfort levels with this highly specialized form of RT. The allowance for an inadequate RT dose of 25 Gy in 5 fractions rendered

Table 3.2 Summary of outcomes with adjuvant chemotherapy or radiation in patients with pancreatic cancer

Trial	*n*	Postoperative regimens	R1 status (%)	LN "+" (%)	Median OS
GITSG 91-73 [26]	43	Observation *vs.* 5-FU + RT → maintenance 5-FU	0	28	11 *vs.* 20 mos
EORTC 40891 [27]	218	Observation *vs.* bolus 5-FU + RT	22	50	12.6 *vs.* 17.1 mos
ESPAC-1 [16]	541	Observation *vs.* bolus 5-FU *vs.* 5-FU + RT *vs.* 5-FU + RT + consolidative 5-FU	18	54	16.9 (obs) *vs.* 21.6 (chemo only) *vs.* 19.9 (CRT) *vs.* 14.2 mos (CRT + chemo)
RTOG 9704 [28]	442	5-FU → CRT (5-FU) → 5-FU *vs.* gem → CRT (5-FU) → gem	34	66	16.7 (5-FU) *vs.* 18.8 mos (gem)
ECOG-FFCD [25]	74	Gem vs. gem → gem + RT	3	70	9.2 *vs.* 11.1 mos

potential subtherapeutic variability that may have compromised treatment outcomes. Ultimately, this trial underscores the crucial need for a close multidisciplinary approach between radiologists, radiation, surgical, and medical oncologists to select which patients to treat with RT and also highlights the need for prognostic biomarkers to aid in optimal patient selection.

Historical efforts to supplement surgery with multimodality treatment involved adjuvant combinations of chemotherapy or RT [24], which lacked the benefit of prognostication and optimal patient selection that is apparent with a neoadjuvant approach described above. Mixed results were seen in the adjuvant setting, with several trials showing minimal improvement in OS when comparing chemoradiation with chemotherapy alone (ECOG-FFCD [25]) or observation (GITSG 91-73 [26], EORTC 40891 [27]), detailed in Table 3.2. The ESPAC-1 trial published in 2001 remains among the most well-known adjuvant therapy trials but is widely criticized for its methodology [16]. It demonstrated a benefit of adjuvant chemotherapy alone (median OS 15.5 months with observation vs. 21 months with chemotherapy) and suggested a surprising detriment to survival with adjuvant chemoradiation (median OS 15.9 months with chemoradiation vs. 17.9 months with chemotherapy alone). These findings require contextualization considering several trial shortcomings, including lack of loyalty to protocol assignment, with incomplete chemotherapy in 50% of the patients, subtherapeutic RT in 33% of the patients, and 33% of patients in observation and chemotherapy alone arms who unexpectedly underwent RT [16]. There was also selection bias in treatment choice, with physician input incorporated into randomization and background therapy, inconsistent RT dose, and no central quality assurance of RT. Thus, it is challenging to appreciate the true value or lack thereof regarding adjuvant RT based on these trials. The ongoing Phase III trial RTOG 0848 may address this open-ended question [28, 29], but notably does not utilize modern systemic therapy.

Overall, in contrast to neoadjuvant chemoradiation, postoperative RT appears to be more toxic due to anastomoses and bowel falling into the radiation field [30]. Chemotherapy may be given before the RT to avoid the additional toxicity of concurrent treatment. Ultimately, indications for postoperative radiation therapy in pancreatic cancer are rare and typically include a positive margin at the time of surgery in a patient for whom there is no evidence of relapse or increasing CA-19-9 after the completion of the adjuvant chemotherapy. We hold a relatively high threshold to offer adjuvant RT and instead attempt to reserve RT as an option in the future in the event of localized local or regional relapse.

As a result of the above evidence, ASTRO has issued conditional recommendations [31] for neoadjuvant treatment of BR pancreatic cancer with 45–50.4 Gy in 180–200 cGy fractions, or dose escalation with SBRT to 30–33 Gy in 6–6.6 Gy fractions with a consideration for a simultaneous integrated boost of up to 40 Gy to the tumor vessel interface. However, in light of the Alliance trial results described above [23], our practice has not involved dose escalation for neoadjuvant RT in the treatment of BR pancreatic cancer.

In practice, RT dosing and fractionation in resectable and BR pancreatic cancer is decided on a case-by-case basis with multidisciplinary discussion, prognostication, and physician preference (Fig. 3.6a).

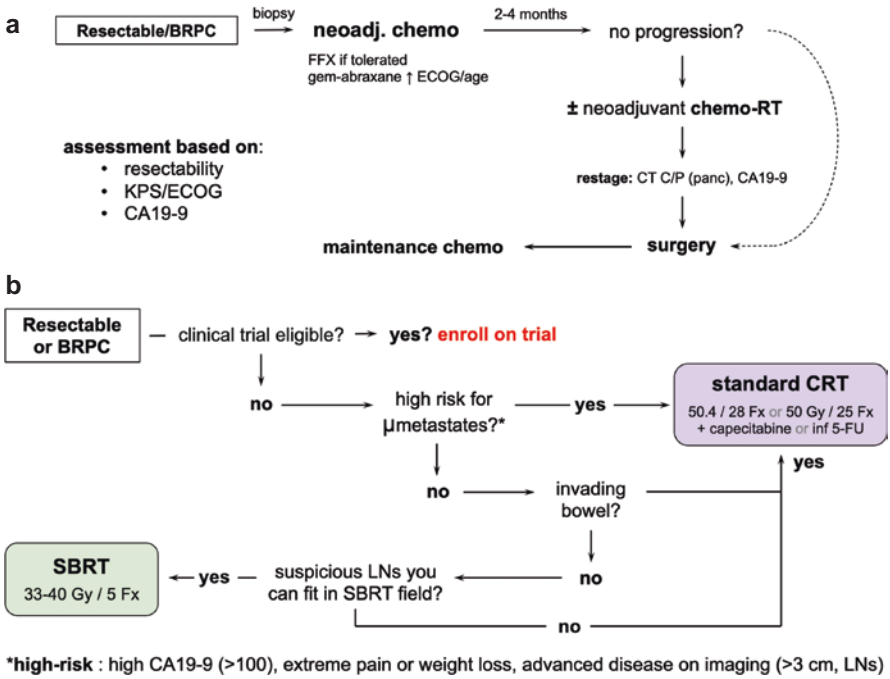

Fig. 3.6 Treatment approach for the management of resectable or borderline resectable pancreatic cancer. (**a**) Resectable and BR pancreatic cancer via biopsy. (**b**) Resectable and BR pancreatic cancer clinical trail

Within this treatment paradigm, we consider radiation regimens based on the expected biology and anatomy of disease (Fig. 3.6b). A preoperative radiation regimen that may be considered for patients who are deemed almost certain surgical candidates involves 3D radiation or intensity modulated radiation therapy (IMRT) delivered to a dose of 30 Gy in 10 fractions [32]. A more standard approach is to deliver 50 Gy in 25 fractions with IMRT. For high-risk patients, prognostication for the risk of micrometastases affords the possibility that surgery may not transpire. High-risk disease is defined by the presence of elevated CA 19-9 levels, symptoms, or features of advanced disease on imaging. For these patients, treatment is favored with long-course concurrent chemoradiation to 50–50.4 Gy in 180–200 cGy fractions, as opposed to highly conformal SBRT that is suboptimal by itself by way of its narrow treatment field. SBRT would also be contraindicated in patients with tumor invading bowel, or for whom the proximity of tumor to luminal structures is $\leq$1 cm.

Locally Advanced Pancreatic Cancer

Patients with locally advanced pancreatic cancer (LAPC) present with localized disease that has extensive involvement of major neighboring vessels, making surgical resection infeasible. For LAPC patients, both systemic therapy and RT tend to be utilized. Systemic therapy is typically delivered first, allowing for a "test of biology" to address both the primary tumor while assessing risk of distant metastatic disease progression or development, since this is the primary driving pattern of spread for pancreatic ductal adenocarcinoma [30]. Typically, the current treatment paradigm is such that LAPC patients are treated with approximately 6 months of systemic therapy, generally with multi-agent regimens, such as FOLFIRINOX or gemcitabine/abraxane. Those without evidence of distant progression after systemic therapy are then often dispositioned to consolidative RT [33]. This strategy helps identify patients that have occult distant disease and that would not benefit from RT. Krishnan et al. published a retrospective series of over 300 patients with LAPC in 2007 that were either treated with chemoradiation or gemcitabine-based induction chemotherapy followed by RT, with 85% of patients treated to a dose of 30 Gy in 10 fractions [33]. Patients treated with induction chemotherapy before RT had improved recurrence patterns and overall survival, suggesting that induction chemotherapy could help identify patients with rapid distant progression and exclude those from receiving additional unnecessary and potentially harmful local treatment [33]. The benefit of RT in addition to chemotherapy in patients with LAPC was also suggested in another retrospective study by Huguet et al., which examined patients enrolled on the GERCOR studies and divided them into two cohorts: patients treated with chemotherapy alone or chemoradiation to a dose of 55 Gy in 30 fractions as well as a conedown 10 Gy boost over 8 fractions delivered in the last 2 weeks of treatment [34]. Results of this study showed that adding RT after disease control with initial chemotherapy leads to improved progression-free and overall survival [34].

Promising results from those two studies were later tested in the LAP07 phase III randomized controlled trial [35]. The trial included patients with LAPC that were treated with 4 months of chemotherapy and showed stable disease. After successful induction chemotherapy, patients were randomized to continue chemotherapy alone or receiving chemoradiation to a dose of 54 Gy in 30 fractions. While the trial did not show any difference in overall survival between the two arms, patients treated with additional RT had lower rates of local progression (32% vs. 46% in the chemotherapy-only arm), without having a significant increase in grade 3+ toxicity [35]. The decrease in local progression with chemoradiation was not correlated to quality of life, which was not examined in this cohort, unfortunately. Other notable limitations of the trial included the presence of RT deviations in 60% of the chemoradiation arm, 20% of the chemotherapy arm undergoing RT, and the use of gemcitabine, which was later found to be inferior to FOLFIRINOX.

One of the main challenges in treating LAPC is that pancreatic adenocarcinoma is often very radioresistant, and hence higher doses of RT are needed to achieve proper local control [36]. However, dose escalation can be very challenging with LAPC owing to potential toxicity to nearby organs at risk, particularly the duodenum. One of the first studies to analyze dose escalation in LAPC was a study by Krishnan et al., which included patients treated with induction chemotherapy followed by IMRT [36]. The study compared clinical outcomes between patients receiving RT with biologically effective dose (BED) higher or lower than 70 Gy, demonstrating that a BED >70 Gy was associated with improved overall survival and local-regional control. Furthermore, the study showed that treatment with BED >70 Gy was safe, as no additional toxicity was noted in this cohort of patients [36]. A more recent study by Reyngold et al. assessed the role of ablative RT in LAPC. Patients in this study were treated with a BED of 98 Gy and showed promising overall survival (median OS from diagnosis: 26.8 months, median OS from RT: 18.4 months) and local-regional failure rates (12-month: 17.6%, 24-month: 32.8%), while still showing tolerable treatment toxicity [37]. Results from those studies show safe and promising clinical outcomes for dose escalation in LAPC [38]. A phase I/II trial is currently assessing the role of radiomodulation with GC4419 in LAPC to allow for further dose escalation with SBRT [39]. Patients on this trial are treated with 50–55 Gy in 5 fractions in the hope of achieving stronger local control and better overall survival rates, while still showing tolerable toxicity. Conceptually, results suggest that currently, these dose-escalated regimens potentially confer some advantage over conventional doses. However, this remains driven primarily by nonrandomized data, and these observations should be interpreted with caution.

For LAPC, we employ a management schema that considers the array of possible RT regimens specified by anatomical considerations and coverage goals (Fig. 3.7). There are a variety of approaches in terms of dose-fractionation, ranging from conventional fractionation to 50.4 Gy in 28 fractions, or dose escalation with either SBRT to a dose of 50–55 Gy in 5 fractions, or hypofractionated ablative RT to 67.5 Gy in 15 fractions, or ablative RT consisting of 75 Gy in 25 fractions. Ultimately,

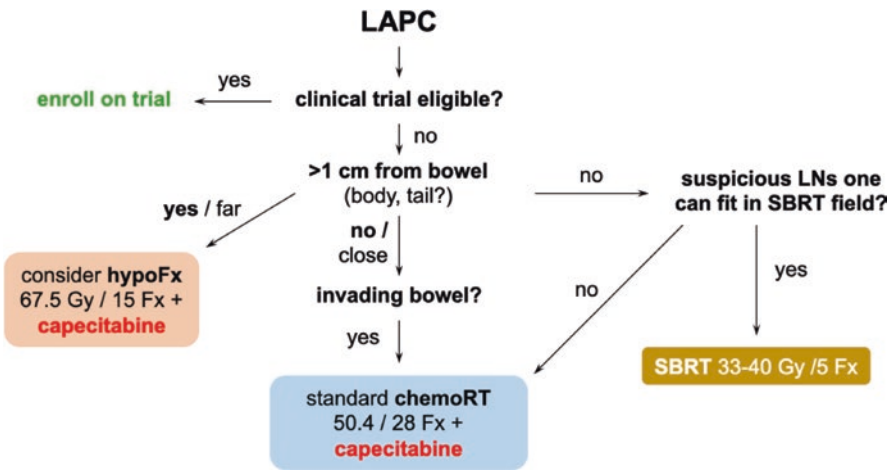

Fig. 3.7 Treatment approach for the management of locally advanced pancreatic cancer

while further progress is needed to demonstrate overarching benefits of dose-escalated RT for LAPC compared to no radiation or conventional RT, the strategy appears promising.

Palliative Radiation Therapy

Palliative RT is occasionally offered to patients with pancreatic cancer presenting with poor performance status or metastatic pancreatic cancer. Patients may present with celiac artery compression syndrome, which may manifest as a constellation of symptoms, including epigastric pain shooting to the back, "gnawing" abdominal pain, or nausea and emesis [40]. The main aim in such patients would be to alleviate abdominal or epigastric pain caused by the tumor compressing upon the celiac artery or plexus. Nevertheless, limited data exist on the effectiveness of palliative RT in patients with advanced pancreatic cancer.

A small retrospective study in Poland analyzed the role of palliative RT in 31 patients with unresectable pancreatic cancer, where 26 (84%) had M0, and 5 (16%) had M1 disease, and the median ECOG performance status was 2 [41]. Patients in this study were treated with 6–30 Gy delivered over 1–10 fractions. Treatment was overall well-tolerated, with no finding of treatment interruptions or hospitalization due to toxicity. Only mild early toxicity was noted in 30% of patients, and no grade 3+ early or late toxicity was seen in the study. The study also analyzed pain intensity associated with pancreatic cancer prior to RT, and 1 month after treatment. Approximately half of the patients (55%) achieved good pain control after palliative RT with no pharmacological therapy, and 40% of patients reduced their analgesic requirements [41]. In another prospective study, Tian et al. enrolled 31 patients with stage III or IV pancreatic cancer and treated them with palliative RT using 40–42 Gy

over 7–10 fractions [42]. The trial was designed to assess quality of life using patient reported outcomes and showed that a considerable proportion of patients showed improvements in pain following therapy [42]. According to the BPI, 57% of patients had significant improvement in abdominal symptoms 1 month after therapy, and 43% of patients reported improvement in daily life parameters such as mood, sleep, walking, and work [42].

As noted above, the radioresistance of pancreatic ductal adenocarcinoma may mean that even palliative approaches require dose escalation to optimally palliate patients. A recent single-arm phase II trial was published in 2022 that assessed the use of single-fraction celiac plexus radiosurgery in patients with upper abdominal cancers (including pancreatic cancer), who presented with moderate to severe retroperitoneal pain [43]. The study evaluated 18 patients that were treated with a single fraction of 25 Gy to the entire retroperitoneal celiac plexus. Results from this trial show that single-fraction radiosurgery was safe and tolerable with only mild grade 1–2 toxicity noted. Moreover, 84% of patients reported pain improvement 3 weeks after therapy, with median pain level decreased from 6/10 at baseline to 3/10. Further improvements were noted 6 weeks post-RT, with median pain level at 2.8/10 on the pain scale and 4 patients with complete pain eradication [43]. This study offers very promising results for the use of single-fraction radiosurgery as an option for celiac plexus pain palliation, especially compared to nerve block, which is an invasive procedure with a variable success rate and complication risks, including hypotension.

Future Directions and Promising Technologies

Recent interest has emerged in the use of particle therapy to treat pancreatic cancer. More specifically, proton and carbon therapy both show promising results in treating localized pancreatic cancer. Proton therapy enables the delivery of radiation with minimal or no exit dose, allowing for target dose escalation, while minimizing radiation side effects to normal tissue beyond the target [11]. A phase I/II trial by Terashima et al. assessed the role of proton therapy in patients with LAPC using either 50 Gy in 25 fractions, 67.5 Gy in 25 fractions, or 70.2 Gy in 26 fractions and demonstrated similar clinical outcomes to historical data with minimal grade 3+ toxicity [44, 45]. Carbon therapy is a rarer form of particle-based therapy that has shown promising results in many disease sites, including pancreatic cancer. The use of carbon ions offers some advantages over proton- and photon-based RT [46]. Carbon ions have a higher relative biological effectiveness and less lateral scattering. Moreover, carbon ion therapy has a relatively lower oxygen enhancement ratio, signifying that the tumor-killing effect of carbon ions is independent of tumor oxygenation [47]. This property of carbon therapy is particularly desirable in pancreatic malignancies, owing to the hypoxic and radioresistant tumor environments of pancreatic cancer. Despite some data showing the effectiveness of carbon therapy, the major limitation of this therapy is its limited availability in cancer centers, with only a few centers offering this modality across the world. The CIPHER trial is an

ongoing phase III trial comparing the use of IMRT to carbon therapy in patients with LAPC, and will help oncologists better understand the role of carbon therapy in pancreatic cancer (NCT03536182) [48].

Lastly, FLASH-RT is a modern advanced radiation modality that delivers ultra-high doses of radiation to the tumor target, while sparing neighboring normal tissue, a phenomena being dubbed the FLASH effect [49]. While conventional radiation modalities deliver radiation at rates smaller than 0.1 Gy/s, radiation delivery with FLASH-RT is typically higher than 40 Gy/s [50, 51]. FLASH therapy has been studied in preclinical models with promising results in multiple disease sites, and FLASH-RT could potentially be well-suited to treat pancreatic cancer owing to its highly radioresistant tumor environment and close proximity of organs at risk [52]. Currently, IntraOp Medical has developed an electron-based FLASH LINAC that has recently been approved for use in preclinical and human studies and will hopefully be tested in future clinical trials, but will likely be focused on treatment of dermal malignancies initially due to its shallow penetration [53]. Future studies could include intraoperative FLASH but that is speculative at this time. Proton FLASH studies are ongoing. Higher energies may allow for treatment of deep-seated tumors, including possibly pancreatic cancer.

To bolster the therapeutic ratio, combinatorial approaches are being investigated that use either radiosensitizers to amplify radiation target effects or radioprotectors to fortify adjacent normal tissue, including the stomach or duodenum. As introduced above, a phase I/II trial is determining if radioprotection by GC4419 may enable dose escalation with SBRT in LAPC [39]. Furthermore, non-SBRT courses of RT are routinely delivered in our practice with concurrent radiosensitization with capecitabine. Nanoparticles are also being developed to support these aims, with taggable cargo that may influence the therapeutic ratio by synergizing with radiation to enhance target sensitivity [54].

Finally, there is dynamic evolution in our traditional understanding of metastatic disease as being incurable [55]. A frontier of investigation is devoted to the potential conversion of patients with a few sites of metastatic disease into a curable state. The EXTEND trial is an ongoing phase II trial at the MD Anderson Cancer Center that will assess the role of RT in patients with solid tumors, including pancreatic cancer, presenting with oligometastatic disease, and will hopefully shed light on the role of consolidative RT in the oligometastatic setting (NCT03599765) [56].

Summary

RT is a common modality in pancreatic cancer regardless of disease stage. Neoadjuvant therapy is commonly employed in patients with resectable or BR pancreatic cancer, with the principal goal of sterilizing surgical margins after resection and, by doing so, limiting tumor recurrence after surgery. Patients with LAPC also benefit from local treatment with RT to delay or abrogate local progression, especially since surgical resection is often not feasible in those patients. Owing to the aggressive nature of LAPC, dose escalation is typically needed to achieve proper

local control and improve survival rates. Limited data exist on the effectiveness of palliative RT in advanced pancreatic cancer. However, owing to promising results from small retrospective and prospective studies, this approach could be considered to alleviate pain in patients with LAPC or metastatic pancreatic cancer. Lastly, while photon-based therapy has shown positive results in the past, modern therapies including particle-based RT and FLASH-RT are being studied. Cutting edge ongoing investigation may help identify the role of these modern therapies in the treatment of pancreatic cancer.

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