# Intraoperative Radiotherapy in the Era of Intensive Neoadjuvant Chemotherapy and Chemoradiotherapy for Pancreatic Adenocarcinoma

*Florence K. Keane, MD,* Jennifer Y. Wo, MD,† Cristina R. Ferrone, MD,‡ Jeffrey W. Clark, MD,§ Lawrence S. Blaszkowsky, MD,§ Jill N. Allen, MD,§ Eunice L. Kwak, MD, PhD,§ David P. Ryan, MD,§ Keith D. Lillemoe, MD,‡ Carlos Fernandez-del Castillo, MD,‡ and Theodore S. Hong, MD†*

**Objectives:** Improved outcomes with FOLFIRINOX or gemcitabine with nab-paclitaxel in the treatment of metastatic pancreatic adenocarcinoma (PDAC) have prompted incorporation of these regimens into neoadjuvant treatment of locally advanced unresectable PDAC. Whereas some patients remain unresectable on surgical exploration, others are able to undergo resection after intensive neoadjuvant treatment. We evaluated outcomes and toxicity associated with use of intensive neoadjuvant treatment followed by intraoperative radiotherapy (IORT) in combination with resection or exploratory laparotomy.

**Methods:** We retrospectively analyzed patients with locally advanced unresectable or borderline-resectable PDAC who received intensive neoadjuvant treatment with induction chemotherapy and chemoradiotherapy followed by exploratory laparotomy in an IORT-equipped operating suite between 2010 and 2015. Surgical outcomes and overall survival (OS) were compared.

**Results:** Of 68 patients, 41 (60.3%) underwent resection, 18 (26.5%) had unresectable disease, and 9 (13.2%) had distant metastases. Of 41 resectable patients, 22 received IORT for close/positive resection margins on intraoperative frozen section. There was no significant difference in operative times or morbidity with addition of IORT to resection. Median OS was 26.6 months for all patients who underwent resection, 35.1 months for patients who underwent resection and IORT, and 24.5 months for patients who underwent resection alone ($P$ = NS). Of 18 patients with unresectable disease, all but 1 received IORT, with median OS of 24.8 months. IORT was associated with increased hospital stay (4 vs. 3.5 d), but no significant difference in operative times or morbidity.

**Conclusions:** IORT in addition to intensive neoadjuvant chemotherapy and chemoradiotherapy was not associated with increased toxicity when used with resection or exploratory laparotomy, and was associated with encouraging survival rates in patients with close/positive margins and patients with unresectable disease.

**Key Words:** pancreatic cancer, locally advanced pancreatic cancer, chemotherapy, resection, radiotherapy

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From the *Harvard Radiation Oncology Program, Harvard Medical School; Departments of †Radiation Oncology; ‡Surgery; and §Medicine, Division of Medical Oncology, Massachusetts General Hospital, Boston, MA.

The authors declare no conflicts of interest.

Reprints: Florence K. Keane, MD, Harvard Radiation Oncology Program, Harvard Medical School, Massachusetts General Hospital, 100 Blossom St., Cox 3, Boston, MA 02114. E-mail: fkeane@partners.org.



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In the year 2016, it is estimated that there will be 53,070 new diagnoses and 41,780 deaths from pancreatic cancer in the United States.[1] Approximately 40% of patients present with locally advanced unresectable or borderline resectable disease. Despite treatment with neoadjuvant chemotherapy and chemoradiotherapy, few patients are able to proceed to surgical resection, and survival is poor.[2–5]

In the metastatic setting, the Action Clinique Coordonnés en Cancérologie Digestive 11 (ACCORD 11) trial and the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) demonstrated significantly improved survival rates in patients treated with fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX)[6] or gemcitabine with albumin-bound paclitaxel particles (nab-paclitaxel)[7] when compared with gemcitabine monotherapy. Although there are not yet available randomized data in the nonmetastatic setting, many centers have incorporated these regimens into neoadjuvant treatment for patients with locally advanced unresectable or borderline-resectable disease, with improvements in systemic control and resection rates.[8–11]

However, radiographic assessment after intensive neoadjuvant treatment is challenging and may not be representative of resectability. Therefore, in patients who do not have evidence of distant metastases after neoadjuvant treatment, our institution proceeds with surgical exploration with intraoperative radiotherapy (IORT) used for patients in whom the tumor remains unresectable or in patients who undergo resection with close/positive resection margins on intraoperative frozen section. We previously reported our results in 194 patients treated between 1978 and 2010.[12,13] We set out to update our published experience to include patients with imaging concerning for persistent locally advanced unresectable/borderline-resectable lesions after completion of intensive neoadjuvant treatment. Our aims were to assess resection rates after intensive neoadjuvant treatment, compare toxicities associated with addition of IORT to either resection or surgical exploration, and to assess the impact of IORT on overall and progression-free survival (PFS) in patients treated with intensive neoadjuvant chemotherapy.

## MATERIALS AND METHODS

### Patient Cohort

With approval from the institutional review board, we retrospectively collected clinicopathologic data for all patients with persistent locally advanced unresectable or borderline-resectable pancreatic adenocarcinoma (PDAC) after completion of intensive neoadjuvant chemotherapy and chemoradiotherapy.

Patients underwent exploratory laparotomy in an IORT-equipped operating suite between 2010 and 2015. We defined locally advanced unresectable or borderline-resectable lesions based on the Americas Hepato-Pancreato-Biliary Association (AHBPA)/Society of Surgical Oncology (SSO)/ Society for Surgery of Alimentary Tract (SSAT) consensus guidelines.[14] Tumors were considered borderline-resectable if there was encasement of the superior mesenteric vein (SMV) or portal vein (PV) without arterial encasement, reconstructible short-segment SMV or PV occlusion, abutment of the superior mesenteric artery (SMA) with involvement of <180 degrees or the vessel circumference, or gastroduodenal artery encasement up to the hepatic artery with either short-segment involvement or abutment of the hepatic artery without celiac axis involvement. Locally advanced unresectable disease was defined as involvement of > 180 degrees of the SMA, long-segment occlusion of the SMV or PV, or celiac axis involvement. Patients with resectable disease based on radiographic evaluation after neoadjuvant therapy were not considered IORT candidates and were therefore excluded from this analysis.

Data collected included demographics, Charlson comorbidity score,[15] details of neoadjuvant therapy (chemotherapy regimen, number of cycles, radiotherapy dose), pretreatment and posttreatment CA19-9 level (U/mL), type of surgery (Whipple procedure, distal pancreatectomy, or exploratory laparotomy with or without gastrojejunostomy and cholecystectomy), estimated intraoperative blood loss, postoperative complications, hospital length of stay, 90-day readmission rate, and 90-day mortality rate. For patients able to undergo resection, pathologic data collected included lymph node involvement, lymphovascular invasion, perineural invasion, and margin status. A positive resection margin was defined as presence of tumor cells on any specimen margin.[16] We defined a "close" margin as tumor located <5 mm from a resection margin.

## Neoadjuvant Treatment

Patients received either FOLFIRINOX, gemcitabine with nab-paclitaxel, or FOLFOX with the intention of dose escalating to FOLFIRINOX. FOLFIRINOX was administered every 14 days and consisted of 5-FU 400 mg/m$^2$ on day 1, followed by a 1200 mg/m$^2$/d infusion for 46 hours, leucovorin 400 mg/m$^2$ on day 1, oxaliplatin 85 mg/m$^2$ on day 1, and irinotecan 180 mg/m$^2$ on day 1. Patients received prophylactic pegfilgrastim 6 mg 24 hours after the 5-FU pump was disconnected. A median of 8 cycles was delivered. Gemcitabine with nab-paclitaxel was administered on days 1, 8, and 15 of a 28-day cycle and consisted of gemcitabine 1000 mg/m$^2$ and nab-paclitaxel 125 mg/m$^2$. Patients received a median of 8 cycles.

Following neoadjuvant chemotherapy, patients received external-beam radiotherapy (EBRT) with concurrent chemotherapy. The gross tumor volume was defined as the primary tumor and any enlarged lymph nodes >1 cm. The clinical target volume included these areas as well as the porta hepatis, celiac axis, SMA, and pancreaticoduodenal nodes. The planning target volume was typically a 0.5-cm radial and 0.7-cm craniocaudal expansion on the clinical target volume. Patients were treated to a median dose of 50.4 Gy in 1.8 Gy fractions. A dose-painted in-field boost to potentially at-risk margins along vasculature was incorporated in certain cases (total dose of 58.8 Gy). EBRT was delivered with concurrent chemotherapy consisting of capecitabine delivered at 825 mg/m$^2$ twice daily or infusional 5-FU at a dose of 225 mg/m$^2$. Chemotherapy during the course of EBRT was administered 5 days per week.

## IORT

In patients who were able to undergo resection after neoadjuvant treatment, IORT was administered in patients with close or positive surgical margins on intraoperative frozen section. In patients with an unresectable tumor but no evidence of metastatic disease, IORT was administered to the intact pancreas based on our experience showing excellent local control and survival rates in selected patients with locally advanced, unresectable disease.[13]

Complete details of the IORT technique at our institution have been previously described.[12,13] Following assessment of either the primary tumor or the resection bed by the surgeon and radiation oncologist, a metal applicator (median diameter 5 cm; range, 4 to 8 cm) was selected and used to enclose either the pancreatic tumor or resection bed with an approximately 1 cm surrounding margin. Prescription depth (median energy, 9 MeV; range, 6 to 18 MeV, and median isodose line, 80%; range, 80% to 90%) of the electrons was chosen based on both radiographic and observed clinical depth of the tumor. Care was taken to retract surrounding normal tissue. Radiation dose was specified based on resection status. After resection, a median dose of 10 Gy (range, 8 to 13 Gy) was delivered to the resection bed and positive margins. In unresectable tumors, a median dose of 15 Gy (range, 15 to 17 Gy) was administered to the tumor. When patients receive IORT for unresectable disease, we commonly perform gastrojejunostomy, as edema and subsequent duodenal narrowing can lead to gastric outlet obstruction. In patients who are not IORT candidates for IORT, gastrojejunostomy is performed selectively.

## Statistical Analysis

We compared distribution of operative outcomes stratified by resection status and receipt of IORT using the Wilcoxon rank-sum test[17] and the Fisher exact test, as appropriate. Our primary endpoint was overall survival (OS). Dates of death were obtained from the medical record and/or Social Security Death Index. The secondary endpoint was PFS, defined as survival until the development of local progression and/or distant metastases. Local progression was defined as recurrent disease in the resection bed, progression of the primary tumor in unresected tumors, and/or development of regional lymphadenopathy. Times were measured relative to date of tissue diagnosis and censored at date of last follow-up when applicable. The Kaplan-Meier method[18] was used to estimate OS and DFS and associated 95% confidence intervals. All tests were 2-sided and performed using SAS version 9.3 (SAS Institute, Cary, NC).

# RESULTS

## Overall Cohort

We identified 68 patients with persistent locally advanced unresectable or borderline-resectable lesions and no evidence of distant metastases on follow-up imaging after completion of intensive neodjuvant treatment. Baseline patient characteristics are summarized in Table 1. Median age was 63 years old. Median Charlson comorbidity score was 3 (range, 0 to 6). The majority of patients (n = 60, 88.2%) had locally advanced unresectable disease as determined by pretreatment imaging.

**TABLE 1.** Clinical Characteristics

| Characteristic | Entire Cohort (n = 68) |
|---|---|
| Age at diagnosis (y) | |
| Median | 63 |
| Range | (37-80) |
| Sex | |
| Male (n [%]) | 37 (54.4) |
| ECOG performance status (n [%]) | |
| 0 | 31 (45.6) |
| 1 | 36 (52.9) |
| 2 | 1 (1.5) |
| Charlson comorbidity score | |
| Median | 3 |
| Range | 0-5 |
| BMI (kg/m$^2$) | |
| Median | 23.7 |
| Range | 17.2-34.4 |
| Tumor size on CT (cm) | |
| Median | 3.6 |
| Range | 1.8-7.1 |
| Tumor resectability at diagnosis (n [%]) | |
| Locally advanced unresectable | 60 (88.2) |
| Borderline resectable | 8 (11.2) |

BMI indicates body mass index; CT, computed tomography.

**TABLE 2.** Summary of Neoadjuvant Treatment

| Characteristic | Entire Cohort (n = 68) |
|---|---|
| Neoadjuvant chemotherapy (n [%]) | |
| FOLFIRINOX | 59 (86.8) |
| Gemcitabine with nab-paclitaxel | 4 (5.8) |
| FOLFOX | 5 (7.4) |
| Cycles of neoadjuvant chemotherapy | |
| Median | 8 |
| Range | 4-12 |
| Median RT dose (range) (Gy) | 50.4 (24-55) |
| IMRT dose painting to vasculature to 58.8 Gy (n [%]) | 40 (58.8) |
| Concurrent chemotherapy during chemoradiotherapy (n [%]) | |
| CI 5-FU | 41 (60.4) |
| Capecitabine | 21 (30.9) |
| CI 5-FU + other | 2 (2.9) |
| Gemcitabine | 2 (2.9) |
| None | 2 (2.9) |
| Pretreatment CA19-9 (median [range]) | 221.0 (2-25,020) |
| Posttreatment CA19-9 (median [range]) | 27 (1-529) |

CI 5-FU indicates continuous infusional 5-fluorouracil; IMRT; intensity-modulated radiotherapy; RT, radiotherapy.

## Neoadjuvant Treatment

Details of neoadjuvant treatment are listed in Table 2. There was a decrease in median CA19-9 from a median of 221 to 27 U/mL after completion of neoadjuvant therapy.

### Chemotherapy

All patients received intensive neoadjuvant chemotherapy. The majority of patients received FOLFIRINOX (n = 59, 86.8%). We also included patients who received gemcitabine with nab-paclitaxel (n = 4, 5.8%) and patients who were started on FOLFOX with the intent to intensify to FOLFIRINOX if possible (n = 5, 7.4%).

### EBRT

All patients received neoadjuvant radiotherapy, of whom 66 (97.1%) received concurrent chemotherapy for radiosensitization. Median EBRT dose was 50.4 Gy (range, 24 to 55 Gy). A total of 40 patients received a dose-painted boost with intensity-modulated radiotherapy to 58.8 Gy to areas of involved vascular margins.

## Operative Outcomes

All patients had imaging concerning for persistent unresectable disease after neoadjuvant treatment; however, 41 patients (60.3%) were able to undergo resection. Operative outcomes for patients able to undergo resection are detailed in Table 3. Twenty-two patients (53.7%) received IORT for positive/close margins on intraoperative frozen section, of whom 16 patients (72.7%) had an R1 resection or tumor present within 5 mm of the resection margin on final pathology. Nineteen patients who did not receive IORT had an R0 resection on intraoperative frozen section and final pathology. Seven of 19 patients had close margins on final pathology (36.8%), 3 of whom underwent extensive vascular resections and therefore did not receive IORT ($P = 0.03$). More patients undergoing resection alone had venous resections (7 vs. 2 patients, $P = 0.03$), as we limit IORT use in patients who undergo venous resections given limited long-term toxicity data. Median operative time was approximately 40 minutes longer with IORT (412 vs. 370 min, $P = 0.45$), but this was not statistically significant. There was no significant increase in estimated intraoperative blood loss, postoperative complications, 90-day readmission rates, or postoperative death in

**TABLE 3.** Operative Outcomes for Patients Who Underwent Resection After Neoadjuvant Treatment

| | n (%) | | |
|---|---|---|---|
| Characteristic | Resection Alone (n = 19) | Resection + IORT (n = 22) | *P* |
| Operation | | | 0.95 |
| Whipple | 14 | 16 | |
| Distal pancreatectomy | 5 | 6 | |
| Venous resection | 7 (36.8) | 2 (9.1) | 0.03 |
| Vascular resection with grafting | 0 | 1 (4.5) | 0.35 |
| Involved lymph nodes | 5 (26.3) | 6 (27.3) | 0.95 |
| Lymphovascular invasion | 9 (47.4) | 5 (22.7) | 0.10 |
| Perineural invasion | 11 (57.9) | 17 (77.3) | 0.18 |
| R0 resection on final pathology | 19 (100) | 18 (81.8) | 0.05 |
| Close or positive margins on final pathology | 7 (36.8) | 16 (72.7) | 0.03 |
| OR time (min) | 370 (176-645) | 412 (263-611) | 0.45 |
| Blood loss (mL) | 500 (100-2750) | 600 (300-2300) | 0.34 |
| Postoperative complications | 8 (42.1) | 4 (18.2) | 0.09 |
| LOS (d) | 7 (4-32) | 6 (4-13) | 0.15 |
| 90-d readmission rates | 6 (31.6) | 5 (22.7) | 0.52 |
| 90-d morbidity rates | 2 (10.5) | 1 (4.5) | 0.46 |
| Progression pattern | | | |
| Local | 6 (31.6) | 6 (27.2) | 0.76 |
| Distant metastases | 9 (47.4) | 11 (50) | 0.87 |
| Multiple sites | 3 | 2 | |
| Liver | 2 | 7 | |
| Lungs | 4 | 0 | |
| Peritoneal | 1 | 2 | |

IORT indicates intraoperative radiotherapy; LOS, length of stay.

patients who received IORT in addition to surgical resection versus those who underwent resection alone.

Operative outcomes for patients with persistent unresectable disease on surgical exploration after neoadjuvant treatment are listed in Table 4. Of 27 patients, 17 did not have evidence of metastatic disease and received IORT. Ten patients did not receive IORT; 9 had peritoneal and/or hepatic metastases, and 1 was found to have a primary lesion which was too large for safe IORT administration. Median operative time was approximately 30 minutes longer with the addition of IORT to exploratory laparotomy (124 vs. 98 min, $P = 0.18$). There was no significant difference in estimated intraoperative blood loss, rates of postoperative complications, 90-day readmission rate, or rate of postoperative death. IORT use was associated with statistically but not clinically significantly longer hospital length of stay (4 vs. 3.5 d, $P = 0.01$).

## OS and PFS

Median follow-up was 20.8 months, and median OS, including patients who had metastatic disease at the time of surgical exploration, was 24.8 months (Fig. 1). Median OS was 26.6 months for all patients who underwent resection, 24.5 months for patients who underwent resection alone, and 35.1 months for patients who received IORT in addition to resection ($P$ = NS) (Fig. 2). Median PFS was 16.3 months for patients who underwent resection alone, and 21.0 months for patients who underwent IORT in addition to resection ($P = 0.09$). Local progression was 31.6% with resection alone and 27.2% with IORT and resection ($P = 0.76$). There was no significant difference in rates of distant metastases.

For patients with unresectable disease, median OS was 24.8 months for patients who received IORT (Fig. 2), and PFS was 16.1 months.

**TABLE 4.** Operative Outcomes for Patients With Unresectable Disease After Neoadjuvant Treatment

| | n (%) | | |
|---|---|---|---|
| **Characteristic** | **Laparotomy + IORT (n = 17)** | **Laparotomy Alone (n = 10)** | ***P*** |
| Operation | | | |
| Gastrojejunostomy | 15 (88.2) | 3 (30.0) | 0.004 |
| Cholecystectomy | 7 (41.2) | 4 (40.0) | 0.99 |
| OR time (min) | 124 (62-253) | 98 (31-185) | 0.18 |
| Blood loss (mL) | 55 (negligible-400) | 48.5 (negligible-200) | 0.42 |
| Postoperative complications | 5 (29.4) | 2 (20) | 0.69 |
| LOS (d) | 4 (3-12) | 3.5 (1-10) | 0.01 |
| 90-d readmission rates | 4 (23.5) | 1 (10.0) | 0.62 |
| 90-d morbidity rates | 0 | 1 (10.0) | 0.37 |
| Progression pattern | | | |
| Local (progression of primary tumor) | 10 (58.8) | 4 (40.0) | 0.35 |
| Distant metastases | 11 (64.5) | 9 (90.0) | 0.15 |
| Multiple sites | 6 | 2 | |
| Liver | 6 | 5 | |
| Lung | 1 | — | |
| Peritoneal | 4 | 6 | |

IORT indicates intraoperative radiotherapy; LOS, length of stay.

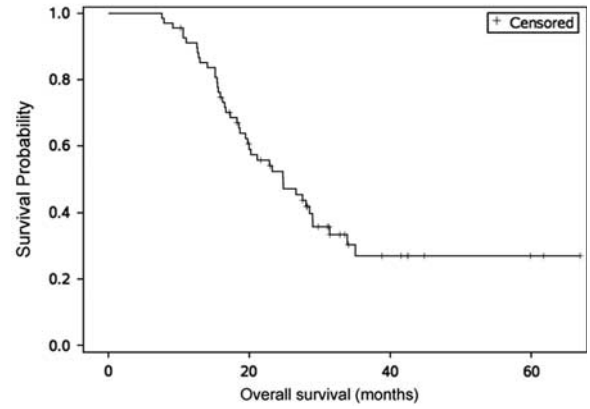


**FIGURE 1.** Overall survival (OS) of entire cohort (months).

## DISCUSSION

In this consecutive series of patients with locally advanced unresectable or borderline resectable PDAC treated with intensive neoadjuvant chemotherapy and chemoradiotherapy followed by surgical exploration, we found that intensive neoadjuvant treatment resulted in impressive resection rates and that IORT was safely tolerated in conjunction with both surgical exploration and resection. Intensive neoadjuvant treatment followed by IORT was associated with impressive median survival rates, despite the fact that patients only received IORT in the setting of either a close/positive margin or unresectable disease.

With the adoption of intensive chemotherapy regimens, survival and systemic control have significantly improved in metastatic PDAC,[6,7] prompting a shift in management of locally advanced unresectable/borderline-resectable disease. Single-institution series have reported encouraging rates of both resection and systemic control with incorporation of FOLFIRINOX and other regimens into neoadjuvant treatment for locally advanced unresectable disease.[8,9,11,19,20] The improvement in the OS rates in this series compared with other IORT series[21,22] is likely due, at least in part, to the use of intensive neoadjuvant treatment regimens and the resulting improvement in systemic control and R0 resection rates.

These R0 resection rates have occurred in the setting of postneoadjuvant imaging that is often consistent with

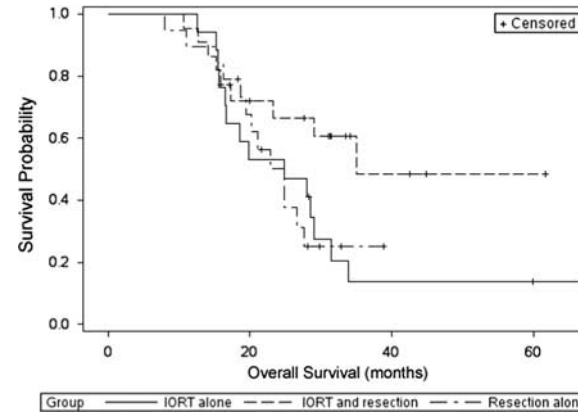


**FIGURE 2.** Overall survival (OS) grouped by resection status and use of intraoperative radiotherapy (IORT) (months).

unresectable disease.[9,10] At our institution, Ferrone et al[9] reported that 35 of 40 patients (92%) with unresectable disease on imaging after FOLFIRINOX had an R0 resection. Similarly, all patients in our series had imaging concerning for R1 resection or unresectable disease, but 37 patients (90.2%) had an R0 resection. Although there are no randomized data on rates of resection after neoadjuvant treatment in this population, patients with adequate performance status and no distant metastases on restaging merit consideration of surgical exploration to assess for resectability. The surgeon knows that he or she may find metastatic disease at the time of exploration, that resection may not be feasible, or that margins could be positive or very close.

Therefore, as patients have received a full course of neoadjuvant chemotherapy and EBRT with concurrent chemotherapy, it is reassuring to have additional resources to treat unresected tumor or for margin enhancement. At our institution, we have been using IORT for this purpose. This requires the presence of a radiation oncologist for its delivery, but has been simple and not time consuming. Median operative times were approximately 30 minutes longer in patients receiving IORT for both resected and unresected patients, but these differences were not statistically significant. Furthermore, as our previous experience and this series show, IORT does not add morbidity to the operation. The availability of IORT provides an additional justification for the potential value of surgical exploration, as there is an intervention available even for patients whose tumors will not be resected or for those who have a R1 resection. In the process we have found that many of these tumors are resectable despite imaging suggesting otherwise.

Resection after neoadjuvant treatment is more technically challenging than upfront resection. We did not see a significant difference in operative toxicities in the current study because all patients received neoadjuvant therapy; however, prior series have demonstrated increased toxicity associated with resection after neoadjuvant treatment, with increased operative times and intraoperative blood loss.[9] Venous resections were required in 22% of patients who underwent resection. Given the significant risks associated with resection after neoadjuvant treatment, patients must undergo rigorous restaging before surgical exploration to assess for distant metastases.

The use of radiotherapy in treating PDAC remains controversial, and this is also true for IORT. The LAP 07 study did not show an improvement in OS with addition of chemoradiotherapy to induction chemotherapy[23]; however, induction chemotherapy in this study consisted of gemcitabine, which is inferior to FOLFIRINOX or gemcitabine with nab-paclitaxel in the metastatic setting.[6,7] There are no randomized data on IORT, and results have potential to be compromised by selection bias. However, many criticisms of IORT are based on results from an era with suboptimal staging and inadequate systemic control. We take care to use IORT judiciously, reserving it for patients with locally advanced unresectable disease or close/positive resection margins.

As systemic therapy improves, the ability to achieve local control will likely play an increasing role in improving patient outcomes, and the role of radiotherapy will need to continue to be reevaluated. Local control rates with IORT are difficult to compare to historical series given limited data in this population; however, in this cohort the local control rates in patients treated with neoadjuvant therapy, resection, and IORT were quite favorable compared with series of patients with resectable PDAC at diagnosis.[24] There was a trend toward improved local control with IORT and resection, which was not statistically significant; however, patients receiving IORT had less favorable resection margins as noted previously. The role of IORT in patients with unresectable disease after neoadjuvant treatment is particularly intriguing. In this cohort, IORT was associated with a median OS of 24.8 months. As noted above, comparisons with historical series are challenging given changes in practice patterns and patient heterogeneity, but there was a suggestion of improved local control in our cohort compared with historical series of chemotherapy and chemoradiotherapy.[13,25] Further prospective study is ongoing.

There is also a growing body of literature supporting the role of stereotactic body radiation therapy (SBRT) in the treatment of both locally advanced unresectable and borderline resectable PDAC, with encouraging local control rates and low rates of toxicity.[26–30] A recent phase II multi-institutional study demonstrated that gemcitabine followed by fractionated SBRT was associated with encouraging local control rates, improved patient quality of life, and minimal toxicity.[29] An institutional series of neoadjuvant chemotherapy and SBRT found that 21% of patients were able to undergo resection despite imaging suggesting persistent unresectable disease.[30] Trials of SBRT with more intensive neoadjuvant chemotherapy regimens are ongoing.[31,32]

Other forms of local therapy have been utilized in pancreatic cancer. In a recent publication, Martin et al[33] describe the use of irreversible electroporation (IRE) in a cohort of 200 patients with locally advanced PDAC. All patients received neoadjuvant chemotherapy and 52% received neoadjuvant radiotherapy. Approximately 75% of patients were treated with IRE alone and 25% underwent resection with IRE for margin enhancement. There was no difference in median survival of resected versus nonresected patients (28.3 vs. 23.2 months). Of note, other institutional series have reported higher complication rates with IRE, with one prospective series of 50 patients by Kluger and colleagues reporting a 90-day mortality rate of 12%. Of the 6 patients who died within 90 days of treatment, 5 received IRE for primary tumor control.[34]

There are limitations to our study. First, it is a retrospective, single-institution study, and patient numbers were small. This may have limited power to see a difference in toxicities with addition of IORT to resection or surgical exploration. Second, as we only had access to patients who were scheduled for surgical exploration, we could not assess patients who progressed during neoadjuvant treatment. This speaks to the importance of rigorous restaging before surgical exploration, as there are patients who will progress during neoadjuvant treatment. Third, overall follow-up time remains somewhat limited, which may have limited ability to see long-term toxicities. Fourth, randomized data on the use of FOLFIRINOX, gemcitabine with nab-paclitaxel, or FOLFOX in the neoadjuvant setting are not yet available. Whereas retrospective series have been promising, prospective data are needed to fully assess these regimens. Prospective trials are ongoing.[35–38]

In summary, the use of IORT after neoadjuvant chemotherapy and chemoradiotherapy was well tolerated, and was associated with encouraging median survival rates when incorporated into treatment of patients with unresectable disease or close or positive margins after resection. Further follow-up is needed, but these improved results suggest that certain patients with well-controlled systemic disease may benefit from aggressive local therapy that includes IORT.

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