9-16-2022

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Citation

Chuong, M. D., Herrera, R., Ucar, A., Aparo, S., De Zarraga, F., Asbun, H., Jimenez, R., Asbun, D., Narayanan, G., Joseph, S., Kotecha, R., Hall, M. D., Mittauer, K. M., Alvarez, D., McCulloch, J., Romaguera, T., Gutierrez, A., & Kaiser, A. (2022). Causes of Death Among Patients With Initially Inoperable Pancreas Cancer After Induction Chemotherapy and Ablative 5-fraction Stereotactic Magnetic Resonance Image Guided Adaptive Radiation Therapy. *Advances in radiation oncology*, *8*(1), 101084. https://doi.org/10.1016/j.adro.2022.101084

Advances in Radiation Oncology (2023) 8, 101084

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Causes of Death Among Patients With Initially Inoperable Pancreas Cancer After Induction Chemotherapy and Ablative 5-fraction Stereotactic Magnetic Resonance Image Guided Adaptive Radiation Therapy

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Received 2 June 2022; accepted 16 September 2022

Abstract

Purpose: Nearly all patients with pancreatic ductal adenocarcinoma (PDAC) eventually die of progressive cancer after exhausting treatment options. Although distant metastases (DMs) are a common cause of death, autopsy studies have shown that locoregional progression may be directly responsible for up to one-third of PDAC-related deaths. Ablative stereotactic magnetic resonance-guided adaptive radiation therapy (A-SMART) is a novel treatment strategy that appears to improve locoregional control compared with nonablative radiation therapy, potentially leading to improved overall survival.

Methods and Materials: A single-institution retrospective analysis was performed of patients with nonmetastatic inoperable PDAC treated between 2018 to 2020 using the MRIdian Linac with induction chemotherapy, followed by 5-fraction A-SMART. We identified causes of death that occurred after A-SMART.

Sources of support: No financial support was provided for this research.

Disclosures: Dr Chuong reports grants, personal fees, and nonfinancial support from ViewRay; personal fees and nonfinancial support from Sirtex; and grants from Novocure outside of the submitted work. Dr Hall reports personal fees from IBA, grants from the Florida Department of Health, and nonfinancial support from the Children's Oncology Group and Proton Collaborative Group outside of the submitted work. Dr Kotecha reports personal fees and nonfinancial support from Elekta, other support from Novocure, personal fees from Accuray, grants and personal fees from ViewRay, personal fees from Elsevier, and grants from Medtronic, Blue Earth Diagnostics, Novocure, GT Medical Technologies, AstraZeneca, and Exelixis outside of the submitted work. Dr Gutierrez reports personal fees and nonfinancial support from ViewRay outside of the submitted work. Dr Mittauer reports personal fees and nonfinancial support from ViewRay and other support from MR Guidance, LLC outside of the submitted work.

Data sharing statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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https://doi.org/10.1016/j.adro.2022.101084

Results: A total of 62 patients were evaluated, of whom 42 (67.7%) had died. The median follow-up time was 18.6 months from diagnosis and 11.0 months from A-SMART. Patients had locally advanced (72.6%), borderline resectable (22.6%), or resectable but medically inoperable PDAC (4.8%). All patients received induction chemotherapy, typically leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin (69.4%) or gemcitabine/nab-paclitaxel (24.2%). The median prescribed dose was 50 Gy (range, 40-50), corresponding to a median biologically effective dose of 100 Gy_{10}. Post-SMART therapy included surgery (22.6%), irreversible electroporation (9.7%), and/or chemotherapy (51.6%). Death was attributed to locoregional progression, DMs, cancer-related cachexia/malnutrition, surgery/irreversible electroporation complications, other reasons not due to cancer progression, or unknown causes in 7.1%, 45.2%, 11.9%, 9.5%, 11.9%, and 14.3% of patients, respectively. Intra-abdominal metastases of the liver and peritoneum were responsible for 84.2% of deaths from DMs.

Conclusions: To our knowledge, this is the first contemporary evaluation of causes of death in patients with PDAC receiving dose-escalated radiation therapy. We demonstrated that the predominant cause of PDAC-related death was from liver and peritoneal metastases; therefore novel treatment strategies are indicated to address occult micrometastatic disease at these sites.

Introduction

In 2022, approximately 62,210 new diagnoses and 49,830 deaths are expected in the United States from pancreatic ductal adenocarcinoma (PDAC), making this disease the 4th most common cause of cancer-related deaths.[1] The prognosis of PDAC is poor, largely because most patients are not surgical candidates because of either locally advanced tumor and/or distant metastases (DMs).[2] Even patients without radiographically apparent DMs who undergo resection likely already have occult micrometastatic disease that eventually will progress and become detectable.[3]

Despite the high mortality of PDAC, few studies describe the causes of PDAC-related death. A small number of autopsy studies of resected and unresected patients have shown that death from PDAC is most commonly due to DMs, typically involving the liver and peritoneum.[4-9] On the other hand, local progression may be responsible for up to one third of deaths from PDAC, even in the presence of limited DMs, which highlights the importance of achieving durable locoregional control (LRC).[7]

Nonablative radiation therapy (RT) improves LRC, but does not improve overall survival (OS) compared with chemotherapy alone for patients with locally advanced pancreas cancer, as demonstrated in the phase 3 LAP07 trial.[10] More recently, retrospective studies using ablative radiation doses have demonstrated higher LRC and OS compared with historical nonablative outcomes.[11-13] For example, we recently presented the multi-institutional outcomes of 148 patients with inoperable PDAC, including 2-year LRC at 83% and 2-year OS at 52.7%.[14] Although an association between ablative radiation dose and OS has not been studied prospectively, radiation dose escalation has been hypothesized to prevent death related to locoregional progression (LRP), and thereby improve OS in a carefully selected subset of patients with a lower competing risk of death from DMs.[15]

To the best of our knowledge, no published data describe the cause of death in patients with PDAC after receiving ablative RT, which was the objective of the current analysis.

Methods and Materials

After obtaining institutional review board approval, we performed a single-institution retrospective analysis of patients with biopsy-proven PDAC who were treated with induction chemotherapy, followed by ablative stereotactic magnetic resonance image guided adaptive RT (A-SMART) in 5 consecutive fractions on the MRIdian Linac (ViewRay, Oakwood Village, OH) between 2018 and 2020.

The primary objective of this analysis was to determine the causes of death for patients who died after A-SMART by performing a comprehensive review of available medical records. If the specific cause of death was not overtly documented in the medical record, we used the best clinical judgment about the probable cause of death based on information available before the date of death. For example, death was attributed to hepatic failure if there were extensive and progressive liver metastases, significantly elevated liver function test values, and no other known competing risk of death. We categorized the cause of death as being due to local progression, distant progression, cancer-related cachexia, reasons not related to cancer progression, or unknown causes. The Research Electronic Data Capture system was used to collect and manage data.

Patients were staged using endoscopic ultrasound and computed tomography (CT) scans of the chest, abdomen, and pelvis. Most patients also had a staging magnetic resonance imaging scan of the abdomen, but a positron emission tomography scan was rarely used. Initial resectability was determined according to the National Comprehensive Cancer Network guidelines.

Our A-SMART planning and delivery approach has been previously published.[12] Patients were typically treated in midinspiration breath hold; therefore, an integral target volume was not used, which was made possible by the MRIdian Linac's ability to automatically trigger and hold the beam based on the position of the target lesion. The highest priority when optimizing the original plan and adapted plans was to ensure that organ-at-risk constraints were met, and then secondarily to maximize target volume coverage by at least the prescription dose.

Although our initial target volumes only included gross disease, there was a systematic transition in our department in early 2019 to routinely treating elective volumes, including a radial 5-mm expansion around at least the most proximal 2 to 3 cm of the celiac axis and superior mesenteric artery.[16,17] The planning target volume was created from a 3-mm uniform expansion of the gross tumor volume or otherwise the clinical target volume if one was created. Our organ-at-risk dose constraints were previously published.[12]

All patients received induction chemotherapy, and none received concurrent chemotherapy during A-SMART. Chemotherapy was typically not given after A-SMART unless there was evidence of tumor progression either based on radiographic studies and/or CA19-9 increase, although maintenance chemotherapy was occasionally used at the discretion of the treating medical oncologist. Irreversible electroporation (IRE) was considered for patients after A-SMART if there was suspicion or confirmation of LRP. Surgery was offered to patients based on a multidisciplinary assessment of treatment response. Patients were followed with computed tomography and/or magnetic resonance imaging scans, along with routine laboratory testing, including CA19- 9 every 3 months after A-SMART.

Results

A total of 62 consecutive patients with PDAC were evaluated after receiving induction chemotherapy and then A-SMART, of whom 42 (67.7%) had died. The median follow-up time was 18.6 months from diagnosis and 11.0 months from A-SMART. Baseline patient/tumor characteristics and treatment details are summarized in Table 1. Briefly, the median age was 66 years (range, 35-91 years), most patients had tumors in the head of the pancreas (n = 43; 88.6%), and Eastern Cooperative Oncology Group performance status score of 0 to 1 was common (n = 60; 96.8%). Most patients had locally advanced disease (72.6%), but others had borderline resectable (22.6%) or resectable but medically inoperable PDAC (4.8%). No patient had confirmed distant metastatic disease at the time of A-SMART.

Induction chemotherapy typically consisted of leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin (n = 43; 69.4%) or gemcitabine/nab-paclitaxel (n = 15; 24.2%), for a median of 4.2 months (range, 0.2-13.3 months). The median prescribed RT dose was 50 Gy (range, 40-50 Gy) in 5 fractions, and the median biologically effective dose was 100 Gy_{10} with 50 Gy was prescribed to 55 patients (88.7%). The elective volume was prescribed as 33 Gy or 35 Gy using a simultaneous integrated boost. Fifty patients (80.6%) were treated to both gross disease and elective regions, and the remainder was treated to gross disease alone. Post-SMART therapy included surgery (n = 14; 22.6%), IRE (n = 6; 9.7%), and/or chemotherapy (n = 32; 51.6%).

The median follow-up time was 18.6 months from diagnosis. Median local control, progression-free survival, and OS from diagnosis were not reached, 20 months, and 23 months, respectively. The 1- and 2-year local control rates were 98.3% and 87.7%, respectively, and the 1- and 2-year progression-free survival rates were 88.4% and 40%, respectively. In addition, the 1- and 2-year OS rates were 90.2% and 45.5%, respectively.

The causes of death are summarized in Tables 2 and 3. The most common cause of PDAC-related death was DMs (n = 19; 45.2%), including hepatic lesions causing liver failure (n = 6; 14.3%), peritoneal carcinomatosis causing bowel obstruction or large volume ascites (n = 10; 23.8%), respiratory failure from lung metastases (n = 2; 4.8%), and brain metastasis (n = 1; 2.4%). Intra-abdominal metastases of the liver and peritoneum were responsible for 84.2% of deaths from DMs.

Three patient deaths (7.1%) were attributed to LRP, and 2 of these patients also had DMs at the time of death. All 3 patients received at least 3 months of induction chemotherapy, followed by A-SMART prescribed to 50 Gy. Two patients treated with elective volume coverage later had a Whipple procedure and achieved negative margins with excellent pathologic response (both ypT1N0), but developed locoregional recurrence and died of bowel ischemia and cholangitis at 23.2 months and 31.9 months after A-SMART, respectively. One patient who was treated for gross disease only received IRE for regional progression outside of the planning target volume, and died of bleeding due to bowel invasion from uncontrolled tumor growth 7.3 months after A-SMART.

Death from cancer-related cachexia/malnutrition occurred in 5 patients (11.9%), of whom 2 had local-only progression, 2 had distant-only progression in the liver or lung, and 1 had local and distant progression in the liver. Causes of death not attributed to cancer progression (n = 9; 21.4%) included head trauma from a fall (n = 1), sepsis/infection (n = 3), and complications after surgery or IRE (n = 4). The 3 patients who died of sepsis/infection all developed peritoneal metastases after A-SMART, and were treated with chemotherapy although there was no recent radiographic evidence of disease progression shortly before the patient deaths. We cannot rule out that occult progression in the peritoneum or elsewhere may have contributed to the patient deaths, although there was no conclusive evidence to attribute these deaths to cancer progression at the time of this analysis.

Complications after surgery (n = 3) or IRE (n = 1) consisted of bleeding in the operative bed (n = 3) and hepatic ischemia (n = 1). All 4 patients were prescribed 50 Gy, 3 were treated with elective volumes, 2 had portal vein resection (2 had no vascular resection), and the median time from A-SMART to surgery/IRE was 5.3 months (range, 1.4-10.3 months). No patient who proceeded to surgery had evidence of cancer progression. A cause of death could not be determined for 6 patients (14.3%) because of limited documentation.

Table 1 Baseline patient, tumor, and treatment characteristics

Characteristic	n (%)
Patients, N	62
Age, y, median (range)	66 (35-91)
Sex	
Male	35 (59.3)
Female	24 (40.7)
Eastern Cooperative Oncology Group performance status score	
0-1	60 (96.8)
2	2 (3.2)
Histology	
Adenocarcinoma	62 (100)
Tumor location	
Head	55 (88.7)
Body/tail	7 (11.3)
Largest tumor size, cm, median	3.8 (1.5-6.9)
Resectability	
Locally advanced	45 (72.6)
Borderline resectable	14 (22.6)
Resectable, medically inoperable	3 (4.8)
Clinical T stage	
1	1 (1.6)
2	13 (21.0)
3	9 (14.5)
4	39 (62.9)
Clinical N stage	
0	43 (69.4)
1	18 (29.0)
2	1 (1.6)
Clinical M stage	
0	62 (100)
CA19-9, U/mL, median	
Initial diagnosis	168.7 (0.9-12.6)
Before stereotactic magnetic resonance-guided adaptive radiation therapy	45.2 (1-3686)
Induction chemotherapy regimen	
Leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin	43 (69.4)
Gemcitabine/nab-paclitaxel	15 (24.2)
Gemcitabine	4 (6.4)
Induction chemotherapy duration, months, median	4.2 (0.2-13.3)
Radiation dose	
Total prescribed dose, Gy, median	50 (40-50)
Total prescribed fractions	5
Elective volume coverage	
Yes	50 (80.6)
No	12 (19.4)
After stereotactic magnetic resonance-guided adaptive radiation therapy	
Surgery	14 (22.6)
Irreversible electroporation	6 (9.7)
Chemotherapy	32 (51.6)

(*continued on next page*)

Discussion

The causes of death among patients with PDAC have been reported by a handful of studies, most of which were conducted several decades ago. Douglass et al. performed an autopsy analysis of 108 patients with PDAC between 1973 to 1989, and found that the most common causes of cancer-related death were hepatic failure from liver metastases (20.4%), brain metastases (7.4%), lung metastases (5.6%), and peritoneal metastases causing bowel obstruction (4.6%).[4] Sepsis was a frequent cause of death in 31.5% of patients, although whether some deaths were due to locoregional recurrence, especially those related to cholangitis, is unclear.

Subsequent studies have provided greater clarity that locoregional recurrence is responsible for patient mortality even in the presence of limited DMs. Ishikawa et al. reported that, among 54 patients with PDAC who had a Whipple procedure between 1985 to 1989, most died because of regional or hepatic recurrence.[8] Interestingly, 23 patients (43%) received preoperative RT (50 Gy/25 fractions) and had a significantly lower rate of death due to regional recurrence and a higher incidence of death from hepatic metastases than those who did not receive RT. Although 1-year OS was superior among those who received preoperative RT (75% vs. 43%; $P < .05$), the 3- and 5-year OS rates were not different, perhaps because of the limited effectiveness of systemic therapies available in the 1980s to control DMs. The same investigators later demonstrated that, although hepatic failures were much less common in resected patients who received prophylactic hepatic infusional 5-fluorouracil versus surgery alone, the 3-year rate of death from locoregional recurrence alone was similar (23%-28%) regardless of chemotherapy.[18]

In a study of 89 patients, Nakahashi et al. reported hepatic failure as a cause of death in 23% of patients, which is similar to the results of previous studies and our current study, and locoregional causes of death from bowel hemorrhage/perforation or sepsis in 9%.[6] However, there was no identified cause of death in more than half

Table 2 Causes of death among patients with initially nonmetastatic pancreas cancer who received induction chemotherapy and ablative stereotactic magnetic resonance image guided adaptive radiation therapy

Cause of death	n (%)
Bowel obstruction/ascites from peritoneal metastases	10 (23.8)
Hepatic failure from liver metastases	6 (14.3)
Unknown	6 (14.3)
Cachexia/malnutrition	5 (11.9)
Sepsis/infection not attributed to cancer progression	4 (9.5)
Complications after surgery/irreversible electroporation	4 (9.5)
Respiratory failure from lung metastases	2 (4.8)
Bowel bleed/ischemia from locoregional cancer progression	2 (4.8)
Cholangitis from locoregional cancer recurrence after surgery	1 (2.4)
Brain metastasis	1 (2.4)
Head trauma	1 (2.4)

of patients. More recently, a rapid autopsy study by Iacobuzio-Donahue et al. demonstrated that nearly one third of patients died because of LRP.[7]

Thus, although there is a common perception that patients with PDAC almost exclusively die of distant progression, patients die of a spectrum of other reasons, including LRP, as demonstrated in our study. RT improves LRC over chemotherapy alone, and decreases the probability of severe morbidity and potentially mortality due to LRP for some patients.[10] Whether the LRC benefit shown in prior studies using nonablative radiation doses can be augmented through substantial dose escalation has recently become a topic of interest.[15] Death due to LRP in the current study was rare (n = 3; 7.1%), occurring after surgical resection in 2 patients and after IRE in 1. Of note, 2 of 3 patients with LRP also had DMs.

Therefore, our hypothesis is that radiation dose escalation may positively affect OS by preventing or delaying death due to LRP in a subset of patients who do not rapidly develop DMs after A-SMART. Additional studies are undoubtedly needed to further evaluate this hypothesis, although we believe our current analysis is valuable given the paucity of published data describing causes of death in patients with pancreas cancer. If such an association between radiation dose, LRC, and OS is eventually confirmed, then patient selection for radiation dose escalation would become paramount, although biomarkers to identify appropriate patients are currently limited.[19]

Table 3 Local/distant pancreas cancer progression versus other or unknown causes of death after ablative stereotactic magnetic resonance image guided adaptive radiation therapy

Cause of death	n (%)
Distant cancer progression	19 (45.2)
Causes not associated with cancer progression	9 (21.4)
Unknown	6 (14.3)
Cancer-related cachexia/malnutrition	5 (11.9)
Locoregional cancer progression	3 (7.1)

As expected, most PDAC-related deaths were due to intra-abdominal disease progression in the liver and peritoneum. Intra-abdominal metastases of the liver and peritoneum were responsible for 84.2% of deaths from DM. Occult micrometastatic disease likely was present at these locations at the time of initial diagnosis, and not completely eradicated with induction chemotherapy. Novel therapies are being studied to address this challenge, including immunotherapy[20] and targeted systemic agents.[21] We have developed a phase 2 trial evaluating the use of tumor-treating fields applied to the entire abdomen as maintenance therapy after induction chemotherapy and A-SMART for patients with locally advanced pancreas cancer, which will soon be open at our institution. Preclinical and early clinical data demonstrate that tumor-treating fields are effective against PDAC, and could potentially at least delay liver and peritoneal progression, which may affect OS.[22,23]

Approximately 20% of deaths were due to causes not attributed to cancer progression. Four deaths (9.5%) were from sepsis without an identifiable cause based on available records, and we cannot rule out that occult disease progression may have contributed. Four deaths (9.5%) occurred after either surgery (n = 3) or IRE (n = 1), with nearly all related to bleeding in the irradiated area. Mortality due to pancreaticoduodenectomy can occur even if neoadjuvant therapy is not delivered with a 90-day incidence of up to 2% to 4%.[24] Neoadjuvant chemotherapy and/or nonablative RT may increase the operating time, but do not appreciably increase postoperative mortality.[25] The safety of surgery after ablative RT, with or without vascular resection, is poorly understood, and future studies are very much needed.

A recently presented retrospective analysis from the Henry Ford Cancer Institute found that

postpancreatectomy hemorrhage was higher in patients who received A-SMART (n = 21) versus nonablative chemoradiation (n = 44).[26] We are comprehensively reviewing our institutional peri- and postoperative outcomes in patients who had surgery after A-SMART, and expect to present these results soon. In the meantime, we urge caution when pursuing surgery after A-SMART, especially when considering performing vascular resections. Our current institutional practice is to not perform arterial resections after A-SMART in the absence of data showing its safety. The phase 2 SMART trial (NCT03621644) completed accrual in 2021, and we eagerly await the results, especially since surgery was permitted after 50 Gy in 5 fractions.

This study has several limitations, including its retrospective single-institution design and the small number of patient deaths. The median follow-up time after A-SMART is short, and we plan to update this analysis once we have a larger number of patients who have died. Our study cohort is heterogeneous with respect to the nonuniform utilization of elective volume coverage, use of various prescription doses, and different cancer therapies after A-SMART. Perhaps most importantly, a cause of death was almost never specifically identified in the medical records, and we needed to use the best medical judgment based on the available documentation. We were not able to evaluate whether the use of elective volume coverage affected outcomes, because there were too few deaths attributed to LRP. Lastly, insufficient information was available to confidently attribute a cause of death in almost 15% of patients.

Conclusions

We demonstrated that intra-abdominal DMs were the most common cause of PDAC-related death, and local progression was an infrequent cause of PDAC-related death in patients who received induction chemotherapy followed by A-SMART. Novel therapies are needed to address occult micrometastases, especially those that lead to death from liver metastases and peritoneal carcinomatosis.

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