Advances in Radiation Oncology (2023) **8**, 101266

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Predictors of Acute and Late Toxicity in Patients Receiving Chemoradiation for Unresectable Pancreatic Cancer

Rishi Das, MD, MPH,[a,1] Madeline R. Abbott, MS,[b,1] Scott W. Hadley, PhD,[c] Vaibhav Sahai, MBBS, MS,[d] Filip Bednar, MD, PhD,[e] Joseph R. Evans, MD, PhD,[c] Matthew J. Schipper, PhD,[b,c] Theodore S. Lawrence, MD,[c] and Kyle C. Cuneo, MD[c,*]

[a]Department of Internal Medicine, University of Southern California, Los Angeles, California; [b]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan; [c]Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan; [d]Department of Internal Medicine, Hematology and Oncology, University of Michigan, Ann Arbor, Michigan; and [e]Department of Surgery, University of Michigan, Ann Arbor, Michigan

Received 8 December 2022; accepted 28 April 2023

Purpose: Patients with pancreatic cancer undergoing chemoradiation therapy may experience acute and chronic side effects. We conducted an exploratory analysis of patients with locally advanced pancreatic cancer (LAPC) undergoing definitive chemoradiation to identify factors influencing the occurrence of gastrointestinal (GI) bleeding, short-term radiation side effects, patterns of failure, and survival.

Methods and Materials: Under an institutional review board–approved protocol, we retrospectively studied patients with LAPC treated with chemoradiation. Statistical models were used to test associations between clinical characteristics and outcomes, including upper GI bleeding, radiation treatment breaks, and weight loss during therapy.

Results: Between 1999 and 2012, 211 patients were treated with radiation for pancreatic cancer. All patients received concurrent chemotherapy with either gemcitabine (174) or 5-fluorouracil (27), and 67 received intensity modulated radiation therapy (IMRT). Overall, 18 patients experienced an upper GI bleed related to treatment, with 70% of bleeds occurring in the stomach or duodenum, and among those patients, 11 (61%) patients had a pancreatic head tumor and 17 (94%) patients had a metallic biliary stent. IMRT was associated with decreased risk of postradiation nausea (odds ratio, 0.27 [0.11, 0.67], $P = .006$) compared with 3-dimensional conformal radiation. Regarding long-term toxicities, patients with a metallic biliary stent at the time of radiation therapy were at a significantly higher risk of developing upper GI bleeding (unadjusted hazard ratio [HR], 15.41 [2.02, 117.42], $P = .008$), even after controlling for radiation treatment modality and prescribed radiation dose (adjusted HR, 17.38 [2.26, 133.58], $P = .006$). Furthermore, biliary stent placement was associated with a higher risk of death (HR, 1.99 [1.41, 2.83], $P < .001$) after adjusting for demographic, treatment-related, and patient-related variables.

This study was supported with Departmental Funding from the Department of Radiation Oncology at the University of Michigan. Research reported in this publication was also supported by the National Cancer Institutes of Health under Award Number P30 CA046592. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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

[1] R.D. and M.R.A. contributed equally to this work as co-first authors.

*Corresponding author: Kyle C. Cuneo, MD; E-mail: kcuneo@umich.edu

https://doi.org/10.1016/j.adro.2023.101266

Conclusions: Metallic biliary stents may be associated with an increased risk of upper GI bleeding and mortality. Furthermore, IMRT was associated with less nausea and short-term toxicity compared with 3-dimensional conformal therapy.

Introduction

Approximately one-third of patients with pancreatic cancer present with either borderline resectable or locally advanced pancreatic cancer (LAPC) disease.[1] Patients with locally advanced disease can be challenging to treat because of disease-related symptoms and the relatively high radiosensitivity of adjacent organs, including the bowel, stomach, liver, and kidneys. This group of patients has a poor prognosis, and locoregional therapies can result in acute and late toxicities that affect quality of life.[2]

The role of radiation therapy for borderline resectable and LAPC has evolved over time, owing to conflicting results across clinical trials. LAP07 was an international phase 3 trial that compared the results of chemotherapy alone versus chemoradiation after induction chemotherapy with gemcitabine with or without erlotinib in patients with LAPC. The trial demonstrated no significant overall survival or progression-free survival benefit with the addition of radiation therapy; however, radiation resulted in significantly improved local control and prolonged time to second-line therapy.[3] A systematic review of studies[4] investigating the role of consolidation radiation therapy demonstrated improvement in 1-year survival in the context of concurrent 5-fluorouracil use and at least 3 months of induction chemotherapy.

Most recently, the results from the PREOPPANC phase 3 trial comparing neoadjuvant chemoradiation to upfront surgery in patients with resectable and borderline resectable pancreatic cancer were reported. Preoperative therapy demonstrated improvements in the local response as measured by an increase in R0 resection rates (71% vs 40%), an improved median overall survival that increased from 13.2 months to 17.6 months (P = .029) among borderline resectable patients undergoing neoadjuvant chemoradiation, and an increased median survival that improved from 19.8 months to 35.2 months (P = .029) in patients who were able to undergo surgery and receive adjuvant chemotherapy.[5]

Although radiation therapy in combination with chemotherapy is used to improve locoregional control, its use can also result in acute and late gastrointestinal (GI) toxicities ranging from nausea and loss of appetite to GI bleeding and ulceration.[6] As a result, radiation therapy for the pancreas presents unique challenges, given the sensitivity of the adjacent bowel and stomach, which can produce acute symptoms linked to mucosal injury and inflammation, and produce chronic symptoms months to years later linked to fibrosis and vascular sclerosis, such as biliary stricture, chronic diarrhea, malabsorption, small bowel obstruction, ulceration, and hemorrhage.[7] A better understanding of factors related to toxicity would be clinically useful and potentially beneficial to patients.

Toxicity profiles can vary between intensity modulated radiation therapy (IMRT) and 3-dimensional conformal radiation techniques (3DCRT). Prior studies have demonstrated the comparative efficacy of newer methods such as IMRT over 3DCRT, with a reduction in GI toxicity.[8] IMRT, as a more conformal technique, also allows for radiation dose escalation without significant increase in GI toxicities.[9]

GI toxicity represents a significant factor in pancreatic cancer morbidity and mortality, but there has been limited characterization of the risk of acute and chronic toxicity across treatment modalities. Therefore, we conducted an exploratory analysis of LAPC patients undergoing definitive chemoradiation to identify factors influencing the occurrence of acute and late toxicities.

Methods and Materials

Patient population

Under an institutional review board–approved protocol, we performed a retrospective cohort analysis of 213 patients, of which the vast majority were patients with unresectable pancreatic cancer treated with definitive intent chemoradiation between 1999 and 2012. Forty-two patients were on clinical trial protocols, some of which were dose-escalation studies. All patients in the data set who received definitive radiation therapy were eligible for our analysis, except for patients with GI bleeding before the start of radiation, resulting in an analytical sample size of 211 patients.

Diagnosis and staging

Almost all patients included in the study had a pathologic diagnosis of pancreatic cancer deemed to be unresectable after evaluation by a specialist pancreas surgeon, typically in the setting of a multidisciplinary tumor board. All patients underwent computerized tomography and/or magnetic resonance imaging to rule out distant metastatic disease and to determine local tumor stage.

Treatment

Multiple radiation techniques were used in the study. Most of the patients were treated with 3DCRT or IMRT. Target volumes for the cases typically involved the primary tumor and radiographically involved nodes, if present, with a margin. Typical margin size involved a 5 mm gross expansion for clinical target volume and 5 mm expansion for planning target volume. The vast majority of patients underwent motion management with daily imaging for setup. Elective nodal irradiation was not routinely performed. Biologic effective dose was calculated with $\alpha/\beta = 4$ for normal tissue, using the prescription dose as a surrogate for normal tissue dose for organs adjacent to the target.

Statistics

Initially, we sought to determine whether treatment modality affected the risk of short-term toxicities and disease progression using weighted regression models, where weights were estimates of the inverse probability of treatment. The short-term toxicities were defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Significant toxicities included nausea (grade ≥2), fatigue (grade ≥2), and abdominal pain (grade ≥2), as well as hospitalization for any treatment-related issue and whether the patient required a toxicity break during radiation. These variables were assessed using weighted logistic regression. The short-term toxicity of weight loss, measured immediately after radiation and 3 months after, was modeled using weighted linear regression. Inverse probability weighting (IPTW) was used to adjust for imbalances in clinical characteristics between radiation treatment groups. We have illustrated the standardized differences to summarize imbalances in patient characteristics between 2 radiation groups, in which the orange dots demonstrate a preadjustment imbalance in patient characteristics and the yellow squares indicate balancing after IPTW (Fig. E1).

Patient-level weights were defined as the inverse of the model estimated probability of receiving the observed, with treatment probabilities estimated using a propensity score model that included age, tumor location, Eastern Cooperative Oncology Group (ECOG) performance status, and concurrent chemotherapy treatment. For simplicity, a single propensity model was fit for all patients with complete data because outcomes were missing for some patients. Firth's method was used to provide finite parameter estimates for rarer short-term outcomes (eg, abdominal pain). We did not adjust for concurrent multiagent chemotherapy treatment in our propensity model, owing to extreme propensity scores, and instead adjusted for this covariate in our outcome models for the short-term toxicity outcomes.

We also assessed potential associations between the short-term toxicities and biliary stent placement. To account for variation in the timing of stent placement, the presence of a stent was defined relative to the time at which the outcome of interest was recorded. Average differences in patient toxicities by placement of a biliary stent were assessed using 2-sided t tests and χ^2 tests.

Second, we sought to examine patient and clinical factors associated with long-term toxicity (upper GI bleed), survival, and disease progression (local and systemic). We assessed associations between demographic, disease, and treatment characteristics with outcomes of interest using Cox proportional hazards models with administrative censoring at 3 years. Biliary stent placement was treated as a time-varying covariate. For patients with multiple stents and stent replacements (n = 7), we considered only the initial placement. Owing to the scarcity of observed GI bleed events, variable inclusion in this model was determined through a stepwise selection procedure based on Akaike information criterion. Akaike information criterion–based stepwise selection was also used when modeling overall survival. Local and distant progression were modeled using weighted Cox proportional hazards models as a time-to-first-progression event, in which an earlier recorded progression type served as a censor for the other. Statistical significance was defined as a 2-sided P value of less than .05, and no formal multiplicity corrections were used. R version 3.6 was used for all statistical analyses.

Results

Patient characteristics

The baseline characteristics of the 213 patients included in our study are summarized in Table 1. Full clinical TNM (tumor, node, metastasis) staging was available for 157 of the 213 patients. The remaining patients were characterized as having unresectable, nonmetastatic disease, but specific T and N staging was not reported. The average age of patients treated was 62 years, with most patients (n = 145) falling between the ages of 55 and 75 years. Fifty-seven percent of patients were men. Ninety-four percent had unresectable disease (n = 201); 3% had borderline resectable disease (n = 6); and 1% had resectable (n = 2) disease. The 2 patients with resectable disease did not undergo surgery, owing to patient preference and comorbid medical conditions. ECOG performance status was available for 200 patients, with the following overall performance distribution: 16.5% ECOG 0, 66.5% ECOG 1, 13% ECOG 2, and 1% ECOG 3. Pathology was available for 211 patients, of whom 205 (97%) were classified as having adenocarcinoma and 3 (1.5%) were classified as having neuroendocrine tumors; 3

Table 1 Patient demographics and clinical characteristics

Characteristic	Median (range) or number	Percentage
Age	62 (29-86)	-
Sex		
Male	121	57.3%
Female	90	42.7%
Ethnicity		
Caucasian	179	84.8%
Black	14	6.6%
Asian	2	0.9%
Other	3	1.4%
Unknown	13	6.2%
Resectability staging		
Resectable	2	0.9%
Borderline	6	2.8%
Unresectable	201	95.3%
Unknown	2	0.9%
Surgical resection		
Yes	16	7.6%
No	195	92.4%
Staging		
IB	3	1.4%
IIA	13	6.2%
IIB	30	14.2%
III	101	47.9%
IV	10	4.7%
Unknown	54	25.6%
Nodal status		
Negative	46	21.8%
Positive	24	11.4%
Unknown	141	66.8%
Histology		
Adenocarcinoma	205	97.2%
Neuroendocrine	3	1.4%
Unknown	3	1.4%
Chemotherapy		
Gemcitabine	174	82.5%
5-FU	27	12.8%
Other[†]	10	4.7%
Tumor location		
Head	138	65.4%
Neck	17	8.1%
Body	30	14.2%

(*continued on next page*)

Table 1 (*Continued*)

Characteristic	Median (range) or number	Percentage
Tail	11	5.2%
Uncinate	14	6.6%
Unknown	1	0.5%

Abbreviation: 5-FU = 5-fluorouracil.
† Consisted of a combination of gemcitabine, cisplatin, capecitabine or oxaliplatin.

patients (1.5%) had no pathology but were presumed to have adenocarcinoma (Table 1).

Treatment received

Most patients (99%) received concurrent chemotherapy; a gemcitabine-based regimen (82%) was the most common treatment, followed by a 5-fluorouracil–based regimen (13%). Sixty-nine patients were treated with multiagent chemotherapy, and gemcitabine with a platinum agent was the most common regimen (n = 37, 54%). One hundred seven patients were prescribed 1.8 to 2.0 Gy/fraction to 50 to 54 Gy, 6 patients received 2.3 Gy/fraction to 58 Gy, and 80 patients received 2.4 Gy/fraction or greater to approximately 36 Gy. Sixty-seven patients received IMRT, and 145 patients were treated using non-IMRT techniques, of which the majority were 3DCRT (Table 2). Two patients were excluded from the analysis, as 1 patient had a GI bleed before treatment and 1 patient had incomplete radiation therapy data.

Table 2 Summary of radiation treatment

Characteristic	Number*	Percentage†
Treatment modality		
IMRT	67	31.8%
3D conformal	141	66.8%
2D	3	1.4%
Target		
Pancreas	166	78.7%
Pancreas + lymph node	21	10.0%
Unknown	24	11.3%
Radiation duration (d)		
Average (range)	27 (4-71)	-
Radiation fractions		
Average (range)	2.2 (1.8-4.0)	-
Bowel radiation dose‡		
Minimum	13.1	-
Mean	65.8	-
Median	64.4	-
Maximum	102.3	-

Abbreviations: 3D = 3-dimensional; 2D = 2-dimensional; IMRT = intensity modulated radiation therapy.
* Unless otherwise indicated.
† Values rounded to 1 decimal place; thus, they may not add up to 100% cumulatively.
‡ Calculated as biologic effective dose normalized to $\alpha/\beta = 4$.

Short-term toxicities

Regarding documented short-term toxicities assessed during the radiation course, we found that 25.3%, 15.9%, and 3.8% of patients experienced grade 2 or greater toxicity for nausea, fatigue, and abdominal pain, respectively. In particular, 3.8%, 1.4%, and 0.5% experienced grade 3 nausea, fatigue, and abdominal pain, respectively. No grade 4 toxicities were reported. At 3 months after radiation therapy, the rates of grade 2 or greater toxicities for nausea, fatigue, and abdominal pain were 8.0%, 7.0%, and 3.3%, respectively. A total of 16 patients required hospitalization, of which 7 had received IMRT and 6 had received 3DCRT. A total of 21 patients required a radiation toxicity break; 8 of these patients received IMRT radiation and 8 received 3DCRT (Table 3).

We next examined treatment-related factors to determine their effect on toxicity. Short-term toxicities were compared between patients treated with IMRT and 3DCRT. Of the 67 patients receiving IMRT, 9 reported significant nausea and 8 reported significant fatigue, whereas of the 50 patients receiving 3DCRT, 11 reported significant nausea and 10 reported significant fatigue. Patients treated with IMRT had lower odds of experiencing high-grade nausea (odds ratio [OR], 0.27; $P = .006$) compared with those who were treated with 3DCRT, after adjusting for concurrent treatment with multiagent chemotherapy. IMRT was also marginally associated with lower odds of significant fatigue (OR, 0.43 [0.17, 1.07], $P = .07$). Radiation technique was also associated with weight change during radiation. On average, patients treated with IMRT compared with those treated with conventional radiation therapy lost 4 lb more body weight during radiation, after adjusting for multiagent chemotherapy ($\beta = -4.02$ [−7.77, −0.28], $P = .038$). This

Table 3 Toxicity outcomes

Toxicity	Number	Percentage
Short term*		
Nausea	194	100%
Grade 0	104	53.6%
Grade 1	37	19.1%
Grade 2	45	23.2%
Grade 3	8	4.1%
Grade 4	0	0%
Fatigue	187	100%
Grade 0	82	43.9%
Grade 1	71	38.0%
Grade 2	31	16.6%
Grade 3	3	1.6%
Grade 4	0	0%
Abdominal pain	192	100%
Grade 0	122	63.5%
Grade 1	62	32.3%
Grade 2	7	3.6%
Grade 3	1	0.5%
Grade 4	0	0%
Long term		
Upper gastrointestinal bleeds	18	9%
Radiation toxicity break	21	10%
Postradiation hospitalization	16	8%

* Listed short-term toxicities overlap across patients and do not sum to 211.

significant difference in weight change did not persist 3 months after radiation (Table 4).

Long-term toxicities

We next examined long-term GI toxicities beyond 3 months. Development of an upper GI bleed was the most common severe late toxicity seen in our cohort, ascertained via esophagogastroduodenoscopy. Eighteen patients exhibited upper GI bleeding; the majority (11 of 18) of these events were in the duodenum. Of the 18 patients who experienced a treatment-related GI bleed, 11 had a pancreatic head tumor, and 17 had a metallic biliary stent. On univariate analysis, the presence of a biliary stent during chemoradiation indicated an increased risk of GI bleed development (hazard ratio [HR], 15.4 [2.02, 117.42], $P = .008$). No other factors, including tumor location, performance status, type of radiation, or concurrent chemotherapy, were associated with GI bleeding risk on univariate analysis (Table 5). Given the potential for tumor location to affect stent placement, we performed a multivariate analysis incorporating tumor location, treatment technique, and radiation dose. After adjusting for tumor location, the presence of a biliary stent was strongly associated with an increased risk of GI bleed (HR, 24.8 [3.08, 200.04], $P = .003$). Additionally, when we incorporated IMRT and radiation dose in our models, the presence of a biliary stent remained the most robust predictor of GI bleed risk (HR, 17.4 [2.26, 133.58], $P = .006$) (Table 5).

Survival and disease progression

For the last part of our analysis, we examined patient- and treatment-related factors to see how they were associated with long-term survival. Biliary stent placement, higher ECOG score, and use of multiagent concurrent chemotherapy were significantly associated with increased hazard of death (HR_{stent}, 1.99 [1.41, 2.83], $P < .001$), (HR_{ECOG}, 1.69 [1.24, 2.30], $P = .001$), ($HR_{multiagent}$, 1.77 [1.12, 2.81], $P = .014$) after adjusting for demographic, treatment-related, and patient-related variables.

Although multiagent concurrent chemotherapy was associated with all-cause mortality, concurrent chemotherapy with single-agent gemcitabine (adjusted HR, 1.50 [0.91, 2.48], $P = .113$) was not statistically significantly associated with increased mortality risk, suggesting that concurrent gemcitabine alone is safe and effective with radiation. In addition, higher age trended toward an increased hazard of death (HR, 1.02 [1.00, 1.03], $P = .055$) (Table 6).

Furthermore, treatment modality (IMRT) did not statistically affect time to local progression (HR, 1.04 [0.45, 2.39], $P = .931$) or time to systemic progression of disease (HR, 1.40 [0.82, 2.39], $P = .219$) (Table 4). This was further illustrated using Kaplan-Meir curves, which were weighted using IPTW and stratified by multiagent chemotherapy and radiation treatment modality (Figs. E2 and E3).

Discussion

The role of radiation therapy in pancreatic cancer is evolving as more sophisticated treatment techniques are developed and better systemic therapies are discovered. Chemoradiation is known to be effective at providing local control in unresectable patients; however, several factors, including the potential for toxicity and risk of distant metastases, has made its routine use less appealing. For this project, we sought to determine potential predictors of toxicity using a large database of patients treated with various techniques, dose fractionation schedules, and concurrent chemotherapy regimens. Our main findings were that IMRT was associated with less short-term toxicity compared with 3DCRT and that the presence of a biliary stent was strongly associated with developing a GI bleed after treatment, even after adjusting for tumor location and radiation dose.

Table 4 Inverse probability weighting regression models for short-term toxicities and disease progression

Variable Outcome	IMRT vs non-IMRT radiation		
	Estimate	**95% CI**	***P* value**
Logistic regression (odds ratio)			
Radiation toxicity break (ref = no)	0.93	(0.31, 2.83)	.903
Hospitalization (ref = no)	1.53	(0.56, 4.21)	.408
End-radiation nausea grade (ref: <2)	0.27	(0.11, 0.67)	.006
End-radiation fatigue grade (ref: <2)	0.43	(0.17, 1.07)	.070
End-radiation abdominal grade (ref: <2)	0.13	(0.00, 1.45)	.107
Cox regression (hazard ratio)			
Time until local progression	1.04	(0.45, 2.39)	.931
Time until systemic progression	1.40	(0.82, 2.39)	.219
Linear regression (effect size)			
Weight change: during radiation	−4.02	(−7.77, −0.28)	.038
Weight change: 3 mo postradiation	−2.33	(−7.41, 2.75)	.37

Abbreviations: IMRT = intensity modulated radiation therapy; ref = reference.
We also adjusted for concurrent treatment with multiagent chemotherapy, as this variable is not adjusted for in the inverse probability weighting. Robust standard errors (sandwich estimates) are reported for all models except for the outcome of abdominal grade.

Previous studies have examined the dosimetric advantages of IMRT in the abdomen. Jin et al[10] demonstrated that IMRT results in a lower V10, V20, and mean radiation dose to the duodenum compared with 3DCRT. Other reports have shown that the V30, V45, and V50 to the small bowel correlate with small bowel toxicity. IMRT has been previously shown to significantly reduce these dose-volume parameters of the small bowel, resulting in lower toxicity rates.[11,12] In our study, a significantly lower rate of nausea was seen in patients receiving IMRT versus traditional radiation techniques. As our treatment volumes typically encompassed only the gross tumor volume with a margin, diarrhea was not as frequent in our cohort as was reported in the previously mentioned studies, likely due to the omission of elective nodal radiation.

An upper GI bleed event was the most common long-term toxicity identified in our analysis. Almost all the patients who had a GI bleed had a metal biliary stent at the time of radiation (94%). Several factors may potentially confound this association. Patients who require a stent typically have tumors in the head of the pancreas adjacent to the duodenum, and patients requiring a stent may have larger and potentially more invasive tumors. After adjusting for factors such as tumor location and radiation dose in a multivariate analysis, the persistence and strength of this association suggests a clinically relevant association after attempting to control for confounding variables. One explanation of the stent's effect on GI bleeding risk is that damage from radiation is exacerbated by inflammation associated with the stent. Radiation-induced GI ulcers and bleeds are late effects related to chronic inflammation and tissue injury and are mediated by cytokines and other factors.[13] The presence of a biliary stent is also associated with local inflammation in the duct itself and in adjacent tissue. In some patients, this acute inflammatory process may persist and become exaggerated, resulting in ischemia, ulceration, and fibrotic changes.[6] A study by Ballinger et al[14] examined cytokine levels in patients with malignant bile duct obstruction before and after stenting. This study found that the levels of certain cytokines, such as IL-6, decrease after stent placement; however, tumor necrosis factor α levels remain elevated. The tumor necrosis factor axis is well established to play a role in inflammation and radiation toxicity.[14] Additionally, rabbit models have demonstrated the effects of biliary stents on chronic inflammation in the pancreas and duodenum.[15] It is likely that this chronic inflammatory state of the tissue surrounding the stent plays a role in the development of GI toxicity by increasing the levels of inflammatory cytokines, which can lead to injury and impair the healing response after radiation therapy.

Another explanation for the increased toxicity seen with a biliary stent is that the stent may alter the dose in adjacent tissue, owing to its high Z properties. No previous study has examined the dosimetric effects a biliary stent has on surrounding tissues; however, a prior report has studied the effect of metal esophageal stents. Using Monte Carlo dose simulation methods, this study showed that the tissue adjacent to a metal stent may receive up to a 7.8% greater dose for a stainless-steel stent and up to 8.8% for a polyflex stent. Newer metal alloys such as nitinol were associated with less dose enhancement, at 2% to 2.5%.[16,17] Other studies have shown similar findings with esophageal stents.[18,19]

Table 5 Regression models for upper GI bleeding

Univariable Cox hazards models for time to upper GI bleed					
Covariate	**Hazard ratio**	**95% CI**	***P* value**	**LRT**	**Sample size**
Age	1.01	(0.96, 1.06)	.725		211
Tumor location				0.971	210
Head	1.13	(0.24, 5.29)	.878		
Uncinate	0.98	(0.08, 11.42)	.986		
Neck	1.04	(0.19, 5.72)	.964		
Body	1.64	(0.33, 8.23)	.548		
ECOG*	1.27	(0.54, 3.00)	.583		198
Biliary stent	15.41	(2.02, 117.42)	.008		210
IMRT radiation	0.81	(0.29, 2.28)	.686		211
Concurrent chemotherapy agent				0.718	208
5-FU	0.42	(0.03, 6.77)	.541		
Gemcitabine	0.88	(0.10, 8.00)	.912		
Multiagent	0.75	(0.20, 2.79)	.666		
Bowel radiation dose	0.99	(0.96, 1.02)	.625		192
Cox hazards model for time until upper GI bleeding using stepwise selection					
Covariate	Hazard ratio	95% CI	*P* value		
Tumor location (head)	0.36	(0.12, 1.05)	.061		
Biliary stent	24.82	(3.08, 200.04)	.003		
Cox hazards model for upper GI bleeding with radiation covariates					
Covariate	Hazard ratio	95% CI	*P* value		
Biliary stent	17.38	(2.26, 133.58)	.006		
IMRT radiation	0.86	(0.20, 3.75)	.841		
Bowel radiation dose	1.01	(0.96, 1.06)	.717		

Abbreviations: 5-FU = 5-fluorouracil; ECOG = Eastern Cooperative Oncology Group; GI = gastrointestinal; IMRT = intensity modulated radiation therapy; LRT = likelihood ratio test.
* ECOG is parameterized as an ordinal variable.

Many of the limitations of our study can be linked to the assessment of relatively rare outcomes and the statistical methods used for accurate data assessment. Owing to the small number of events relative to the patient population size, outcomes such as GI bleeding and toxicity grade exhibited wide confidence intervals during statistical modeling. These wide confidence intervals remained after Firth penalized estimation. In assessing short-term

Table 6 Cox hazards model for all-cause mortality using stepwise selection

Covariate	**Hazard ratio**	**95% CI**	***P* value**
Age	1.02	(1.00, 1.03)	.055
ECOG	1.69	(1.24, 2.30)	.001
Tumor location (body)	1.50	(0.96, 2.34)	.072
IMRT radiation	1.32	(0.93, 1.89)	.125
Concurrent chemotherapy (gem)	1.50	(0.91, 2.48)	.113
Concurrent chemotherapy (MA)	1.77	(1.12, 2.81)	.014
Biliary stent	1.99	(1.41, 2.83)	<.001

Abbreviations: ECOG = Eastern Cooperative Oncology Group; gem = gemcitabine; IMRT = intensity modulated radiation therapy; MA = multiagent chemotherapy.

toxicities, the use of multiagent chemotherapy resulted in extreme propensity scores, requiring a separate adjustment of this variable in our analysis. Although this reduced extreme weights, it limited our ability to draw causal conclusions. Furthermore, given that tumors located in the tail of the pancreas did not demonstrate bleeding events, this location was not adjusted for in the models. However, as only 12 patients had pancreatic tail tumors in our analysis, we do not believe this omission to have significantly influenced the analysis. Furthermore, individual-level dosimetric data were limited in our data set; however, it was assumed that prescription dose was a good surrogate marker for maximum bowel dose.

Conclusion

In synopsis, our analysis indicated that IMRT is associated with less short-term toxicity, as demonstrated by the reduction in nausea grade after radiation therapy. Furthermore, biliary stent placement was associated with higher all-cause mortality and an increased risk of postradiation GI bleed. Therefore, our analysis indicates the need for caution when treating patients with biliary stents undergoing definitive radiation therapy, as closer post-therapy monitoring for GI bleed or adjusted dose constraints may be warranted.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We acknowledge the instrumental role of the Department of Radiation Oncology at the University of Michigan in allowing for the creation of our research database for analysis.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101266.

References

1. Shaib WL, Ip A, Cardona K, et al. Contemporary management of borderline resectable and locally advanced unresectable pancreatic cancer. *Oncologist*. 2016;21:178-187.
2. Robin TP, Goodman KA. Radiation therapy in the management of pancreatic adenocarcinoma: Review of current evidence and future opportunities. *Chin Clin Oncol*. 2017;6:28.
3. Hammel P, Huguet F, Van Laethem JL, et al. Effect of chemoradiotherapy versus chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib the LAP07 randomized clinical trial. *JAMA*. 2016;315:1844-1853.
4. Chang JS, Chiu YF, Yu JC, Chen LT, Ch'ang HJ. The role of consolidation chemoradiotherapy in locally advanced pancreatic cancer receiving chemotherapy: An updated systematic review and meta-analysis. *Cancer Res Treat*. 2018;50:562-574.
5. Versteijne E, Suker M, Groothuis K, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: Results of the Dutch randomized phase III PREOPANC trial. *J Clin Oncol*. 2020;38:1763-1773.
6. Shadad AK, Sullivan FJ, Martin JD, Egan LJ. Gastrointestinal radiation injury: Symptoms, risk factors and mechanisms. *World J Gastroenterol*. 2013;19:185-198.
7. Liu GF, Bair RJ, Bair E, Liauw SL, Koshy M. Clinical outcomes for gastric cancer following adjuvant chemoradiation utilizing intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2012;84:S318-S319.
8. Prasad S, Cambridge L, Huguet F, et al. Intensity modulated radiation therapy reduces gastrointestinal toxicity in locally advanced pancreas cancer. *Pract Radiat Oncol*. 2016;6:78-85.
9. Goto Y, Nakamura A, Ashida R, et al. Clinical evaluation of intensity-modulated radiotherapy for locally advanced pancreatic cancer. *Radiat Oncol*. 2018;13:118.
10. Jin L, Wang R, Jiang S, et al. Dosimetric and clinical toxicity comparison of critical organ preservation with three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and RapidArc for the treatment of locally advanced cancer of the pancreatic head. *Curr Oncol*. 2016;23:41-48.
11. Nakamura A, Shibuya K, Matsuo Y, et al. Analysis of dosimetric parameters associated with acute gastrointestinal toxicity and upper gastrointestinal bleeding in locally advanced pancreatic cancer patients treated with gemcitabine-based concurrent chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;84:369-375.
12. Poppe MM, Narra V, Yue NJ, Zhou J, Nelson C, Jabbour SK. A comparison of helical intensity-modulated radiotherapy, intensity-modulated radiotherapy, and 3D-conformal radiation therapy for pancreatic cancer. *Med Dosim*. 2012;36:351-357.
13. Kim JH, Jenrow KA, Brown SL. Mechanisms of radiation-induced normal tissue toxicity and implications for future clinical trials. *Radiat Oncol J*. 2014;32:103-115.
14. Ballinger AB, Woolley JA, Ahmed M, et al. Persistent systemic inflammatory response after stent insertion in patients with malignant bile duct obstruction. *Gut*. 1998;42:555-559.
15. Liu Y, Zheng S, Li N, Guo H, Zheng Y, Peng J. In vivo response of AZ31 alloy as biliary stents: A 6 months evaluation in rabbits. *Sci Rep*. 2017;7:40184.
16. Chen YK, Schefter TE, Newman F. Esophageal cancer patients undergoing external beam radiation after placement of self-expandable metal stents: Is there a risk of radiation dose enhancement? *Gastrointest Endosc*. 2011;73:1109-1114.
17. Francis SR, Anker CJ, Wang B, et al. Self-expanding stent effects on radiation dosimetry in esophageal cancer. *J Appl Clin Med Phys*. 2013;14:4218.
18. Li XA, Chibani O, Greenwald B, Suntharalingam M. Radiotherapy dose perturbation of metallic esophageal stents. *Int J Radiat Oncol Biol Phys*. 2002;54:1276-1285.
19. Darwin P, Goldberg E, Li XA. Comparison of radiation dosimetry effects of metallic biliary stents. *Gastrointest Endosc*. 2004;59:182.