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Hypofractionated intensity-modulated radiotherapy in locally advanced unresectable pancreatic cancer: A pilot study

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ABSTRACT

Purpose: To test feasibility and safety of hypofractionated intensity modulated radiotherapy (H-IMRT) in pancreatic adenocarcinoma (PAC) treatment.
Methods: Patients with unresectable nonmetastatic PAC were prospectively enrolled on a pilot study. Patients received H-IMRT to gross tumor volume to a total dose of 52 Gy (4 Gy/fraction). Toxicity rates, duodenal dosimetric parameters, and clinical outcomes were evaluated.
Results: Ten patients received H-IMRT regimen. Objective tumor response was recorded in all patients but one. Gastrointestinal toxicity was the most common acute side effect and its severity moderately correlated with duodenal maximum dose ($\rho = 0.46$) and percentage of duodenal volume exposed to 5 Gy ($\rho = 0.46$). The 1-year overall and disease-free survival were 83.3% and 68.6%, respectively.
Conclusion: H-IMRT seems to guarantee a high local control rate without severe toxicity. Its use in unresectable nonmetastatic PAC needs to be further investigated.

ARTICLE INFO

Keywords: Radiotherapy; Hypofractionated; IMRT; Pancreas; Duodenum

☆ Conflict of interest statement: None.

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Introduction

Pancreatic adenocarcinoma (PAC) is an aggressive tumor with a poor long-term survival (less than 10% at 5 years), still representing one of the principal causes of cancer death worldwide.[1] A total of 10%-20% of cases have a potentially resectable disease at diagnosis.[2,3] The vast majority of PAC patients present with unresectable locally advanced disease and, at this stage, treatment strategy includes chemotherapy, radiotherapy (RT), or combinations of these approaches.[4] Historically, concurrent chemoradiotherapy seems to guarantee a small median survival benefit over chemotherapy alone (42 weeks vs 32 weeks), but it is associated with higher severe toxicity.[5,6] Over the years, significant technical progress has been made in RT techniques, mainly identified in major accuracy planning and organ at risk (OAR) sparing. The usefulness of stereobody RT (SBRT) technique for prolonging survival and minimizing side effects in PAC patients with unresectable disease has been vastly reported.[7] But SBRT is not accessible in most of RT services.[8] As a result, the greatest possible use should be made of easily available resource, such as intensity-modulated RT (IMRT) technique. IMRT should be combined with hypofractionated scheme, especially in this setting of patients in which quality of life plays an increasingly important role in the evaluation of overall treatment efficacy.

Therefore, we conducted a pilot study to evaluate the feasibility of hypofractionated IMRT, its impact on local tumor control and RT-related side effects. The aim was to offer a shortly RT treatment to PAC patients, in order to better manage toxicity and improve the return to "normal life."

Materials and methods

Patient selection

Patients originated from the Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome. The investigational protocol was reviewed and approved by the institutional review board and the scientific review committee. All patients signed an informed consent before the initiation of hypofractionated IMRT. Eligibility criteria included being $\geq$18 years of age, Eastern Cooperative Oncology Group performance status $\leq$2, adequate renal (normal serum creatinine levels) and liver (total bilirubin level $<$2.5 times upper normal limit; serum transaminases levels $<$2.5 times upper normal limit) function, adequate bone marrow reserve (white blood cell count between 4000 and 12,000 mm^3, neutrophil count $>$ 2000 mm^3, platelet count $>$ 100,000 mm^3, hemoglobin $>$ 9.5 g/dL). Patient exclusion criteria consisted of synchronous tumors, cardiovascular disease, history of neurologic or psychiatric disorders, or previous abdominal-pelvis RT. All patients had biopsy-proven PAC judged unresectable and nonmetastatic by abdominopelvic computed tomography (CT) between May 2015 and May 2016. Magnetic resonance imaging of the abdomen-pelvis was performed in case of uncertain staging.

Criteria defining unresectability status were: (1) solid tumor contact with the superior mesenteric artery or celiac axis $>$180°, (2) body and tail tumor contact with the celiac axis and aortic involvement.

Hypofractionated intensity-modulated RT

All patients were immobilized by a custom made vacuum pillow and midline/lateral tattoo marks. A CT scan with 2 mm slice thickness was performed with oral contrast for delineation of surrounding OARs. Fusion images of CT scan and diagnostic CT/magnetic resonance imaging were used for 3D reconstruction and planning. Delineation of the gross tumor volume and the clinical target volume – defined as tumor lesion and surrounding edema – was performed by the radiation oncologist and the radiologist, both specialized in the gastrointestinal imaging. An

isotropic margin around the clinical target volume of 7 mm in all directions was added to form the planned target volume (PTV). The OARs contoured were the duodenum, the stomach, the liver, the kidneys, and the spinal cord. Once the treatment plan was finalized, total PTV volume and duodenal dosimetric parameters were collected, including duodenal mean dose, duodenal maximum dose (Dmax), and the percentage of the entire organ volume exposed to 5 Gy (V5) and 33 Gy (V33).

RT was delivered with IMRT technique at a planned dose of 52 Gy in 13 daily fractions, with 6-15 MV energy photons. Patient's position (vertebral spine) was checked by electronic portal imaging prior to each treatment. All patients had prophylactic ondansetron 8 mg during the treatment period and pantoprazol 40 mg daily for 4 weeks.

Follow-up

Patients were followed weekly on treatment and up to 6 weeks posthypofractionated IMRT. After treatment, patients were monitored at 3 monthly intervals for 2 years, then every 6 months thereafter. Patients were followed up closely to detect acute and late toxicities. Toxicity scoring was performed using the Common Terminology Criteria for Adverse Events, Version 4.0.[9] A total body CT scan was performed 3 months after the end of hypofractionated IMRT to assess disease response. Objective tumor response for target lesions was evaluated according to response evaluation criteria in solid tumors criteria.[10] Tumor markers carcinoembryonic antigen and carbohydrate antigen 19-9 were also determined.

Study end points and statistical analysis

Primary end point was objective tumor response. Objective tumor response was determined on radiologic imaging 3 months after the end date of RT. A complete response was defined as the disappearance of all target lesions and pathologic lymph nodes (whether target or nontarget) reduction in short axis to $<$10 mm. A partial response was defined as at least 30% reduction in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Progressive disease was defined as an increase of $\geq$20% in the sum of diameters of target lesions, taking as reference the smallest sum on imaging study. Stable disease was defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. Secondary end points included toxicity and compliance with the regimen, overall survival (OS), and disease-free survival (DFS). OS and DFS were calculated in months from the date of the diagnosis to the first event, including date of the last follow-up or death (OS) and/or relapse (DFS). Statistical analysis was carried out using R-Studio 0.98.1091 software. Standard descriptive statistics were used to evaluate the distribution of each factor. Continuous variables were presented as medians and ranges, and dichotomous variables were presented as percentages. Spearman correlation and linear regression were used to determine associations between dosimetric variables and clinical toxicities. Patient follow-up was updated to a minimum of at least 3 months. OS and DFS were estimated by the Kaplan-Meier method and times were reported with 95% confidence intervals (CI). All reported *P* values are 2 sided, and *P* values lower than 0.05 were considered significant.

Results

Patient characteristics

In total, 10 patients with biopsy-proven locally advanced PAC received hypofractionated IMRT. Table 1 summarizes the main demographics. There were 3 male and 7 female patients with

Table 1
Patient characteristics.

Characteristic	Value
Age (y)	
Median (range)	70 (55-85)
Gender	
Male	3
Female	7
Comorbidities	
No	3
Yes	7
TNM prognostic group	
Stage III	10
Tumor location	
Pancreas head	7
Pancreas body-tail	3
Regional lymph node status	
Negative	6
Positive	4

TNM, tumor/node/metastasis.

ages ranging from 55 to 85 years, median age 70 years. At diagnosis 4 patients had lymph node metastases.

Treatment compliance

All patients received the hypofractionated IMRT prescribed total dose (52 Gy in 13 fractions). Due to acute gastrointestinal toxicity, RT was interrupted in 2 patients for 2 and 4 days, respectively. None received concomitant chemotherapy for radiosensitizing purposes, according to study design. Eight patients had prior gemcitabine-based chemotherapy and its regimen was left to the oncologists' discretion. Patients did not develop metastatic disease while receiving systemic chemotherapy but surgical resection was still not feasible after induction chemotherapy. Two patients were not candidates for induction chemotherapy due to inadequate nutritional intake.

Toxicity and dosimetric parameters

Table 2 lists the observed toxicities. Gastrointestinal toxicity was the most common acute RT-related complication, and nausea/vomiting was the most frequent symptom (n = 5). Mild anemia was the main hematological sign (n = 7). There was no evidence of renal toxicity. Globally, severe toxicity (≥G3) was never observed. All toxicities were easily manageable with conservative measures.

Dosimetric parameters are presented in Table 3. The median volumes for pancreatic tumor were 97 cm^3 (range 56-269 cm^3) and the median Dmax exposed on duodenum was 52 Gy. Gastrointestinal toxicity was correlated to dosimetric variables. Higher duodenal Dmax ($\rho = 0.46$) and V5 ($\rho = 0.46$) were found to moderately correlate with greater gastrointestinal toxicity (Fig 1), whereas total PTV volume, duodenal duodenal mean dose, and V33 were not correlative.

Objective tumor response and survival

Objective tumor response at 3 months was complete response (n = 2), partial response (n = 2), and stable disease (n = 5). Only 1 patient had early progression leading to death within 3

Table 2
Hypofractionated intensity-modulated radiotherapy toxicity.

Toxicity	Grade		
	1	2	≥3
Gastrointestinal			
Diarrhea	1	.	.
Nausea	2	3	.
Vomiting	.	3	.
Pain			
Abdominal pain or cramping	2	1	.
Constitutional symptoms			
Fatigue	3	1	.
Fever	.	.	.
Blood count			
Hemoglobin	7	.	.
Leukocytes	.	2	.
Platelets	2	.	.

Table 3
Dosimetric parameters.

Dosimetric variables	Value	
	Median	Range
PTV volume	97 cm^3	56-269
Duodenal Dmax	52 Gy	40-55
Duodenal Dmean	11 Gy	4-32
Duodenal V5	32 Gy	25-50
Duodenal V33	16 Gy	10-38

D, dose; Gy, Gray; max, maximum; PTV, planning target volume; Vx, volume exposed to x Gy.

months after hypofractionated IMRT. Two patients with positive lymph nodes at diagnose down-staged after treatment. The median follow-up time after hypofractionated IMRT was 5 months (range, 3-12), The duration of response was from 3 to 12 months with the median of 3 months. The 1-year OS and 1-year DFS rates were 83.3% (95% CI 0.273-0.975) and 68.6% (95% CI 0.213-0.912), respectively. Kaplan-Meier survival curves are shown in Figure 2. Both curves have large 95% confidence bounds due to small number of patients contributing to them. Two patients presented distant metastasis to liver (n = 1) and lung (n = 1).

Discussion

This pilot study demonstrates that the hypofractionated IMRT regimen under investigation assures an optimal local control of nonmetastatic unresectable PAC, with minimal toxicity profile. Based on the moderate correlation between duodenal dosimetry and severity of gastrointestinal toxicity, it is true that duodenal dosimetric parameters should be considered when planning hypofractionated treatment. This study has a quite long follow-up of patients, with a minimum interval from diagnosis to hypofractionated IMRT of 1 month and a median of 8 months for those patients who received chemotherapy. This pilot hypofractionated scheme can stabilize quality of life and may help patients to maintain an adequate life quality. But, the small number of patients prohibits any major conclusions regarding the efficacy of hypofractionated IMRT. The theoretical advantages of the hypofractionated scheme mainly included: (1) overall treatment time reduction; (2) higher biologically equivalent radiation dose to conventional external beam RT (assuming an α/β ratio of 10 for rapidly proliferating tumor cells); (3) no delays in adjuvant systemic treatment. Taken together, these pros make hypofractionated IMRT an attractive option for patients with unresectable PAC. The goal is to prevent local progression, palliate pain, and

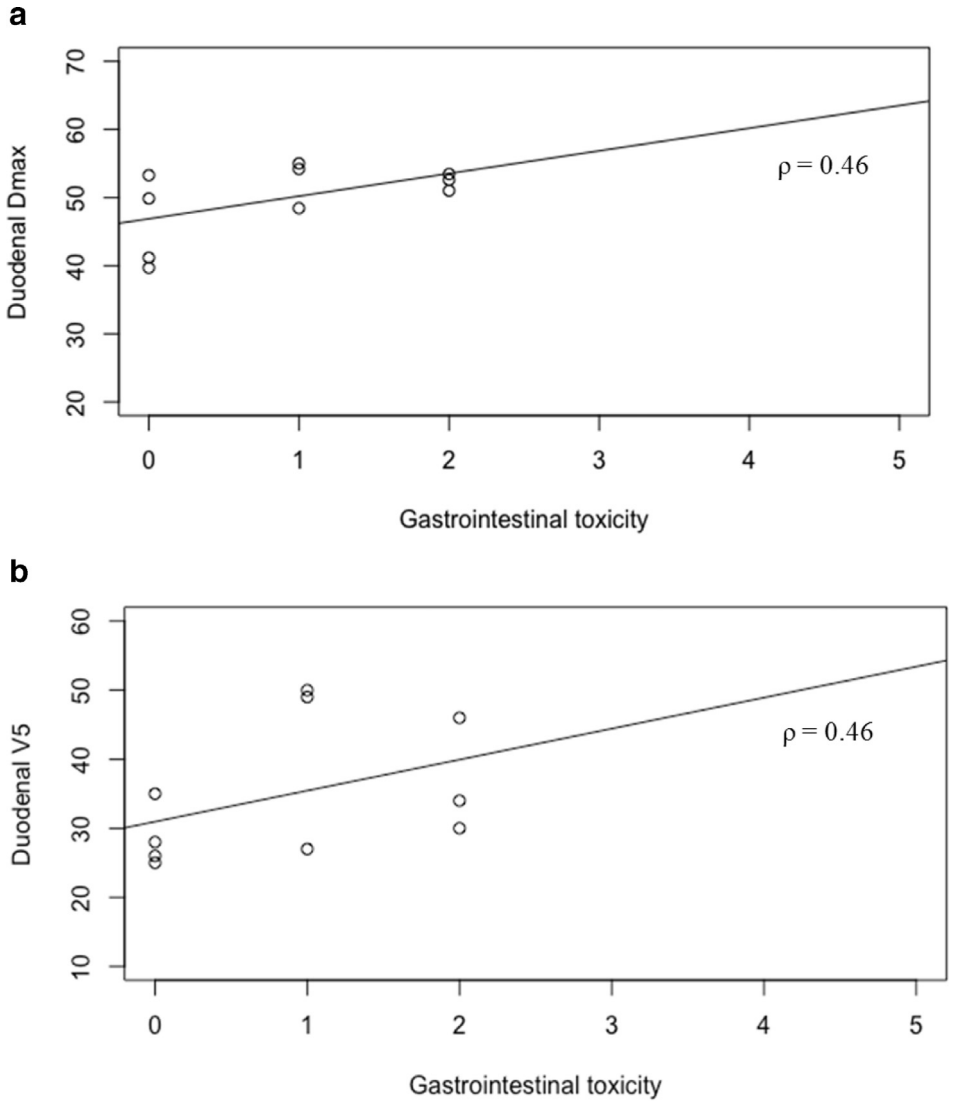

Fig. 1. Fit plots of correlation between gastrointestinal toxicity severity and duodenal maximum dose (Dmax) (a) and the percentage of the entire organ volume exposed to 5 Gy (V5) (b).

improve median survival, delivering dose only to gross tumor volume (plus a small margin) and decreasing treatment duration. Traditionally, RT in locally unresectable PAC includes the use of conventional 3-dimensional RT planning, targeting the primary tumor location and the areas of greatest subclinical tumor concentration. Realistically, daily conventional 3D-RT treatments for approximately 6 weeks can be very wearing for patient and his/her family, making RT completion difficult. For hypofractionated IMRT approach, a dose of 52 Gy in 4 Gy per fraction is given over 2.5 weeks, reducing treatment time and, consequently, problems with transportation, without apparent compromise in survival.

As yet, the hypofractionated IMRT for patients with nonmetastatic unresectable PAC has not been investigated. Recently Rakhra et al[11] reported the pooled data analysis of 3 high-volume US

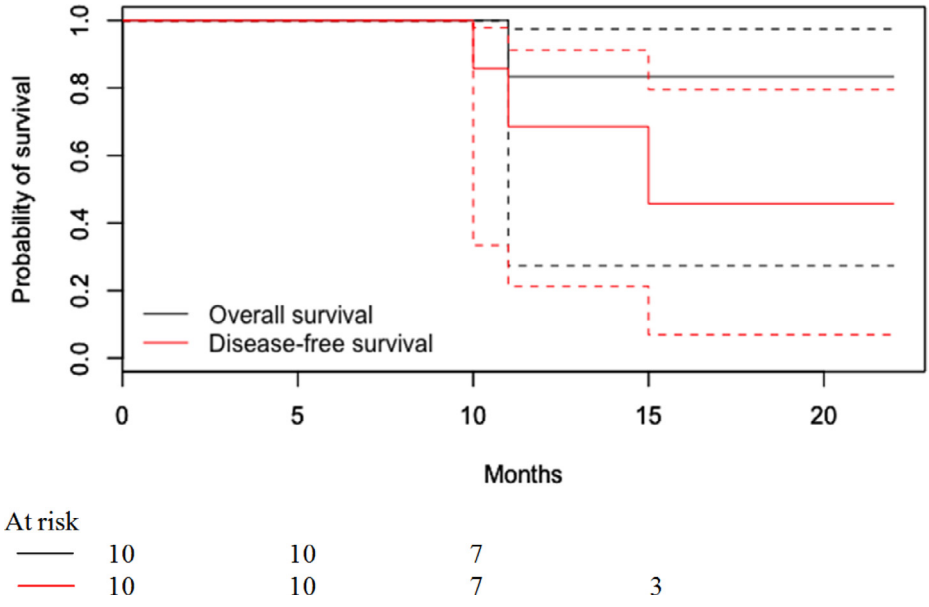

Fig. 2. Kaplan-Meier curves of overall survival and disease-free survival.

centers, testing hypofractionated RT, but with conformal technique. A total of 170 PAC patients, with nonmetastatic unresectable disease, were treated with either hypofractionated conformal RT with a concurrent full-dose gemcitabine-based regimen (n = 118) or standard fractionated RT with concurrent 5-fluorouracil (FU)-based chemotherapy (n = 52). Hypofractionated conformal RT (36-42 Gy, 2.4 Gy/fraction) was delivered to the gross disease, whereas standard fractionation RT (50.4 Gy, 1.8 Gy/fraction) to the gross disease and elective regional nodes. Results demonstrated that hypofractionated conformal RT was associated with improved survival without any increase in toxicity as compared to standard fractionation RT (1-year OS: 52% vs 36%). But interpretation of this data set is limited by its retrospective design in nature, as well as bias attributable to different chemotherapy regimen, different total RT dose or a combination of these factors.

Our results compare favorably with stereotactic series in PAC.[12] There are now different publications containing end results from various types of SBRT, alone or combined with chemotherapy.[13-19] Although the vast majority of these studies are heterogeneous in both the characteristics of patients evaluated and treatment end point definitions, median OS, and local control rates ranged from 5.7 months to 20 months, and from 57% to 100%, respectively. The concept of SBRT for inoperable patients was developed 2 decades ago, revolutionizing radio-resistant tumor management, due to ablative dose delivery within a course of treatment that does not exceed 5 fractions. But this technique requires modern linear accelerator with image-guided RT capabilities and sophisticated treatment planning software.[20] Moreover a careful immobilization, even if less comfortable, as well as a proper patient repositioning is paramount to guarantee a safe treatment. SBRT session takes up to 45 minutes – more time than conventional and hypofractionated IMRT – and it is mandatory to be sure that the patient does not shift his/her position during treatment. This issue could represent a major limit in PAC treatment. In fact, in a high percentage of cases, these patients are over 70 years of age and have problems to maintain position for long time.[21,22] Therefore, elderly PAC patients can benefit from hypofractionated IMRT leading to control the cancer in the most effective way possible and to maximally preserve their autonomy. Independently of patient's age, in these cases with poor estimated survival, several variables, including evaluation of comorbidities and functional, cognitive and psychosocial sta-

tus, should be considered to tailor the best cancer therapy for the individual patient, mainly to achieve a disease control. With hypofractionated IMRT, the intensification of dose implies a more accurate OARs constraints, especially in duodenum Dmax and dose-volume parameters. To reduce severe gastrointestinal toxicity onset, our dosimetric results are in agreement with recommendations based on the national comprehensive cancer network guidelines, as well as specific dose constraints reported in several SBRT studies.[4,14,16,23-25] The analysis by Brunner et al[26] demonstrated that increasing biological equivalent dose resulted in improved local control in SBRT for pancreatic cancer. But the authors also found reduced survival with dose (beyond 75 Gy biological equivalent dose) which they explained by a possible increase in morbidity related to the treatment. This may motivate for use of less hypofractionated RT regimens as the one presented in the present study.

The strength of this paper is the prospective nature of the study. The weakness is the small number of patients. Our hypofractionated IMRT experience will be amplified and more easily judged when the final data have matured. However, it is doubtful that we will be able to determine the relative value of hypofractionated IMRT vs SBRT without a prospective randomized trial of the 2 RT strategies. Further research will be needed to verify these data and a cost-utility analysis should be performed to capture the hypofractionated IMRT cost effectiveness compared to other modalities.

In hopes of promoting consistency in a future trial, this hypofractionated IMRT regimen should be entirely representative of a valid option in unresectable PAC multidisciplinary management.

Conclusion

Hypofractionated IMRT can be considered an emerging application in the management of unresectable PAC, with promising early results in term of durable local control and minimal toxicity. Large scale trial is further required to support its potential role and establish its relevance in comparison to more sophisticated RT techniques.

Clinical Practice Points

- Pancreatic cancer is a relative rare malignancy, with an increase in cases occurring in locally advanced unresectable stage.
- The optimal treatment approach is currently a matter of debate.
- On the basis of the improved patients' quality of life, the hypofractionated intensity-modulated RT has been tested.
- Hypofractionated intensity-modulated RT seems promising in locally advanced unresectable pancreatic patients.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2019.04.003.

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