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FULL PAPER

Is there an oligometastatic state in pancreatic cancer? Practical clinical considerations raise the question

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Objectives: To evaluate the role of stereotactic body radiotherapy (SBRT) as a local ablative treatment (LAT) in oligometastatic pancreatic cancer.
Methods: Patients affected by histologically confirmed stage IV pancreatic adenocarcinoma were included in this analysis. Endpoints are local control (LC), progression-free survival (PFS), and overall survival (OS).
Results: From 2013 to 2017, a total of 41 patients were treated with SBRT on 64 metastases. Most common sites of disease were lung (29.3%) and liver (56.1%). LC at 1 and 2 years were 88.9% (95% CI 73.2–98.6) and 73.9% (95% CI 50–87.5), respectively. Median LC was 39.9 months (95% CI 23.3—not reached).
PFS rates at 1 and 2 years were 21.9% (95% CI 10.8–35.4) and 10.9% (95% CI 3.4–23.4), respectively. Median PFS was 5.4 months (95%CI 3.1–11.3).
OS rates at 1 and 2 years were 79.9% (95% CI 63.7–89.4) and 46.7% (95% CI 29.6–62.2). Median OS was 23 months (95%CI 14.1–31.8).
Conclusions: Our results, although based on a retrospective analysis of a small number of patients, show that patients with oligometastatic pancreatic cancer may benefit from local treatment with SBRT. Larger studies are warranted to confirm these results.
Advances in knowledge: Selected patients affected by oligometastatic pancreatic adenocarcinoma can benefit from local ablative approaches, like SBRT

INTRODUCTION

Despite the significant progress in early diagnosis and the therapeutic improvements over the last decades, the prognosis of pancreatic cancer patients remains dismal. Many patients present with metastatic disease at the time of diagnosis or early develop distant metastases.

As a result of the poor prognosis, the number of therapeutic strategies investigated to extend survival is increasing.

Historically, the standard treatment for metastatic pancreatic tumor was systemic chemotherapy based on gemcitabine with a median overall survival (OS) of about 7 months.[1] More aggressive regimen with FOLFIRINOX (folinic acid- fluorouracil-irinotecan-oxaliplatin) or nab-paclitaxel–gemcitabine improved outcomes with a median OS of 11.1 and 8.5 months, respectively.[2,3]

Oligometastatic pancreatic cancer with a durable stable disease may represent a favorable clinical scenario, opening a crucial prospective for the integration of ablative local therapies in the therapeutic pathway of these patients.[4,5]

The use of stereotactive body radiotherapy (SBRT) was investigated in different settings of primary and oligometastatic disease with encouraging results, utilizing either a single dose or a small number of fractions.[6]

In the last years, the integration of SBRT and systemic therapies provided promising results in the treatment of locally advanced unresectable pancreatic cancer.[7–9]

On the other hand, SBRT approach has been shown to be an effective treatment for inoperable liver and lung metastases,[10,11] particularly in terms of local control (LC).

Different from conventional radiotherapy, SBRT entails precise delivery of high dose in few fractions, with a complete tumor ablation and maximal normal tissue sparing.[12]

Considering the non-invasiveness, the safety, and the efficacy, SBRT represents an ablative local therapy that provides an additional tool in the multimodal treatment of oligometastatic pancreatic cancer.

Aim of current study was to evaluate efficacy of SBRT in these selected setting of patients.

METHODS AND MATERIALS

Study population

In our analysis, we included patients with histologically confirmed diagnosis of pancreatic adenocarcinoma, who developed metachronous or synchronous metastases. We selected patients with a performance status of 0–2, treatment-naïve or previously treated with chemotherapy. Systemic treatment was allowed during and after SBRT. We excluded metastases already locally treated. A maximum of five metastases in up to two sites was allowed. Patients were categorized as oligometastatic *de novo* if they did not previously receive any kind of active therapy, apart primary treatment if oligometastases were metachronous. Patients were considered as "induced oligometastatic" if they had received systemic or other local ablative therapies in their history for metastatic disease. Finally, we also included in this analysis oligoprogressive patients (up to three progressing metastatic sites with all other sites stable or responding to a previous or concurrent medical therapy). Staging was performed with CT, MRI, and/or PET scan according to physician choice. All cases were discussed at the multidisciplinary tumor board and the local ethic committee approved the analysis. The study was conducted in accordance with Good Clinical Practice guidelines, the ethical principles of the Declaration of Helsinki and local regulations. All patients signed informed consent.

Techniques of radiotherapy

In all patients, we delineated the clinical target volume (CTV) with a simulation CT imaging, using a coregistration with MRI scan or PET scan in selected cases. Gross tumor volume (GTV) was equal to CTV and an additional 5 to 10 mm margin was added to CTV to design the planning target volume (PTV). In order to avoid reducing the internal organ movement, we used abdominal compression in case of liver lesions, and we obtained a simulation with a 4D-CT scan in case of moving targets (*e.g.*, lung or liver lesions).

Response assessment

Response to therapy was assessed 3 months after the end of the SBRT, then every 3 months for the first year and every 6 months from the second year. The regular follow-up assessment consisted of clinical evaluation and an imaging exam (CT, MRI, or PET) according to physician preference. Tumor response was graded according to European Organization for Research and Treatment of Cancer Response Evaluation Criteria In Solid Tumors (EORTC-RECIST) criteria v. 1.16. We used PET Response Criteria in Solid Tumors (PERCIST) to assess metabolic response in patients who underwent PET scan for restaging.

Statistical analysis

This was a retrospective single-center analysis. As endpoints, we selected LC, progression-free survival (PFS), and OS. LC was defined as the time from the beginning of SBRT to the progression of treated metastases or last follow-up. PFS was calculated from the beginning of SBRT to the progression of in-field or out-field metastases, while OS was defined as the time from the beginning of SBRT to either death or last follow-up.

We used the log-rank test to perform the univariate analysis and Cox proportional hazards regression to estimate hazard ratios (HR); we ran a multivariable stepwise cox regression analysis with a significance level of $p < 0.05$. Statistical calculations were performed using STATA, v. 13.

RESULTS

From 2013 to 2017, a total of 41 patients were treated with SBRT on 64 metastases. Median age was 66.3 (range 43.5–80.8) and median time from diagnosis of primary tumor to metastatic setting was 17.2 months (range 0–54.2). Most patients (33, 80.5%) underwent surgical removal of the primary tumor, eight of them also received adjuvant chemotherapy and radiotherapy, while 17 received only adjuvant chemotherapy. Performance status was 1 and 2 in 19 (46.3%) and 2 (4.9%) patients, respectively. Majority of patients were treated on *de novo* appearance of metastases (46.3%), followed by induced oligometastatic state (41.5%) and oligoprogressive state (12.2%). Only seven (17.1%) patients were naïve to systemic therapy at time of SBRT and 25 (61%) patients were treated on one single lesion. Most common sites of disease were lung (29.3%) and liver (56.1%). Five (12.2%) patients had extra target lesions not treated with SBRT. Median biologically effective dose (BED) was 105.6 (57.6–262.5).

Tables 1–3 summarize patients and treatment characteristics.

Median follow-up was 23 months (95% CI 14.1–31.8). Best local response was classified as complete response in 12 (29.4%) patients, partial response in 19 (46.3%) patients, stable disease in nine (21.9%) patients and progressive disease in one (2.4%) patient (Table 4). LC at 1 and 2 years were 88.9% (95%CI 73.2–98.6) and 73.9% (95%CI 50–87.5), respectively (Figure 1). Median LC was 39.9 months (95% CI 23.3–not reached). At univariate analysis, none of the analyzed factor impacted on LC.

Distant progression rates at 1 and 2 years were 25.6% (95%CI 13.4–39.8) and 13.2% (95%CI 4–27.1); median distant PFS was 5.8 months (95% CI 3.2–14.7). At univariate analysis for distant PFS, sex (HR 2.32, 95% CI 1.12–4.78;$p = 0.047$) and the presence of extra target disease (HR 2.75, 95% CI 1.01–7.34; $p = 0.047$) were statistically significant. At multivariable analysis for distant PFS, sex (HR 3.21, 95% CI 1.44–7.13;$p = 0.004$) and the presence of extra target disease (HR 5.04, 95% CI 1.65–15.3; $p = 0.004$) continued to be significant.

PFS rates at 1 and 2 years were 21.9% (95% CI 10.8–35.4) and 10.9% (95% CI 3.4–23.4), respectively (Figure 2). Median PFS was 5.4 months (95% CI 3.1–11.3). For PFS, sex (HR 2.50, 95% CI 1.20–5.20; $p = 0.014$), time to metastases (HR 0.96,

Table 1. Patients' characteristics

	Number (%)
Sex	
0	22 (53.6)
1	19 (46.3)
Age, median (range)	66.3 (43.5–80.8) years
Time to metastatic status	17.2 (0–54.2) months
Age at metastatic status	66.9 (44.9–81.9) years
Performance status	
0	20 (48.8)
1	19 (46.3)
2	2 (4.9)
Comorbidities	
No	6 (14.6)
Yes	35 (85.4)
Time from mets to SBRT, median (range)	8.7 (0–44) months
Ca 19.9, median (range)	53 (10–3453)
Missing data:	21 pts
Type oligometastatis status	
De novo	19 (46. 3)
Induced	17 (41.5)
Oligoprogression	5 (12.2)
Timing of metastases	
Synchronous	2 (4.9%)
Metachronous	39 (95.1%)

Table 2. Previous treatments characteristics

Primary treatment	
Radiotherapy	3 (7.3)
Chemotherapy	4 (9.7)
Surgery	8 (19.5)
RT-CHT	2 (4.9)
MT +surgery	16 (39)
Surgery +RT-CHT	8 (19.5)
Previous local tx	
No	24 (58.5)
Yes	17 (41.5)
Previous chemotherapy	
No	7 (17.1)
one line	16 (39)
two lines	12 (29.3)
three or more lines	6 (14.6)
Chemotherapy before SBRT	
Gem +Nabpaclitaxel	10 (24.4)
FOLFOX/XELOX	6 (14.6)
FOLFIRINOX	6 (14.6)
Gemcitabine	20 (48.8)
5FU / Capecitabine	2 (4.9)
GEMOX	3 (7.3)
Cis +Gem	3 (7.3)
Irinotecan	2 (4.9)
Chemotherapy during SBRT	
Gemcitabine	2 (4.9)
Chemotherapy after SBRT	
Gem +Nabpaclitaxel	1 (2.4)
Gemcitabine	2 (4.9)
5FU / Capecitabine	1 (2.4)
Irinotecan	4 (9.7)

95% CI 0.94–0.99; p = 0.034), extra target disease (HR 3.60, 95% CI 1.32–9.81; p = 0.012), BED (HR 1.00, 95% CI 1.00–1.01; p = 0.033) were impacting. At multivariable analysis, sex (HR 4.59, 95% CI 1.90–11; p = 0.001), time to metastases (HR 0.96, 95% CI 0.93–0.99; p = 0.031) and extra target disease (HR 7.36, 95% CI 2.24–24.15; p = 0.001) were statistically significantly associated to PFS.

OS at 1 and 2 years were 79.9% (95% CI 63.7–89.4) and 46.7% (95% CI 29.6–62.2), respectively (Figure 3). In terms of OS, univariate analysis showed that time to metastases (HR 0.95, 95% CI 0.91–0.99; p = 0.036) and BED (HR 1.00, 95% CI 1.00–1.01; p = 0.017) were statistically significant. No factor was significant at multivariate analysis.

DISCUSSION

We reported a single institution retrospective experience on the use of SBRT for oligometastatic pancreatic cancer. Despite the raising interest toward the use of local ablative therapies for oligometastases, patients affected by pancreatic cancer are poorly represented in the main published series. However, our analysis shows that an oligometastatic state could exist also in this setting of patients. We observed a median OS of 23 months, OS at 1 and 2 years were 79.9% (95% CI 63.7–89.4) and 46.7% (95% CI 29.6–62.2), respectively. PFS rates at 1 and 2 years were 21.9% (95% CI 10.8–35.4) and 10.9% (95% CI 3.4–23.4). Median PFS was 5.4 months.

These results are worse if compared with those obtained in a larger series of patients with oligometastatic disease from any primary (median OS 34 months, median PFS 8.7 months).[13] However, considering the dismal prognosis of pancreatic carcinoma when compared with almost all other solid tumors, these survival rates still support the existence of a limited setting of oligometastatic patients. Moreover, compared with results obtainable with standard chemotherapies for metastatic pancreatic adenocarcinoma, our results seem to be very encouraging.[1,2]

Table 3. SBRT characteristics

Number of treated lesions, median (range)	1 (1–4)
1	25 (61)
2	10 (24.4)
3	5 (12.2)
4	1 (2.4)
Site of treated metastases	
Lung	12 (29.3)
Liver	23 (56.1)
Lymph node	5 (12.2)
Lung and liver	1 (2.44)
Extra target lesions	
No	36 (87.8)
Yes	5 (12.2)
BED, median (range)	105.6 (57.6–262.5)
Ablative dose	
No	11 (26.8)
Yes	30 (73.2)
Systemic therapy during SBRT	
No	39 (95.1)
Yes	2 (4.9)
SBRT dose	
Lung:	
32 Gy 4 fx	1 (2.4)
48 Gy 4 fx	11 (26.8)
60 Gy 8 fx	1 (2.4)
Liver:	
45 Gy 6 fx	3 (7.3)
48 Gy 3 fx	1 (2.4)
48 Gy 6 fx	2 (4.9)
54 Gy 3 fx	1 (2.4)
54 Gy 6 fx	3 (7.3)
60 Gy 3 fx	5 (12.2)
60 Gy 6 fx	3 (7.3)
63 Gy 6 fx	1 (2.4)
67.5 Gy 3 fx	2 (4.9)
75 Gy 3 fx	3 (7.3)
Lymph node:	
36 Gy 6 fx	1 (2.4)
45 Gy 6 fx	3 (7.3)
48 Gy 4 fx	1 (2.4)
Systemic therapy after SBRT	
No	32 (78.1)
Yes	9 (21.9)

The key question also is how we can predict the prognosis and distinguish a real oligometastatic patient (with an indolent disease, taking advantage from local ablative therapies) from a false oligometastatic patient, in which the radiologically evident disease is just the tip of the iceberg.

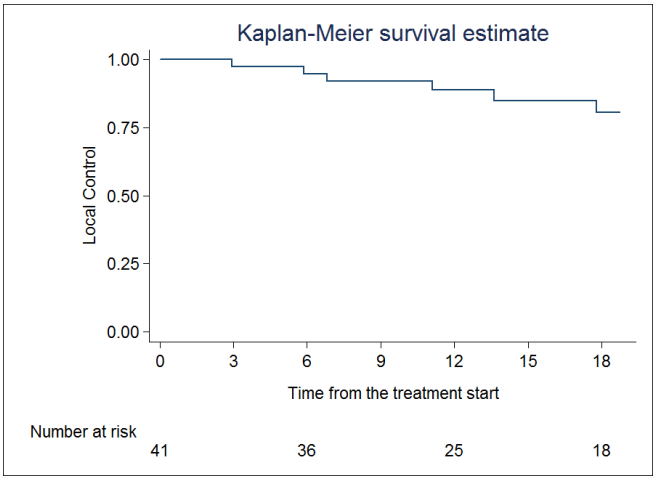
There are few available data in literature about clinical factors able to identify oligometastatic patients. Performance status, multiple metastases, large metastases (>3 cm), metachronous metastases, and pre-SBRT chemotherapy were found as poor prognostic factors by Fode et al.[14] In a similar series, De Vin et al highlighted a relationship between histology, disease-free interval (DFI), site of metastases, and gender, with survival.[15] A recursive partitioning analysis (RPA)[16] based on clinical parameters (primary histology, DFI, number of metastases, age and metastatic site) allowed the discrimination of five different prognostic classes for OS. In our previous experience on oligometastatic patients from different histologies, site of metastases, primary histology, age, local response of the irradiated lesion(s), and presence of extra target disease were all factors related with survival.[13]

The main limitation of these studies is the heterogeneity of analyzed patients, including different primary tumors, histologies, metastatic sites, etc. Therefore, they can give just some indications, not easily applicable in specific disease settings, like pancreatic adenocarcinoma. Indeed, pancreatic cancer is usually not represented in these large database analyses, probably included in the miscellaneous histologies, usually indicated as "others."

Table 4. SBRT and patients outcome

Best local response	
CR	12 (29.4)
PR	19 (46.3)
SD	9 (21.9)
PD	1 (2.4)
Local progression	
No	33 (80.5)
Yes	8 (19.5)
Distant progression	
No	6 (14.6)
Yes	35 (85.4)
Last status	
Ned	3 (7.32)
Alive with metastases	11 (26.8)
Death of disease	25 (60.1)
Death other causes	2 (4.9)

Figure 1. Local control



To the best of our knowledge, the present work is the first aimed at identifying prognostic factors that could predict PFS, OS or LC in oligometastatic pancreatic cancer.

From our data, the presence of extra target disease (*i.e.,* disease controlled by systemic therapy and not directly irradiated) is a predictor of shorter PFS. From this observation, we could derive two possible conclusions. The first message is that, if technically feasible, all visible disease should be irradiated with ablative purposes. Our data are consistent with those reported by Xu et al in oligoprogressive non-small cell lung cancer, where the authors showed that treating just a part of the macroscopic disease with local ablative therapies was less beneficial than treating all visible disease.[17]

Another prognostic factor, predicting both PFS and OS in our patients was the DFI from primary diagnosis to metastases occurrence. Similar observations were reported by Wong and Hong in their studies.[16,18] While Wong suggested DFI as a continuous variable as in our experience, Hong et al used a cut-off of 75 months to separate patients in five different prognostic classes.

Figure 2. Progression-free survival

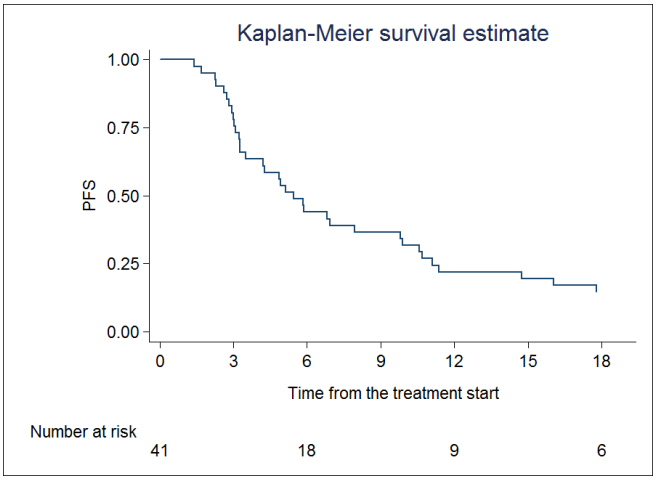
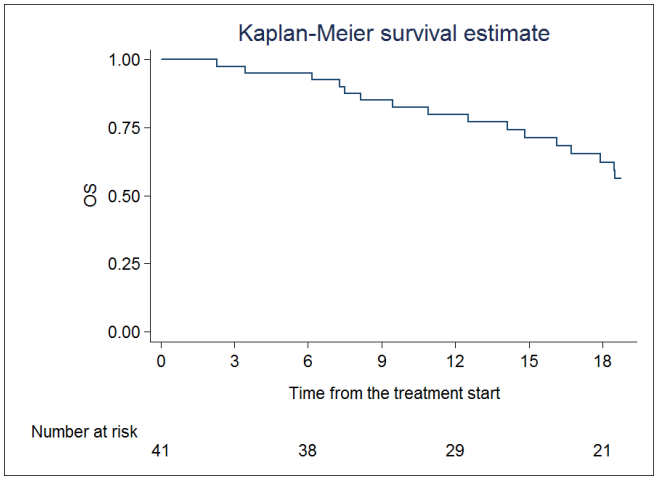


Figure 3. Overall survival



Interestingly, also the dose of RT was correlated with OS in our experience. The delivery of a really ablative dose is necessary to have a real impact on the patients' survival.

Also, Salama et al in a dose escalation trial showed that higher doses are related with higher LC rates.[19] Although with a lower median BED, also Hong et al correlated BED with OS. Indeed, they found that patients treated with BED of >75 had a 3-year OS of 61% compared to 43% (95% CI 34±54%) for those treated with BED <75. Also, PFS and LC were correlated with BED, differently from our results.

Clinical parameters are the easiest to use in the clinical practice as predictive tools for survival, however they are just a surrogate of a different biology of the disease. Therefore, circulating biomarkers, like microRNAs or circulating tumor cells, could give a more realistic picture of the disease behavior. For example, analyzing three different (miR-23b, miR-449a, and miR-449b) researchers were able to identify two different groups of oligometastatic patients with a different prognosis.[18] Similar analysis could be helpful also in identifying oligometastatic pancreatic patients.

Considering a recent study by the University of Texas MD Anderson Cancer Center, in which the genetic mutation/deletion status of the SMAD4 gene was correlated with patterns of recurrence in patients with metastatic disease,[20] this gene could represent a good starting point also in oligometastatic patients.

The implementation of this line of research and the identification of tumor-specific biomarker predictors for local and distant recurrence could guide the patient selection and the choice of therapies toward the integration of systemic and local therapies, such as SBRT.

CONCLUSION

Our results, although based on a retrospective analysis of a small number of patients, show that patients with oligometastatic pancreatic cancer may benefit from local treatment with SBRT.

Further investigations are required for a better definition of a real oligometastatic state and for a better integration of local and systemic therapies.

ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

PATIENT CONSENT

Informed consent was obtained from all individual participants included in the study.

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