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Hypofractionated radiotherapy concomitant to capecitabine after induction chemotherapy for advanced pancreatic adenocarcinoma

Paolo Passoni [a,*], Michele Reni [b,e], Sara Broggi [c], Najla Slim [a], Andrei Fodor [a], Marina Macchini [b], Giulia Orsi [b,e], Umberto Peretti [b], Gianpaolo Balzano [d], Domenico Tamburrino [d], Giulio Belfiori [d], Stefano Cascinu [b,e], Massimo Falconi [d,e], Claudio Fiorino [c], Nadia Di Muzio [a,e]

[a] Department of Radiation Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy
[b] Department of Medical Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy
[c] Medical Physics, IRCCS San Raffaele Scientific Institute, Milan, Italy
[d] Department of Pancreatic Surgery, IRCCS San Raffaele Scientific Institute, Milan, Italy
[e] Vita-Salute San Raffaele University, Milan, Italy

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ABSTRACT

Background and purpose: To assess feasibility, toxicity and outcome of moderately hypofractionated radiotherapy concomitant to capecitabine after induction chemotherapy for advanced pancreatic cancer.

Materials and methods: Patients with advanced pancreatic cancer without distant progression after induction chemotherapy (CHT) were considered. Radiochemotherapy (RCT) consisted of 44.25 Gy in 15 fractions to the tumor and involved lymph-nodes concomitant to capecitabine 1250 mg/m^2/day. Feasibility and toxicity were evaluated in all pts. Overall survival (OS), progression free survival (PFS), distant PFS (DPFS) and local PFS (LPFS) were assessed only in stage III patients.

Results: 254 patients, 220 stage III, 34 stage IV, were treated. Median follow up was 19 months. Induction CHT consisted of Gemcitabine (35 patients), or drug combination (219 patients); median duration was 6 months. Four patients (1.6 %) did not complete RT (1 early progression, 3 toxicity), median duration of RT was 20 days, 209 patients (82 %) received $\geq$ 75 % of capecitabine dose.

During RCT G3 gastrointestinal toxicity occurred in 3.2% of patients, G3-G4 hematologic toxicity in 5.4% of patients. Subsequently, G3, G4, G5 gastric or duodenal lesions occurred in 10 (4%), 2 (0.8%) and 1 patients (0.4%), respectively.

Median PFS, LPFS, and DPFS were 11.9 months (95 % CI:11.4–13), 16 months (95 % CI:14.2–17.3) and 14.0 months (95 % CI:12.6–146.5), respectively.

Median OS was 19.5 months (95 % CL:18.1–21.3). One- and two-year survival were 85.2 % and 36 %, respectively.

Conclusions: The present schedule of hypofractionated RT after induction CHT is feasible with acceptable toxicity rate and provides an outcome comparable with that achievable with standard doses and fractionation.

Introduction

The optimal treatment strategy for locally advanced pancreatic cancer (LAPC) is matter of debate. When the present study was developed, a systematic review on radiochemotherapy (RCT) for LAPC concluded that RCT was not superior to chemotherapy (CHT) in terms of survival and increased toxicity [1].

Considered the frequent metastatic dissemination of LAPC, many Authors from different Institutions, including ourselves, tested induction CHT followed by RCT in patients without progression [2]. Median overall survival (OS) reported by studies that used this approach were 11.6–17 months, comparing favourably against the two treatments delivered separately [3–10], convincing us in applying this promising strategy (induction CHT followed by RCT). More recently, LAP07 trial found that median OS was not significantly different in patients treated with CHT alone vs patients treated with induction CHT followed by RCT:

* Corresponding author at: Department of Radiotherapy, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy.
E-mail address: passoni.paolo@hsr.it (P. Passoni).

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locoregional progression was less frequent in RCT group whereas systemic progression was less common in CHT group [11].

Hypofractionation offers advantages in term of patient and device engagement. The choice of a hypofractionated regimen should be based on radiobiological consideration in order to balance tumor control and toxicity. We opted for a moderately hypofractionated regimen in 15 fractions having biological equivalent dose (BED) comparable to (or slightly higher than) standard doses and fractionation.

We report feasibility, toxicity and efficacy of our protocol [12] of moderately hypofractionated RT after induction CHT for advanced pancreatic cancer (APC) patients.

Materials and methods

Study design and eligibility criteria

The first step consisted of a phase I study delivering 44.25 Gy in 15 fractions to tumor and involved lymph-nodes and a simultaneous integrated boost (SIB) from 48 to 58 Gy to infiltrated vessels concomitant to capecitabine after induction chemotherapy. This phase I study was approved by our Institutional Ethical Committee. A minimum of three patients were treated at each dose level, twenty-five patients were enrolled: despite encouraging results [12], a trend of increase of toxicity with SIB was reported suggesting to deliver higher dose only to selected patients, as explained later [13].

Then, the original protocol was amended and a new observational trial started. All patients provided written informed consent before the start of RCT. Data were retrospectively analysed.

This RT schedule, 44.25 Gy in 15 fractions, was chosen in order to have a biological effective dose (BED) comparable with standard doses and fractionation in about half fractions.

Taking into account the repair rate and delay time to re-population parameters, BED is approximated by formula:

$$BED = nd(1 + d/\alpha/\beta) - \gamma/\alpha(T - TK) \quad (1)$$

where n is the number of fractions; d the daily dose; γ/α the repair rate (assumed to be around 0.6 Gy/day); T the total treatment time (19 days); T_K the proliferation delay (7 days) [14–16]. The resulting BED10 of 44.25 Gy in 15 fractions, 50.4 Gy, and 54 Gy, 1.8 Gy/Fr, were 50 Gy, 48 Gy and 51 Gy, respectively.

Patients were restaged after induction chemotherapy and discussed at multidisciplinary meetings. Considered for RCT were: 1) stage III patients (AJCC/International Union against Cancer (UICC) tumor–node–metastasis (TNM) staging 7th edition) still deemed not resectable, including patients with local progression after chemotherapy, 2) stage IV patients still with complete response of metastases for at least 4 months after induction chemotherapy. Additional inclusion criteria were age 18–80 years, Karnofsky performance-status $\geq$ 70, adequate bone marrow, renal and hepatic function.

Radiotherapy procedure

RCT started 2–4 weeks after induction chemotherapy, apart stage IV patients as described above. Enrolled patients underwent simulation contrast-enhanced computed tomography (CT) and FDG-PET/CT. Primary tumor and enlarged lymph-nodes were defined as GTV. ITV was defined as GTV plus margins of 0.5 in axial and 1.0 cm in cranial-caudal directions. PET positive volume, named Biological Target Volume (BTV), was merged with ITV. ITV/BTV was isotropically expanded of 0.5 cm to generate PTV. A dose of 44.25 Gy in 15 fractions was prescribed to PTV concomitant to capecitabine, 1250 mg/day weekends included.

Stomach, duodenum, liver, kidneys and spinal cord were contoured as organs at risk. Based on a previous study [13], constraints for stomach were: D2%<40 Gy, D25%<36 Gy; constraints for duodenum were: V38 < 30 %, D33%<36 Gy. The overlap between stomach + duodenum and PTV was also defined. Dose prescription to the overlap was 44.25/43.25/42.25 Gy, when overlap volume was <14 cc/<30 cc/30–50 cc. respectively. In case of overlap > 50 cc or dose constraints not respected, 40 Gy in 15 fractions was prescribed (BED_{10} = 43 Gy using formula (A)).

As previously mentioned, a group of patients received an additional boost to a PTV obtained from the infiltrated vessels (48–58 Gy). In addition, 48 Gy to whole PTV (BED_{10} = 56.2 Gy using formula (A)) was prescribed for selected patients with favourable tumor dimensions or tumor anatomic site and respected dose constraints.

All treatment plans were generated using the Tomotherapy® planning optimization system.

A megavoltage CT was performed before each RT fraction and co-registered with the planning CT by means of automatic matching followed by manual correction: tumor surrogate for image guidance when pancreas was not sufficiently visible were anatomic landmarks such as biliary stent, origin of regional arteries and veins.

Patients were examined once a week during the therapy by radiation and medical oncologists. During the follow up, complete history, physical examination, laboratory values CA 19.9 included, and contrast enhanced CT scan were planned every 2–3 months. Patients were followed up for toxicity and outcome until death. Adverse events were classified as acute or late when occurring during the treatment and within 3 months after RCT completion or after 3 months, respectively. Toxicity was scored by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5): the worst score of acute and late toxicity was reported.

Statistical analysis

All treated patients were considered evaluable for feasibility and toxicity but only patients with stage III disease were considered for outcome. Outcome of Stage IV patients will be analysed in a dedicated paper. Kaplan-Meyer curves were estimated both for outcome and toxicity. Progression free survival (PFS), local progression free survival (LPFS), distant progression free survival (DPFS), and overall survival (OS) were defined as the time from the date of CHT initiation to progression or death, to local progression, to distant metastases, and death, respectively. Local progression was defined as progression in the irradiated volume according to RECIST criteria. Time to grade > 2 mucosal toxicity was calculated from the end of the radiotherapy treatment. Patients who died without having late toxicity were censored from toxicity analysis.

Statistical analyses were performed using the MedCalc package (v 15, MedCalc Inc.).

Results

Patient characteristics

From November 2004 to November 2019, 254 patients were treated. Main characteristics of patients are summarized in Table 1. Two hundred and twenty patients had stage III disease, including 22 (10 %) with local progression after induction chemotherapy, and 34 patients had stage IV. All patients received induction chemotherapy. Two hundred and nineteen patients received a combination with at least two drugs, 35 patients received single agent chemotherapy (Table 2). Median duration of chemotherapy was 6 months (range 1–17 months).

Feasibility and toxicity

All 254 patients were evaluable for feasibility and toxicity.

Four pts (1.6 %) did not complete RCT (1 early progression, 3 gastrointestinal toxicities). Twenty-five patients (11 %) received SIB inside the phase I study. We considered this group evaluable also for outcome because SIB was prescribed only to small tumor sub-volume

Table 1
Characteristics of patients.

	Nr
Enrolled patients	254
Age, years, median (range)	66 (40–84)
Male/female (%)	118/136 (46/54)
Median KPS* (range)	90 (70–100)
Histology (%)	
Ductal Adenocarcinoma	250 (98)
Cystadenocarcinoma	2 (0.8)
High grade carcinoma	2 (0.8)
Stage III (%)	220
Lost after radiochemotherapy	3 (1.2)
Evaluable for outcome	217 (98)
Local progression after induction CHT**	22 (10)
Stage IV (stable CR*** of metastases)	34
Location of primary tumor (%)	
Head	141 (55)
Isthmus	30 (12)
Body	58 (23)
Tail	25 (10)

*KPS = Karnofsky performance status; **CHT = Chemotherapy.
*** CR = complete response;

Table 2
Chemotherapy regimens.

Regimen	Nr. pts (%)	Period (years)
Multiple agents		
PEXG	75 (30)	2005–2013
PDXG	14 (5)	2006–2008
PAXG	42 (16)	2013–2019
AG	74 (29)	2014–2019
Folfirinox	7 (3)	2015–2019
GEMOX	5 (2)	2009–2013
Other	2 (0.7)	2009–2014
All	219 (86)	
Single agent		
Gemcitabine	28 (11)	2009–2019
Capecitabine	7 (0.7)	2008–2014
All	35 (14)	

PEXG: cisplatin, epirubicin, capecitabine, gemcitabine [17]. PDXG: cisplatin, docetaxel, capecitabine, gemcitabine [17]. PAXG: cisplatin, nab-paclitaxel, capecitabine, gemcitabine [18]. AG: nab-paclitaxel, gemcitabine [18]. Folfirinox [19]. GEMOX: gemcitabine, oxaliplatin [20].

infiltrating vessels. Thirty-five (13.7 %) patients received 48 Gy to the whole PTV. Thirty-one (12 %) patients received 40 Gy (Table 3). The planned and median duration of radiotherapy were 19 and 20 days respectively. One hundred twenty-six patients (50 %) completed the treatment in 19–20 days, 96 patients (38 %) in 21–23 days, and 28 patients (11 %) in 24–28 days.

One hundred and ninety-eight patients (78 %) received 100 % of capecitabine dose, 11 patients (4 %) received 75–99 %, 16 patients (6 %) received 50–74 % and 4 patients (1.6 %) less than 50 %. The percentage of dose really taken could not be calculated in 8 patients (3 %). Seventeen patients (7 %) did not receive concomitant chemotherapy due to incomplete jaundice resolution (1 patient), patient's refusal (1 patient), not reported reason (1 patient), persistent toxicity after induction CT (14 pts).

Table 3
Number of patients, grouped by stage, who received the doses of RT foreseen by the protocol.

	Doses of RT				
Stage	44.25 Gy	≥48 Gy	40 Gy	InterruptedRadiotherapy	All
	Nr of patients				
III	137	57	22	4	220
IV	22	3	9	0	34
All	159	60	31	4	254

Acute G3 nausea/vomiting, epigastric pain and diarrhoea occurred in 3.2 % of patients, G3 hematologic toxicity in 5 % of patients with only one case of G4 anemia (0.4 %). Ten patients (4 %) had acute or late G3 mucosal lesions consisting of gastric ulcer, gastritis and/or duodenitis; 2 patients (0.8 %) had G4 gastritis and/or duodenitis (Table 4). Of note, the incidence of G > 2 mucosal damage was 9/60 (15 %) in patients who received SIB to infiltrated vessels or 48 Gy to the whole PTV, including a patient who died after gastroscopic diagnosis of gastric antral vascular ectasia, 4/163 (2.5 %) in patients treated with 44.25 Gy, and 0/31 in patients treated with 40 Gy ($p < 0.05$). Median time between the end of RCT and mucosal damage was 18 weeks (range 1–41 weeks). The Kaplan Meyer curve for G > 2 mucosal damage is reported in appendix.

Efficacy

Two hundred and twenty stage III patients were treated: three patients were lost to follow-up, resulting 217 patients evaluable for outcome. Median follow-up was 19 months (4.8–123.8 months). Nine patients (4 %) were resected after RCT. Two hundred and one patients had disease progression (93 %). Three patients died without restaging so that the site of first progression was available in 198 patients. First site of progression was local in 52/198 patients (26 %), distant in 79 patients (40 %), local + distant in 67 patients (34 %). Most patients had more than a single site of metastases: the most frequent sites were liver in 86 cases (43 %), lung in 39 (20 %), peritoneum in 38 (19 %), regional lymph-nodes in 12 (6 %), isolated lymph-node relapse in 1 (0.5 %). Median PFS, LPFS, and DPFS were 11.9 months (95 % CI:11.4–13), 16.0 months (95 % CI:14.2–17.3) and 14.0 months (95 % CI:12.6–146.5), respectively. At 1 year, the local control was 71 % (SD = 0.03), at 2 year 19.7 % (SD = 0.04) (Fig. 1)

Twenty-one out of 52 patients (40 %) who had initial local progression developed metastases after a median time of 3.75 months. Twenty-seven out the 79 (34 %) patients who had initial distant relapse developed local progression after a median time of 3.83 months. Overall, 146/198 patients (73 %) had local progression and 170/198 patients (86 %) had distant progression during their clinical course. Twenty patients (10 %) died with only local progression.

Outcome data of the 22 patients who had local progression after

Table 4
Acute and late toxicity (254 evaluable patients).

	G1	G2	G3	G4	G5
ACUTE					
Nausea/vomiting	70 (27.5%)	44 (17%)	2 (0.8%)		
Epigastric pain	43 (17%)	17 (7%)	4 (1.6%)		
Diarrhea	25 (10%)	16 (6%)	2 (0.8%)		
Asthenia	25 (10%)	15 (6%)			
Abdominal pain	10 (4%)	2 (0.8%)			
Anorexia	18 (8%)	4 (1.6%)			
Weight loss	6 (2%)	2 (0.8%)			
Anemia	17 (7%)	1 (0.4%)	4 (1.6%)	1 (0.4 %	
Thrombocitopenia	23 (4%)	6 (2%)	3 (1.2%)		
Neutropenia	7 (3%)	4 (1.6%)	3 (1.2%)		
Hand-foot Syndrome	1(0.3%)	6 (2 %)			
Gastritis	1 (0.4 %)	2 (0.8 %)	1 (0.4 %)		
Gastric ulcer		3 (1.2%)	1 (0.4%)		
Duodenitis		1 (0.4%)			
Hepatic	16 (6 %)	3 (1.2 %)			
LATE					
Gastro-duodenitis			3 (1.2%)	1 (0.4%)	1 (0.4%)
Duodenitis			2 (0.8 %)	1 (0.4%)	
Gastritis		1 (0.4%)	3 (1.2%)		

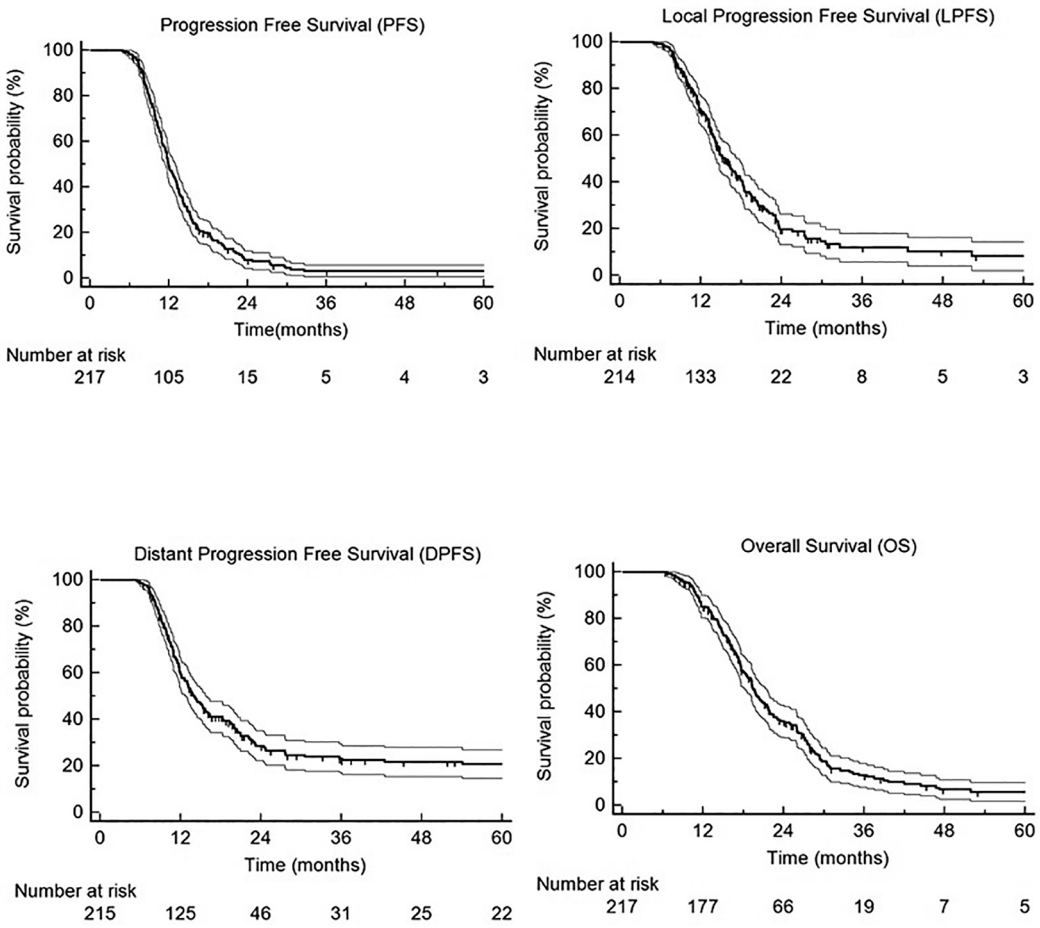

Fig. 1. Outcome data for all stage III patients.

induction CHT, compared with those of the 195 patients without local progression were: PFS 10.8 vs 12.1 months (p = 0.0002); LPFS 14.4 vs 16.3 (p = 0.20), DPFS 10.8 vs 15.2 months (p = 0.0057), Fig. 2.

Considering the 35 patients who received 48 Gy to whole PTV (excluding the 25 patients who received SIB only on infiltrated vessel), 15 out of them (42 %) had local (±distant) progression as first site of progression, not significantly different from local (±distant) progression observed in the group treated with 44.25 Gy: 85/135 (54 %), P = 0.21.

One hundred and sixty-eight patients died. Median survival was 19.5 months (95 % CI:18.1–21.3). One, two and three year survival were 85.2 % (SD = 0.02), 36 % (SD = 0.03) and 12.5 % (SD = 0.02), respectively (Fig. 1).

Median OS was 16.7 for the 22 patients who had local progression after induction CHT and 20.6 months in patients without local progression (p = 0.0001) (Fig. 2). Median OS was 24.1 months for patients who had only local progression as first site of progression after RCT, 19.2 months for patients who had only distant progression, and 16.3 months for patients who had both local and distant progression (p = 0.0032) (Fig. 3).

Discussion

To our knowledge, current study provides results from the largest single-Institute cohort of consecutive APC patients available in literature homogeneously treated with moderately hypofractionated RT delivering BED comparable to standard doses, concomitant to capecitabine after induction chemotherapy. This regimen was feasible in 98.4 % of cases, showed G ≥ 3 acute gastrointestinal toxicity rate of 3.2 % and major (G3-G4) acute and late gastritis, duodenitis, ulcer in 5.2 % of cases, reduced to 2.5 % in the group of patients treated with 44.25 Gy in 15 fractions. Limitations of the present study were its retrospective nature and the lack of a control arm, so we could only compare our results with the literature data. We choose to discuss our results in the context of LAP07 [11] and SCALOP [21] trials in which standard dose and fractionated RT concomitant to capecitabine was administered in one arm vs additional cycles of chemotherapy alone to patients with stable or responding disease after induction chemotherapy consisting of gemcitabine (GMC) with/without erlotinib [11] or GMC plus capecitabine [21].

Feasibility of RT concomitant to capecitabine was provide only by SCALOP trial: 74 % of patients received the full dose of radiotherapy [21]. Acute G3-G4 gastrointestinal toxicity in capecitabine arms of SCALOP and LAP07 was 0 % and 5.9 %, respectively [21,11]. Feasibility and acute toxicity in our study seems to be in line with those reported by the two cited trials. The low rate of late toxicity in our study compares favorably with that reported in a recent review [22].

In addition, in a recent study by our group on patients of the same cohort, dose-volume relationships for duodenum and stomach were refined, showing that the rate of toxicities could be further reduced if strictly applying newer constraints, as reported in Broggi et al [23].

Considering the outcome, the median PFS reported in our trial (11.9 months) is in line with both LAP07 (9.9 months) and SCALOP trial (12 months). Likewise, median LPFS and DPFS were 16 months and 14 months, respectively in our study, 14.6 months and 14.3 in the SCALOP trial, respectively. One-year local control of 71 % in our study seems to be in line with the pooled percentage of 1-year local control of 72.3 % (95 % confidence interval 58.5 %-79 %) provided by a systematic review and pooled analysis of 19 trial of SBRT [24]. A third study can be

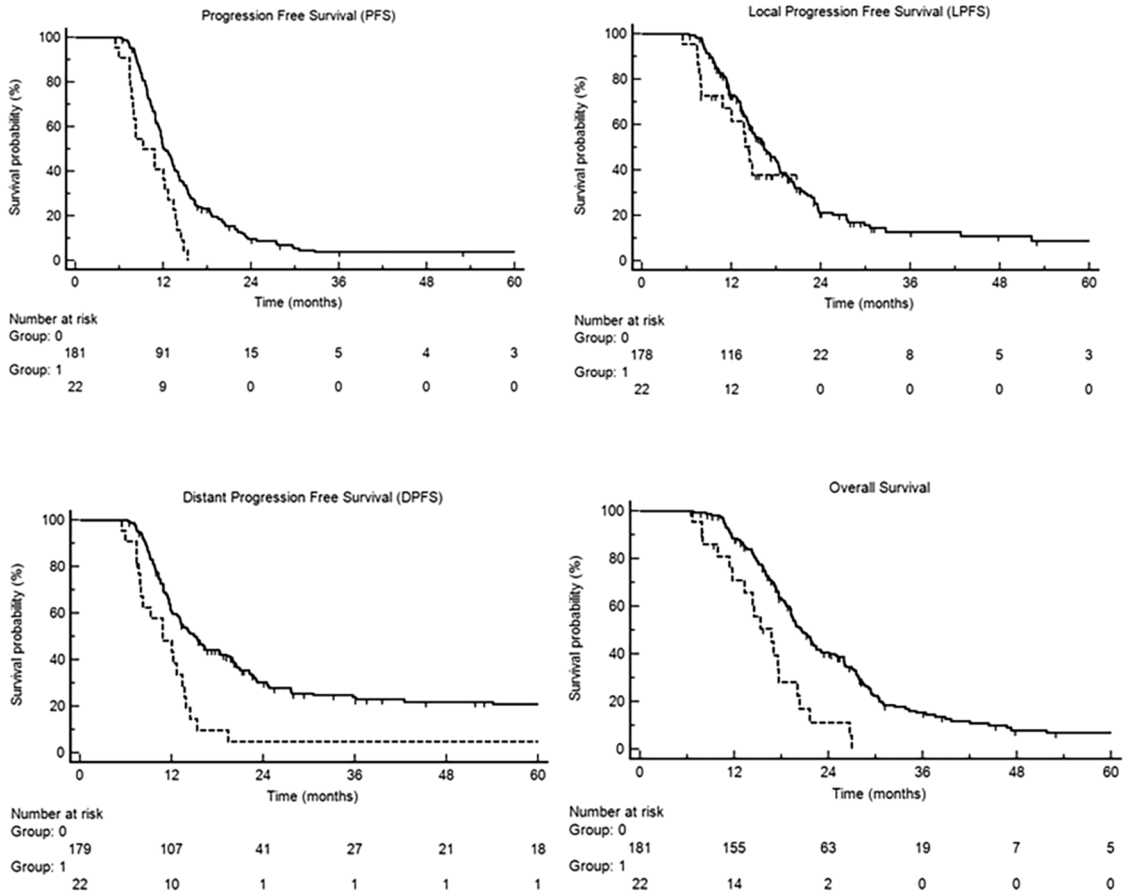

Fig. 2. Outcome data for patients who had local progression after induction chemotherapy (dashed line) versus patients without local progression (continuous line).

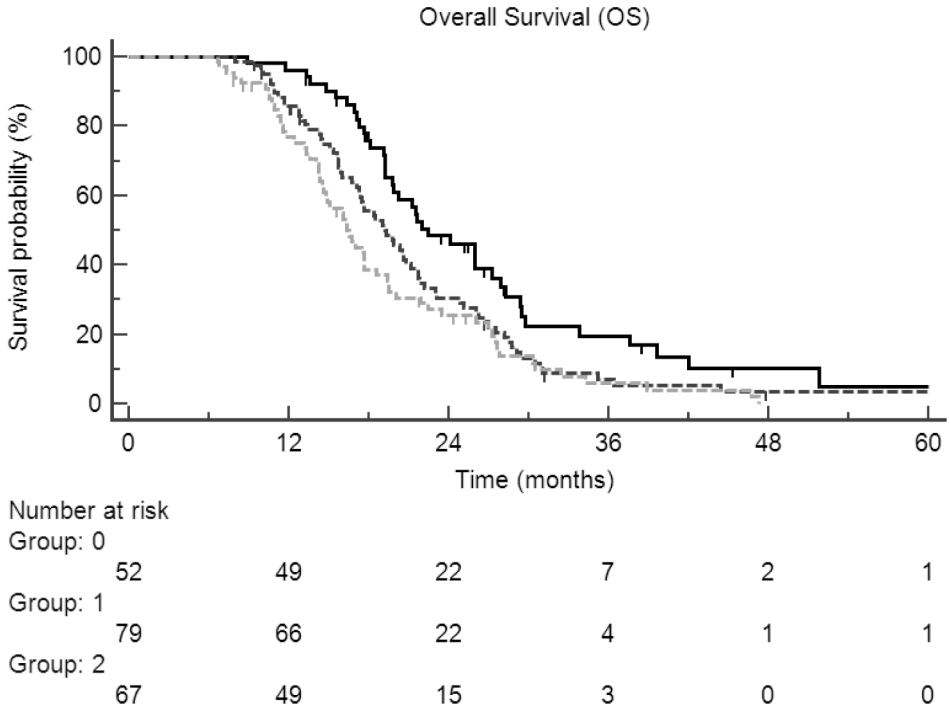

Fig. 3. Overall Survival (OS) depending on the first site of failure after RCT: only local failure (Group 0, continuous black line), only distant failure (Group (1), dashed black line), local and distant failure (Group 3, dashed grey line).

included for comparison: the CONKO-007 phase III trial, so far published only in abstract form. Also in this trial patients without progression after 3 months of gemcitabine or folfirinox were randomized to either continuing CHT for another 3 months or receiving 50.4 Gy in 28 frs concomitant to GMC. Main endpoint was R0 resection rate. The addition of RCT did not improved R0 resection rate. One- and 2-years PFS were 56.3 and 24.1, respectively, in RCT arm. These figures are better than ours: 1-and 2-years PFS were 49.4 % (SD = 0.3), and 8.1 % (SD = 0.2), respectively; however only 4 % of our patients were resected against 25 % of R0 resections in CONKO-007 [25] and 12.1 % provided by a recent systematic review on total neoadjuvant therapy [26]. Median OS was 19.5 months in our series (20.6 months in patients without local progression after induction chemotherapy), as opposed to 15.2 months in both LAP07 and SCALOP trials. One and two year survival were 85.2 % and 36 % in our study, 71.1 and 34.8, respectively in RCT arm of CONKO-007 trial [25].

Patients who had local progression after induction CHT had significantly worse outcome (Fig. 2) but still in line with LAP07 and SCALOP trials. Consequently, also these patients seem to be suitable for RCT.

Only 10 % of patients in the present series died with only local progression, however patients who had only local progression as first site of progression after induction CHT and RCT lived significantly longer than patients who had distant or local + distant progression (Fig. 3). This could simply be expression of a less aggressive disease but also the potential effect of local control on OS.

The more obvious way for improving local control is increasing the radiation dose. In this study patients who received a dose $\geq$ 48 Gy had a not significant (probably due to the small numbers) 12 % reduction of local (±distant) progression compared to patients treated with 44.25 Gy but had an unacceptable mucosal lesions rate (15 %). Accordingly, a dose $\geq$ 48 Gy is not recommended when delivered with the technique used in the present study.

Delivery of higher radiation dose is feasible when using more advanced techniques; at MD Anderson median OS of 47 patients who received $BED_{10} > 70$ Gy was 17.8 months vs 15.0 months of 153 patients treated with $BED_{10} < 70$ Gy ($p = 0.03$), advantage preserved at 2 and 3 years [27]. At MSKCC Reyngold et al. prescribed 98 Gy BED in 15 or 25 fractions depending on the distance between the tumor and stomach/bowel (>or< 1 cm, respectively) for 119 patients. Median survival was promisingly high: 26.8 months. Most patients (86 %) received FOLFIRINOX or GMC/nab-paclitaxel as induction CHT [28]. Of note, the pooled median OS was 24.2 months in a *meta*-analyses of 11 studies using FOLFIRINOX as induction therapy for LAPC [29] so that it is difficult to ascertain the respective impact on survival of high dose radiation and multiagent induction CHT in the MSKCC study.

Despite these promising outcome data the best therapeutic window is not well established. Zhu et al performed a prospective analysis of different regimens of SBRT and CHT on 419 patients: delivery of $BED_{10} \geq 60$ Gy was related with improved PFS and OS [30]. A *meta*-analysis on the effect of dose escalation in SBRT concluded that there was not significant difference in local control rates at 1 year between $BED_{10} < 70$vs $\geq$ 70 [31]. In a systematic review Brunner et al concluded that increasing SBRT dose beyond 75 Gy BED did neither prolong survival nor was safe [32].

Ongoing studies comparing higher vs standard RT dose such as SCALOP-2 [33] and MAIBE [34] trials could establish the impact of dose escalation on local control and OS.

The search for imaging (and/or biological) biomarkers able to select patients that could benefit more from dose escalation seem to be a reasonable priority for LAPC; in a previous study from our group, a simple two-features PET radiomic score was able to stratify patients according to their risk of early metastases [35]. This score is now under external validation and could be a powerful tool in avoiding to deliver more locally aggressive treatment in those patients with high risk of early metastases.

Conclusions

The present schedule of hypofractionated RT after induction chemotherapy is feasible with acceptable acute and late toxicity rate. Outcome data are in line with those achievable with standard doses and fractionation. This suggest that, this schedule may be preferred to other BED-equivalent schedules in the clinical practice, aimed at shortening treatment burden.

CRediT authorship contribution statement

Paolo Passoni: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. **Michele Reni:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – review & editing. **Sara Broggi:** Formal analysis, Methodology, Data curation. **Najla Slim:** Resources, Data curation. **Andrei Fodor:** Resources, Data curation. **Marina Macchini:** Resources, Data curation. **Giulia Orsi:** Resources, Data curation. **Umberto Peretti:** Resources, Data curation. **Gianpaolo Balzano:** Resources, Data curation. **Domenico Tamburrino:** Resources, Data curation. **Giulio Belfiori:** Resources, Data curation. **Stefano Cascinu:** Conceptualization, Methodology, Resources, Writing – review & editing. **Massimo Falconi:** Conceptualization, Methodology, Resources, Writing – review & editing. **Claudio Fiorino:** Conceptualization, Methodology, Resources, Formal analysis, Writing – review & editing. **Nadia Di Muzio:** Funding acquisition, Investigation, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

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.

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Appendix 1

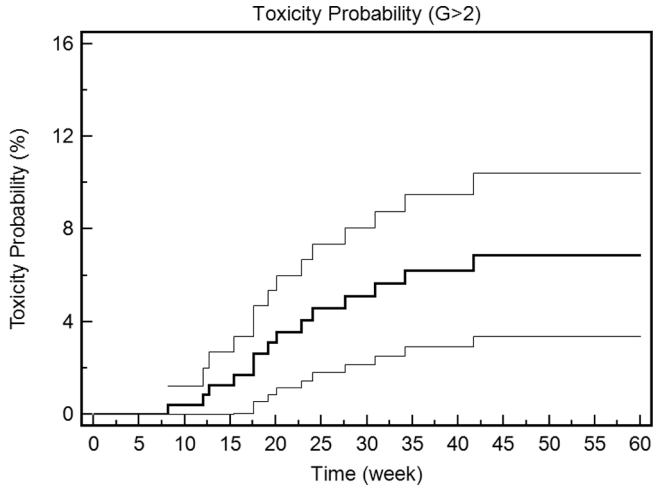

Fig. A1. Cumulative probability of G > 2 mucosal damage (ulcer, duodenitis and/or gastritis)

References

[1] Huguet F, Girard N, Guerche CS, et al. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. J Clin Oncol 2009;27:2269–77.

[2] Crane CH, Varadhachary G, Settle SH, et al. The integration of chemoradiation in the care of patients with localized pancreatic cancer. Cancer Radiother 2009;3:123–43.

[3] Reni M, Cereda S, Balzano G, et al. Outcome of upfront combination chemotherapy followed by chemoradiation for locally advanced pancreatic adenocarcinoma. Cancer Chemother Pharmacol 2009;64:1253–9.

[4] Ko AH, Quivey JM, Venook AP, et al. A phase II study of fixed-dose rate gemcitabine plus low-dose cisplatin followed by consolidative chemoradiation for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2007;68:809–16.

[5] Huguet F, André T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. J Clin Oncol 2007;25:326–31.

[6] Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. Cancer 2007;110:47–55.

[7] Gillmore R, Laurence V, Raouf S, et al. Chemoradiotherapy with or without induction chemotherapy for locally advanced pancreatic cancer: a UK multi-institutional experience. Clin Oncol (r Coll Radiol) 2010;22:564–9.

[8] Nakachi K, Furuse J, Kinoshita T, et al. A phase II study of induction chemotherapy with gemcitabine plus S-1 followed by chemoradiotherapy for locally advanced pancreatic cancer. Cancer Chemother Pharmacol 2010;66:527–34.

[9] Hudson E, Hurt C, Mort D, Brewster AE, et al. Induction chemotherapy followed by chemoradiation in locally advanced pancreatic cancer: an effective and well-tolerated treatment. Clin Oncol (r Coll Radiol) 2010;22:27–35.

[10] Brade A, Brierley J, Oza A, et al. Concurrent gemcitabine and radiotherapy with and without neoadjuvant gemcitabine for locally advanced unresectable or resected pancreatic cancer: a phase I-II study. Int J Radiat Oncol Biol Phys 2007;67:1027–36.

[11] Hammel P, Huguet F, van Laethem JL, et al. Effect of Chemoradiotherapy vs 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;315:1844–53.

[12] Passoni P, Reni M, Cattaneo GM, et al. Hypofractionated image-guided IMRT in advanced pancreatic cancer with simultaneous integrated boost to infiltrated vessels concomitant with capecitabine: a phase I study. Int J Radiat Oncol Biol Phys 2013;87:1000–6.

[13] Cattaneo GM, Passoni P, Longobardi B, Slim N, Reni M, Cereda S, et al. Dosimetric and clinical predictors of toxicity following combined chemotherapy and moderately hypofractionated rotational radiotherapy of locally advanced pancreatic adenocarcinoma. Radiother Oncol 2013;108:66–71. https://doi.org/10.1016/j.radonc.2013.05.011.

[14] Jones B, Dale RG. Mathematical models of tumour and normal tissue response. Acta Oncol 1999;38:883–93.

[15] Colorectal Cancer Collaborative group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomized trials. Lancet 2001;358:1291–304.

[16] Widder J, Herbst F, Dobrowsky W, et al. Preoperative short-term radiation therapy (25 Gy, 2.5 Gy twice daily) for primary resectable rectal (phase II). Br J Cancer 2005;92:1209–14.

[17] Reni M, Cereda S, Rognone A, et al. A randomized phase II trial of two different 4-drug combinations in advanced pancreatic adenocarcinoma: cisplatin, capecitabine, gemcitabine plus either epirubicin or docetaxel (PEXG or PDXG regimen). Cancer Chemother Pharmacol 2012;69:115–23.

[18] Reni M, Zanon S, Peretti U, et al. Nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in metastatic pancreatic adenocarcinoma (PACT-19): a randomised phase 2 trial. Lancet Gastroenterol Hepatol 2018;3:691–7.

[19] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25.

[20] Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009;27:3778–85.

[21] Mukherjee S, Hurt CN, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol 2013;14:317–26.

[22] Reese AS, Lu W, Regine WF. Utilization of intensity-modulated radiation therapy and image-guided radiation therapy in pancreatic cancer: is it beneficial? Semin Radiat Oncol 2014;24:132–9.

[23] Broggi S, Passoni P, Tiberio P, Cicchetti A, Cattaneo GM, Longobardi B, Mori M, Reni M, Slim N, Del Vecchio A, Di Muzio NG, Fiorino C. Stomach and duodenum dose–volume constraints for locally advanced pancreatic cancer patients treated in 15 fractions in combination with chemotherapy. Front Oncol, Volume 12, Article number 983984. https://doi:10.3389/fonc.2022.983984.

[24] Petrelli F, Comito T. Ghidini Aet al: Stereotactic Body Radiation Therapy for Locally Advanced Pancreatic Cancer: A Systematic Review and Pooled Analysis of 19 Trials. Int J Radiat Oncol Biol Phys 2017;97:313–22.

[25] Fietkau R, Ghadimi M, Grützmann R, et al. Randomized phase III trial of induction chemotherapy followed by chemoradiotherapy or chemotherapy alone for nonresectable locally advanced pancreatic cancer: First results of the CONKO-007 trial. J Clin Oncol 2022;40(16_suppl):4008.

[26] Tomasello G, Ghidini M, Ghidini A, et al. Total neoadjuvant therapy for initially inoperable pancreatic cancer: A systematic review of phase 2–3 studies. Radiother Oncol 2021;164:13–9.

[27] Krishnan S, Chadha AS, Suh Y, et al. Focal Radiation Therapy Dose Escalation Improves Overall Survival in Locally Advanced Pancreatic Cancer Patients Receiving Induction Chemotherapy and Consolidative Chemoradiation. Int J Radiat Oncol Biol Phys 2016;94:755–65.

[28] Reyngold M, O'Reilly EM, Varghese AM, et al. Association of ablative radiation therapy with survival among patients with inoperable pancreatic cancer. JAMA Oncol 2021;7:735–8.

[29] Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol 2016;17:801–10.

[30] Zhu X, Shi D, Li F, et al. Prospective analysis of different combined regimens of stereotactic body radiation therapy and chemotherapy for locally advanced pancreatic cancer. Cancer Med 2018;7:2913–24.

[31] Zaorsky NG, Lehrer EJ, Handorf E, et al. Dose Escalation in Stereotactic Body Radiation Therapy for Pancreatic Cancer: A Meta-Analysis. Am J Clin Oncol 2019;42:46–55.

[32] Brunner TB, Nestle U, Grosu A-L, et al. SBRT in pancreatic cancer: what is the therapeutic window? Radiother Oncol 2015;114:109–16.
[33] ClinicalTrials.gov. Systemic therapy and chemoradiation in advanced localized pancreatic cancer-2 (SCALOP-2). https://clinicaltrials. gov/ct2/show/NCT02024009.
[34] ClinicalTrials.gov. Use of high-dose radiation therapy plus chemotherapy to improve the likelihood of surgical treatment in patients with locally advanced pancreatic cancer (MAIBE). https://clinicaltrials.gov/ct2/show/NCT03523312.
[35] Mori M, Passoni P, Incerti E, Bettinardi V, Broggi S, Reni M, et al. Training and validation of a robust PET radiomic-based index to predict distant-relapse free-survival after radio-chemotherapy for locally advanced pancreatic cancer. Radiother Oncol 2020;153:258–64.