



Review Article

The role of biological dose-escalation for pancreatic cancer

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ABSTRACT

The role of chemo-radiotherapy for treatment of locally advanced pancreatic cancer (LAPC) has been discussed for many years, and the absence of an overall survival benefit compared to gemcitabine chemotherapy alone in the recent LAP07 study seems to have increased the controversy. However, even in this study, chemo-radiotherapy resulted in decreased local progression ($p = 0.03$). In combination with increased efficacy of novel systemic therapy consisting of oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX), radiation dose-escalation may show to be beneficial in LAPC. Stereotactic body radiation therapy (SBRT) can be expected to be the most suitable approach to perform local radiation dose-escalation, and has been shown to be both effective and tolerable at doses of 25–35 Gy in 3–5 fractions. Whether further dose-escalation for LAPC will be both feasible and useful is debatable, because of dose restrictions to adjacent critical organs at risk, and the observation that thus far a benefit of delivering BED₁₀ in excess of 70 Gy has not shown to improve local control significantly. If an attempt to further dose-escalate is performed, stereotactic MR-guided adaptive radiation therapy (SMART) theoretically has the highest potential. In addition to superior soft-tissue setup without the need for implanted fiducial markers and online MR-guidance during delivery with minimal safety margins, daily plan adaptation directed at avoiding undue high doses to critical organs such as the duodenum, stomach and bowel are advantages of this technique over current SBRT. This paper aims to illustrate the SMART technique, which has been delivered in 300 fractions for LAPC or locally recurrent pancreatic cancer at Amsterdam UMC since early 2016.

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Contents

1. Introduction	128
2. Biological dose escalation for pancreatic cancer	129
3. MR-guided radiation therapy	129
Conflict of interest	130
References	130

1. Introduction

The incidence of pancreatic cancer has been increasing in the last decades and it has become the third leading cancer-related cause of death in the United States. Despite advancements in surgical procedures and systemic therapy, five-year survival remains below 10% [1]. Although radical surgery can be considered the only

curative treatment, only 10–25% of patients are resectable at the time of diagnosis. For patients with locally advanced, but not metastasized disease, systemic chemotherapy with or without conventionally fractionated radiotherapy is standard of care in most countries. The role of chemo-radiotherapy for locally advanced pancreatic cancer (LAPC) has been discussed for many years, and the absence of an overall survival benefit compared to gemcitabine chemotherapy alone in the recent large LAP07 study seems to have increased the controversy [2]. However, even in this negative study for survival, the use of chemo-radiotherapy with

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54 Gy resulted in significantly improved local control. In recent years, a more efficient but also more toxic systemic therapy regimen consisting of oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX) has been used in patients with LAPC [3]. This novel systemic treatment has renewed interest in chemoradiotherapy for LAPC, with several single center and multicenter studies reported in the last two years [4,5].

Traditionally, conventional radiotherapy for LAPC has been delivered with total doses of 46–60 Gy in 1.8–2.0 Gy per fraction using generous target volumes because of the inclusion of regional nodal areas and necessarily large mobility margins. With respect to loco-regional control, the outcome of such schemes has been highly variable among published studies and is generally reported to be between 50% and 75%. Although based on these figures, there appears to be a rationale for dose-escalation, this is not clinically feasible using these generous radiation fields for toxicity reasons, unless an integrated boost technique for favorable tumors at distance from OARs is used [6]. In recent years, stereotactic body radiation therapy (SBRT) has been introduced for local treatment of LAPC, with or without prior chemotherapy. SBRT is a form of extremely hypofractionated treatment, delivering high biological doses of 23–40 Gy in one to five fractions, generally within two weeks overall treatment time. SBRT is performed with high-precision usually marker-based patient setup and the steep dose gradients associated with SBRT allow for adequate sparing of surrounding normal organs at risk. In contrast to conventional (chemo-) radiation, SBRT for LAPC is generally directed only towards the primary tumor involved nodal disease, if adjacent to the tumor, without elective regional node radiation. Inherent to this approach of target definition with SBRT, marginal or nearby regional relapses have been described [7]. Unfortunately, the outcomes of SBRT for LAPC have not been compared prospectively with those of conventional radiation treatment schemes. A systematic literature review of SBRT for LAPC was performed by Petrelli et al., including 1009 patients in 19 published studies [8]. With the limitations inherent to a systematic review, the pooled 1-year survival was 51.6%. The local control rate after SBRT at one year follow up was 72.3% (95% confidence interval 58.5–79%). Overall, the rate of acute severe toxicity ranged from 0% to 36% with only three studies showing grade ≥ 3 acute toxicity of more than 10%. The incidence of late grade ≥ 3 did not exceed 11% in the included studies.

2. Biological dose escalation for pancreatic cancer

In the abovementioned systematic review, the authors report that total SBRT dose and a higher number of fractions were significantly associated with local control at one year, but further details were lacking [8]. Another meta-analysis dedicated to the topic of radiation dose-escalation for pancreatic cancer by Zaorsky et al. has recently been published [9]. This review included the results of SBRT for non-metastatic pancreatic cancer in 508 patients within a total of 15 studies. Local control at 1 year follow-up could be evaluated both under a fixed effects model and random effects model in 365 patients. Local control for patients treated with a biological effective dose (BED₁₀; alpha/beta 10 Gy) of less than 70 Gy was 72% (fixed effects model) and 60% (random effects model), respectively. For 217 patients treated with a BED₁₀ of 70 Gy or higher, the corresponding local control rates were 82% and 83%. However, meta-regression failed to show a significant relationship between local control and BED₁₀. Interestingly, there also appeared not to be a significant difference in acute or late toxicity rates between both groups. This meta-analysis, however, included borderline resectable patients (N = 65) and patients with locally recurrent pancreatic cancer (N = 60), which may have influenced the outcomes. Furthermore, systemic treatment differed across studies

and definition of local control varied between included series, albeit that most studies used the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Nonetheless, several important conclusions may be derived from the results of this meta-analysis. Firstly, favorable local control rates were observed in this large group of patients after SBRT for predominantly locally advanced pancreatic cancer. Secondly, because no significant benefit could be determined between treatment with BED₁₀ of less or more than 70 Gy, an effect of dose-escalation with SBRT could at best be modest. And finally, the lack of increased acute or late toxicity for SBRT with BED higher than 70 Gy, illustrates that there is still the potential to study dose-escalation prospectively when taking maximum effort to minimize doses to critical organs at risk.

3. MR-guided radiation therapy

One novel technique which could, at least theoretically, achieve safe further dose-escalation in pancreatic cancer is stereotactic MR-guided adaptive radiation therapy (SMART). SMART allows for superior soft-tissue setup without the need for implanted fiducial markers, in combination with real-time MR-guidance during delivery. It offers the opportunity to deliver gated treatment during breath-hold with only minimal safety margins, and daily plan re-optimization can be applied within an acceptable time frame. All these potential advantages can be exploited to prescribe a higher biological dose while avoiding undue high doses to adjacent critical organs such as the duodenum, stomach and bowel. Initial clinical experience with MR-guided radiotherapy has shown that safe delivery of 40 Gy in five fractions, corresponding with a BED₁₀ of 72 Gy, is feasible [10–12]. The overall dosimetric benefit of daily adaptive planning in MRgRT for pancreatic cancer has been reported by a number of recent papers [10,13,14]. General feature of SMART techniques is the priority that is given to high-dose OAR-constraints over optimal target coverage. With small variations between institutes performing SMART for LAPC, the V_{33–35 Gy} of the duodenum, stomach and bowel are kept below 0.5–1 cc [10–14], and because of the close proximity of these OARs this constitutes the major limitation in dose-escalation.

Since the clinical introduction in early 2016, 300 SMART fractions have been delivered to 60 patients with LAPC or recurrent inoperable pancreatic cancer at Amsterdam UMC. Standard dose prescription for SMART has been 40 Gy in five fractions, twice weekly. Only in case of evident local ingrowth of the primary tumor in the stomach or duodenum a lesser dose of 35 Gy in five fractions has been used. Our developed workflow for online plan adaptation in pancreatic cancer in MRgRT has been described in detail previously [14]. Similar to what has been described above, high-dose OAR constraints have been leading in daily plan adaptation. A review of our routine practice of daily plan adaptation in 180 fractions of MRgRT for LAPC showed that this was of clinically relevant benefit in approximately half of fractions, and that on average it improved both OAR sparing and target coverage. Plan adaptation appeared to be mainly important when the distance between the GTV and adjacent OAR's was 3 mm or less, which is the GTV-PTV margin used in clinical practice [15]. However, because the GTV-OAR distance is variable in between patients and in between fractions, it remains difficult to determine upfront which patients with LAPC will benefit from plan adaptation.

In addition to interfractional variation in the relation between the GTV and OAR's, intrafractional changes may also be relevant, in particular during the protracted procedure of SMART delivery. Potential intrafractional changes are the reason for refraining from re-normalizing PTV doses to the limit of OAR constraints for each separate fraction at our institute. In future, however, fast intrafractional plan adaptation based on real-time imaging could be a

relevant improvement of MRgRT, better allowing for local dose-escalation. The potential relevance of intrafractional changes during SMART for LAPC, was recently illustrated by our group in case report [16].

Technical innovations and the relatively low toxicity observed thus far with SMART, has led to new initiatives to attempt local dose-escalation for LAPC. A recent publication suggested that both overall survival and local control may be better when BED₁₀ is larger than 70 Gy [17]. This retrospective multicenter study included a relatively small group of heterogeneous patients with both borderline operable pancreatic cancer and LAPC. As a follow-up of this hypothesis-generating study, a multi-institutional prospective trial has recently been initiated between centers delivering SMART (ClinicalTrials.gov: NCT03621644). The goal of this study is to attempt further dose-escalation in patients with LAPC or borderline operable pancreatic cancer to 50 Gy in five fractions, corresponding to a BED₁₀ of 100 Gy. Primary endpoint of this study will be clinical grade 3 or greater toxicity within 90 days. Also in this trial, the high-dose OAR constraints of a V_{33 Gy} of less than 0.5 cc for duodenum, stomach and bowel prevail over target coverage. This approach is likely to result in full dose-escalation in favorable pancreatic cancer patients with OARs at distance from the primary tumor, and partial PTV dose-escalation in less favorable located pancreatic cancer. The results of this newly started trial remain to be awaited.

In conclusion, biological dose-escalation in the form of SBRT has resulted in high local control rates, even for LAPC, with acceptable early and late toxicity. As previous literature reviews could not definitely show a significant dose-response relation, further local dose-escalation above a BED₁₀ of 70 Gy can at best be expected to result in a modest gain in local control (and overall survival). MR-guided adaptive radiotherapy with plan adaptation can be regarded an optimal technique to pursue further biological dose-escalation, however, high-dose constraints of adjacent OARs will remain the limiting factor.

Conflict of interest

Dr. Lagerwaard reports personal fees from Viewray Inc., outside the submitted work.

Dr. Bruynzeel reports personal fees from Viewray Inc., outside the submitted work.

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