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Hypofractionated radiotherapy in pancreatic cancer: Lessons from the past in the era of stereotactic body radiation therapy

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ABSTRACT

The role of neoadjuvant and definitive radiotherapy combined or not to chemotherapy in the therapeutic approach to pancreatic cancer has not been yet elucidated. There is some evidence in favour of neoadjuvant local and/or systemic approaches that enable surgical resection in patients initially considered to be "borderline resectable". Nevertheless, most of these studies have been conducted using schedules of radiotherapy (treatment volumes, total doses, dose/fraction) that are nowadays considered not efficient enough and/or too toxic.

Recently, stereotactic body radiation therapy (SBRT) has been proposed as a new therapeutic option for pancreatic cancer, both in the neoadjuvant and in the definitive setting. The aim of this study is to review the radiobiological and clinical evidences supporting hypofractionation in pancreatic cancer. Moreover, we performed an extensive review of available clinical and dosimetric data on SBRT in pancreatic cancer.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the 10th cause of cancer, and the 4th cause of cancer death in the USA, with 22,740 estimated new cases and 18,980 estimated deaths in 2013 (Siegel et al., 2013). Epidemiological data from Europe reveal that PDAC is the 6th most frequent cancer and the 5th leading cause of cancer-related death with yearly 70,000 estimated deaths (Ferlay et al.,

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2013). The only potentially curative treatment is a complete surgical resection. After a radical (R0) resection, median survival ranges from 20 to 23 months, as recently reported in a *meta*-analysis by Gillen et al. (2010). Interestingly, the authors also highlighted that one-third of initially unresectable cancers became resectable after neoadjuvant therapy, and these patients presented overall survival rates of 20 months, comparable to those presenting a resectable tumor if R0 resection. For this reason it is of major interest to investigate how neoadjuvant treatment approaches can be further optimized.

To date, the role of preoperative radiation therapy (RT) is still a matter of debate (Gillen et al., 2010). As many patients have already distant metastases at the time of diagnosis, the potential advantage of an improved loco-regional tumor control by RT might be limited (Haeno et al., 2012).

Moreover, early systemic tumor spread probably is an important reason for the disappointing results of trials that investigated neoadjuvant chemo-RT (CRT) in PDAC; and it supports the adoption of short RT schedules to avoid a delay of systemic chemotherapy.

Other important issues including the total dose, large treatment volumes, and schedules of treatment used in previous trials may further contribute to the disappointing results in terms of long-term survival and toxicity rates.

Several technical innovations have been recently introduced in the clinical routine of radio-oncologists. Dedicated linear accelerators for stereotactic body RT (SBRT), specifically developed for stereotactic treatments, allow a drastic reduction of the dose delivered to nearest critical structures and, therefore, to deliver higher doses and more conformal hypofractionated treatments. Modern intensity modulated RT (IMRT) techniques, such as volumetric modulated arc RT or helical tomotherapy, also delivered by using on-board cone-beam or fan-beam CT (image-guided RT, IGRT) to check the position of the patient before treatment, allow in several diseases an increase of the dose to the target volume, while reducing the dose to the organs at risk (OARs) and, therefore, reducing acute and late toxicity (Reese et al., 2014; Bockbrader and Kim, 2009). The recent introduction of IGRT techniques in daily clinical practice permitted daily verification of patient setup and a minimization of the margins as well as a reduction of treatment volumes. In these more favourable technical conditions, a dose escalation is feasible (Henry et al., 2008) and may potentially increase the therapeutic value of RT.

While SBRT has initially been introduced for the treatment of brain tumors and brain metastases, it is now widely and successfully used for the focused irradiation of extracranial primary and secondary targets (Rubio et al., 2013; De Bari et al., 2011, 2014; Arcangeli et al., 2012; Alongi et al., 2012). The role of SBRT for the treatment of PDAC has not been extensively investigated, but its rationale appears to be interesting in this particular clinical setting. Indeed, despite the proximity of the duodenum and the stomach, the small RT volumes of SBRT allow steeper dose distributions and a better sparing of the abdominal OARs, thus, potentially limiting the toxicity.

Some retrospective data for locally advanced PDAC with CRT suggest that total doses of 54 Gy or more in patients with low risk of metastatic dissemination (*i.e.,* a minimum post-CRT CA 19–9 < 90 U/mL) improved the likelihood of prolonged survival (Golden et al., 2012). Therefore, patients presenting low levels of CA 19-9 after neoadjuvant chemotherapy, but still not resectable, could be candidate to neo-adjuvant CRT in order to increase the chance of operability. Indeed, some surgical series already showed that patients presenting lower pre- (Kim et al., 2011; Hallemeier et al., 2011) and/or postoperative CA 19-9 levels presented better prognosis (Kondo et al., 2010), probably because in these patients the burden of systemic tumor is significantly lower, thus increasing the interest of local treatments.

The aim of this review is to summarize data about the emerging role of SBRT in the management of PDAC. In the initial part of the article, we also give an overview of the role of hypofractionated radiotherapy in this clinical setting, in order to highlight the potential interest of this kind of fractionation in the treatment of PDAC To this end, current reported series were searched, and the available evidence is shown.

2. Neoadjuvant radiochemotherapy in pancreatic cancer before the SBRT era: only failures?

Historically, neoadjuvant CRT has been proposed to increase resectability rates of locally advanced PDAC that have been considered non-resectable upfront. Despite the potential interest of this kind of approach, no high level evidence is available on the role of neoadjuvant RT +/− chemotherapy (CTX). A recent trial by Casadei et al., enrolling patients with resectable PDAC (and not, noteworthy, unresectable or "borderline tumors"), randomized patients in two arms (surgery alone vs. chemoradiation and surgery) (Casadei et al., 2015). The study was closed prematurely due to the insufficient patient recruiting; and no conclusion could be drawn from this limited trial on only 38 patients.

Moreover, the definition of resectable tumors and "borderline tumors" was neither always clear in the available studies and, more in general, nor consistent amongst them. Recently, the International Study Group of Pancreatic Surgery (ISGPS) published a consensus statement for the definition of borderline resectable PDAC, globally supporting the criteria established by the National Comprehensive Cancer Network (NCCN) (Bockhorn et al., 2014). These criteria are based on the most well-established and broadly accepted, CT-based classification developed at the MD Anderson Cancer Center (Varadhachary et al., 2006).

A particular attention should be given to the analysis of the five phase II studies published from the MD Anderson Cancer Center (Lim et al., 2012). In these studies, the number of enrolled patients ranged between 28 and 90 patients, and increased over the years. The definition of "resectable" tumors was clear and remained unchanged over several years. Also, the operative techniques were unchanged. After neoadjuvant treatment combining RT and CTX, the rate of patients being candidates for surgery ranged from 69% to 85%. Noteworthy, the rate of vessel resections ranged between 20% and 50%, confirming that these rates of operability strongly depended on the surgical technique and expertise. Moreover, better results were obtained with more hypofractionated regimens. In the study 88-004, CRT was delivered using 50.4 Gy external RT combined or not to intraoperative RT (IORT, 10–20 Gy) and 5-fluorouracil (5-FU) (300 mg/m^2, continuous infusion, 5 days/week). Finally, 17/28 patients were operated (the others were excluded before or during surgery because of evidence of a metastastic disease progression), and 83% of them could receive an R0 resection (Evans et al., 1992).

Interestingly, in the study 93-007, authors used the same type of chemotherapy but switched towards a more hypofractionated RT schedule (30 Gy, 3 Gy/fraction with or without 10–15 Gy IORT) (Pisters et al., 1998). Only by changing the fractionation, the rate of R0 resection increased up to 90%. Noteworthy, the rate of patients needing a vessel resection was higher than in the previous study (50%), potentially contributing to the higher rate of R0 resections.

The same hypofractionated RT schedule, associated to different types of CTX (5-FU, paclitaxel, gemcitabine), was adopted in some following studies published by the same authors (Varadhachary et al., 2008; Pisters et al., 2002; Evans et al., 2008): the rate of patients finally resected remained quite constant (ranging between 57% and 66%).