The role of stereotactic magnetic resonance-guided adaptive radiation therapy (SMART) in locally advanced and borderline resectable pancreatic cancer

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) generally carries a poor prognosis. The recent National Pancreatic Cancer Audit (NPaCA) (1) published in 2024 reported a 1-year survival rate of 25–26% in England and Wales.

Most patients (68–69%) present with metastatic disease (2). For the minority who present with non-metastatic disease, tumours are typically divided into surgically resectable, borderline-resectable, and unresectable.

Most non-metastatic patients are borderline-resectable or unresectable (1). Surgery currently remains the only potentially curative treatment option, the focus for inoperable patients shifts to disease control and quality of life (QoL) improvements. Typically, patients undergo a course of systemic therapy followed by consolidation abdominal radiotherapy +/– concurrent chemotherapy (3).

Chuong *et al.* (4) describe using an advanced radiotherapy technique (magnetic resonance-guided adaptive radiotherapy) to deliver a high (ablative) dose of radiotherapy, and describe their experience with toxicities, local control (LC), and overall survival (OS) outcomes.

Background: the evolution of precision radiotherapy techniques from chemoradiotherapy to stereotactic ablative body radiotherapy (SABR)

The delivery of high-dose radiotherapy to the pancreas is challenging for two reasons. Firstly, the pancreas is near critical organs at risk (stomach, duodenum, bowel) which are mobile and have significant intrafractional and interfractional movement. Secondly, the quality of conventional cone-beam computed tomography (CT) imaging limits confident delineation of organs at risk (5), and poses challenges for daily alignment even if adaptive radiotherapy is not being used.

Stereotactic magnetic resonance-guided adaptive radiotherapy (SMART) assists with both issues, allowing daily on-set adaptation of organs at risk online, and more confident delineation of these organs.

The LAP-07 trial (6) was published in 2016. This was an international phase 3 trial to see if chemoradiotherapy improved outcomes in unresectable PDAC. Patients received 4 months of induction systemic therapy

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(chemotherapy *vs.* chemotherapy + erlotinib), followed by further chemotherapy *vs.* chemo-radiotherapy at 54 Gy in 30 fractions over 6 weeks with concurrent capecitabine. This trial demonstrated no OS benefit of chemo-radiotherapy compared to chemotherapy. Median OS from date of first randomisation was not statistically different in the chemoradiotherapy arm compared to the chemotherapy arm (15.2 *vs*. 16.5 months). However, chemoradiotherapy was associated with improved local progression-free survival (PFS) when compared to chemotherapy (32% *vs.* 46%) and freedom from further therapy (6.1 *vs.* 3.7 months).

The SCALOP2 trial (7) was published in 2024 and comprised of two variables—assessing addition of nelfinavir, and dose escalation radiotherapy (50.4 Gy/28 fractions *vs*. 60 Gy/30 fractions) using precision radiotherapy techniques. This trial demonstrated no OS benefit from nelfinavir or dose escalated chemo-radiotherapy. However, there was a trend to improvement in local tumour control and QoL measures with the high-dose chemo-radiotherapy. Crucially, it demonstrated the safety of dose escalation with modern image guided and intensity modulated radiotherapy techniques with no increased toxicity from the higher 60 Gy dose arm.

In 2015 (8), Herman *et al.* published their experience with prescribing 33 Gy in 5 fractions, prescribed to cover >90% of the modified planning target volume (mPTV), peaked to 130%. From date of diagnosis, they reported a median OS of 13.9 months, a 1-year LC rate of 78%, and a median PFS of 7.8 months demonstrating the potential for hypofractionated radiotherapy.

Krishnan *et al.* in 2016 (9) reported that pancreatic tumours receiving a biologically equivalent dose of more than 70 Gy had a superior OS compared to lower dosed tumours. A meta-analysis by Tchelebi *et al.* in 2020 also concluded an improved 2-year OS, and a significant improvement in acute toxicity with stereotactic body radiation therapy (SBRT) compared to conventionally fractionated radiotherapy (10).

The hypofractionated treatment effects in the clinic (HyTEC) review (11) was published in 2021. The authors conducted a pooled analysis of tumour control, and utilised tumour control probability models to predict a dose response for LC to pancreatic cancer. The authors postulated that the 1-year LC rate for 33 Gy/5 fractions was 77% without surgery, and a dose of 36 Gy/3 fractions corresponded to a 1-year LC rate of 86%. Below 24 Gy/3 fractions, the tumour control was <70%.

In 2022, Bordeau *et al.* (12) in Montpellier, France reported on their prospective registry of 70 patients receiving 50 Gy/5 fractions, reporting only low-grade toxicities and a 1-year OS/LC rate of 68.6%/86.5% from SMART respectively, and a median OS for 20.9 months.

In 2024, the team at Oxford, UK (13) published their retrospective outcomes with SMART with a prescription dose of 35–40 Gy/5 fractions. Chemotherapy was not mandated. In this cohort, 87% (48/55) received induction chemotherapy, with 67% (37/55) receiving FOLFIRINOX. Chemotherapy was delivered for a median of 13 weeks. They reported a median local PFS of 8 months, median OS of 12 months, 1-year LC rate of 65%, and a median metastasis-free survival (MFS) of 6 months post-SMART.

Although studies to date have not demonstrated an improvement in OS, previous trials have suggested a correlating trend between dose delivered and local progression free survival—leading to improvements in QoL, pain. This suggests a potential additive benefit to systemic therapy, which remains the backbone of treatment for pancreatic cancer.

Scientific contribution of the article

The authors describe a multi-centre, single arm, phase 2 study of SMART prescribed to 50 Gy in 5 fractions for patients with borderline-resectable or unresectable (locally advanced) pancreatic cancer. A previous article published in 2023 (14) was published with a median follow up time of 8.8 months, discussing acute toxicities (within 90 days of SMART) in detail and will not be covered in this commentary in significant detail. The authors concluded that the incidence of acute grade 3+ (G3+) gastrointestinal toxicity was 8.8%.

This current article describes clinical outcomes and long-term toxicities with a median follow up time of 14.2 months from SMART.

Inclusion criteria included the requirement of at least 3 months of induction chemotherapy and a carbohydrate antigen 19-9 (CA19-9) ≤500 U/mL after induction chemotherapy, with no restriction on tumour size.

One hundred and thirty-six patients were enrolled from 13 institutions across three countries. Most patients were recruited from four centres. FOLFIRINOX +/– another regime was given in 81.7% (n=111) of patients. Chemotherapy was given for a mean of 4.5 months.

Primary endpoint was acute G3+ toxicity definitely related to SMART. Secondary endpoints were 2-year OS after PDAC diagnosis, 6-month distant progression-free

survival (DPFS) after SMART and QoL at 3 and 12 months after SMART. LC was not a formal endpoint but was evaluated.

A dose of 50 Gy/5 fractions was prescribed to the planning target volume (PTV). Most fractions (93.1%) required on table adaptation.

Post-SMART therapy was allowed at physician's discretion, including chemotherapy and/or surgery. Chemotherapy was given to 24.3% of patients. Details of regimes and duration were not available. The study stratified patient outcomes based on patients who did not receive surgery post-SMART, and patients who did receive surgery post-SMART. Surgery was performed in 47 (34.6%) of patients; the ypT0 rate was 3/47 (6.4%), and 7 (14.9%) had an R1 positive margin.

The authors report a 16.1% G3+ toxicity rate. The details for this toxicity were described in 2023, and they divided toxicities into possibly, probably, and definitely related to SMART. They report an 11.5% G3+ possibly, and 4.6% G3+ probably related to SMART with a G5 toxicity rate of 0.8% (n=1) in a patient with local failure at the site of a bleeding malignant ulcer.

In the non-surgical cohort, one-year LC rate appears to be between 75–80%, median LC rate was not reached, median OS approximately 13 months, and survival rate at 2 years was 26%. In the surgical cohort, the one-year LC rate was approximately 92%, median LC rate was not reached, median OS was not reached, and survival at 2 years was 67%.

Strengths of the research

The authors claim that this is the first prospective study of ablative 5-fraction SMART for borderline-resectable and unresectable (locally advanced) PDAC.

To the best of their knowledge, this is also the biggest SBRT trial for locally advanced, non-metastatic PDAC.

Toxicities were judged by a Clinical Events Committee who were not directly involved in the study but had experience of managing PDACs.

The reported outcomes in this study demonstrated better LC rates than similar studies prescribing a lower dose of radiation, and treatment was generally well tolerated.

Limitations and future directions

The authors acknowledge that there was no uniform pre-determined definition of borderline-resectable *vs.* unresectable (locally advanced)—allowing for individual institutions to provide local definitions. This may have resulted in local institutional variations. Post-SMART, patients may have become resectable, but again there was no pre-defined criteria for trial dissections, again this being left to local institutional protocols.

The radiotherapy protocol was amended early on to allow an optional clinical target volume (CTV), which was not defined in the study protocol and was at the discretion of the treating physician. This could include an isotropic expansion, optional inclusion of 'at risk' areas, or no CTV at all. There was no central QA process of the radiotherapy contours and plans, which may allow for significant variations in contouring.

Data post-SMART chemotherapy was not collected, both in terms of regime, and length of treatment, and so there was little indication of a freedom from treatment time, and how patients experienced and tolerated further lines of treatment.

Mapping of recurrence in relation to the RT volumes was not published in this paper but would be of interest to help guide future contouring atlases.

Implications and impacts

While head-to-head comparisons should be avoided, this article, alongside recent findings from the Oxford team, seems to bolster the HyTEC group's dose effect hypothesis, indicating that local tumour control in PDACs is linked to higher radiation dosages. Advances in modern radiotherapy, particularly magnetic resonance-guided daily adaptation, enable clinicians to accurately target tumours with increased doses. However, further clinical trials are essential to explore how these precision techniques can be optimised to enhance patient outcomes.

Future precision radiotherapy clinical trials need to look in more detail at specific outcome measures. These might include pain, QoL, freedom from treatment time, patient-reported experience measures (PREMs) and patient-reported outcome measures (PROMs). Examples of prospective trials in this area are the ongoing LAPSTAR trial (15), and the planned NRG GI-011/LAP100 trial (16).

A key area for future research is optimising the scheduling and the integration of these techniques into to the treatment paradigms for locally advanced, non-metastatic PDAC. Although current evidence does not demonstrate a clear OS advantage for precision radiotherapy, alternative end points should be considered to improve and

rationalise the utility of these options.

Increasing radiotherapy dose typically comes at a trade off with toxicities. However, with the increasing utility of adaptive radiotherapy techniques, this allows radiotherapy to be delivered accurately and confidently with daily onset adaptations. The trade-off for this is the resource intensiveness of adaptive radiotherapy to deliver higher doses, and this area requires further study from a health economics perspective to justify the additional costs and resources involved.

Although there are limitations to this study, this prospective phase 2 study adds to the increasing body of evidence that dose escalation may allow better LC outcomes in non-metastatic PDACs, and further larger studies are required.

Conclusions

Advances in modern radiotherapy techniques have allowed higher doses of radiotherapy to be delivered safely to the pancreas. LC rates have improved, but OS rates remain poor. Further radiotherapy studies should focus on LC rates, patient reported outcomes measures, QoL scores, and freedom from further treatment time.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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