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Combined chemotherapy and endoscopic ultrasound-guided intratumoral 32P implantation for locally advanced pancreatic adenocarcinoma: a pilot study

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Fig. 1s, 2s, Table 1s, 2s
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ABSTRACT

Background This study evaluated clinical outcomes of combined chemotherapy and endoscopic ultrasound (EUS)-guided intratumoral radioactive phosphorus-32 (^{32}P) implantation in locally advanced pancreatic adenocarcinoma (LAPC).

Methods Consecutive patients with newly diagnosed LAPC were recruited over 20 months. Baseline computed tomography and ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}FDG) positron emission tomography–computed tomography were performed and repeated after 12 weeks to assess treatment response. Following two cycles of conventional chemotherapy, patients underwent EUS-guided ^{32}P implantation followed by six chemotherapy cycles.

Results 12 patients with LAPC (median age 69 years [interquartile range 61.5–73.3]; 8 male) completed treatment. Technical success was 100 % with no procedural complications. At 12 weeks, median reduction in tumor volume was 8.2 cm^3 (95 % confidence interval 4.95–10.85; P = 0.003), with minimal or no ^{18}FDG uptake in nine patients (75 %). Tumor downstaging was achieved in six patients (50 %), leading to successful resection in five (42 %), including four R0 resections (80 %).

Conclusions EUS-guided ^{32}P implantation was feasible, well tolerated, and resulted in a 42 % surgical resection rate. Further evaluation in a larger randomized multicenter trial is warranted.

Introduction

Pancreatic ductal adenocarcinoma is a deadly disease, in which 80 % of patients present with locally advanced or metastatic disease [1]. The current standard of care for locally advanced pancreatic adenocarcinoma (LAPC) is chemotherapy, which improves survival [2]. However, the rate of tumor downstaging allowing surgical resection after chemotherapy is only approximately 3 % [3]. When stereotactic body radiotherapy is added to chemotherapy, this proportion increases marginally to 7 %–10 % [3].

The implantation of radioactive particles directly into a tumor bed is known as brachytherapy. Endoscopic ultrasound (EUS)-guided implantation of iodine-125 and computed to-

mography (CT)-guided implantation of phosphorus-32 (^{32}P) have both been described in LAPC [4–6]. Beta ray-emitting ^{32}P has better tissue penetration and longer effective biological activity, lasting up to 86 days, compared with gamma ray-emitting ^{125}I, which lasts for 59 days [6]. Compared with a CT-guided approach, an EUS-guided approach potentially has a lower risk of bleeding, fistula formation, pain, and seed translocation [7].

A novel liquid form of ^{32}P has been developed (OncoSil; OncoSil Medical Ltd., Sidney, Australia), which can be administered using a 22-gauge EUS needle [8]. This is particularly beneficial in tumors of the uncinate process where using a large 19-gauge needle can be challenging. This pilot study evaluated the clinico-radio-pathological outcomes of combined chemotherapy and EUS-guided implantation of ^{32}P for patients with LAPC from a single tertiary referral center in Australia. This study was an extension of the multicenter PanCO study, to which our center contributed four patients [8]. Following positive outcomes from this study in our cohort, we consulted with OncoSil Medical Ltd. who agreed to provide ^{32}P for injection and permitted inclusion of these patients in the current, independent study.

Methods

Patients

Consecutive patients with histologically proven LAPC between 2 cm and 6 cm in maximal diameter were recruited from June 2017 to January 2019, from our weekly multidisciplinary team meeting. LAPC was defined according to National Comprehensive Cancer Network guidelines with > 180° contact or invasion into the celiac artery, superior mesenteric artery, superior mesenteric vein, or portal vein [9]. Exclusion criteria were pregnancy, multiple primary lesions, prior radiotherapy/chemotherapy for pancreatic ductal adenocarcinoma, previous history of malignancy within 5 years of diagnosis, local tumor invasion, allergy or hypersensitivity to silicon/phosphorus, medications that increase bleeding risk, poor functional status, medical comorbidities, distant metastases, or uncontrolled coagulopathy (see **Table 1 s** in the online-only Supplementary material). Patients were followed up for 1 year after injection of ^{32}P. The study was approved by the Royal Adelaide Hospital Research Ethics Committee (SSA/17/RAH/215). Informed written consent was obtained from all patients prior to the study.

Protocol

Pre-study assessment

All patients had abdominal (pancreatic protocol), chest CT, single photon emission computed tomography (SPECT) and ^{18}F-2-fluoro-2-deoxy-D-glucose–positron emission tomography (FDG-PET), which was assessed centrally to determine tumor volume (**Fig. 1 s**). The concentration of ^{32}P was 6.6 MBq/mL to deliver an absorbed dose of 100 Gy (±20 %), which was determined to be 8 % of tumor volume based on safety data from a Phase 1 study of six patients with LAPC. This was manufactured 4 weeks prior to the procedure by OncoSil Medical Ltd. and prepared 48 hours prior to the procedure by physicists at the Department of Nuclear Medicine. The protocol was used with permission from OncoSil Medical Ltd.

Study outline

Recruited patients were assessed by a dedicated study oncologist (N.S.) and were assessed for either FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin) or gemcitabine/nab-paclitaxel, based on their age, comorbidities, and preferences.

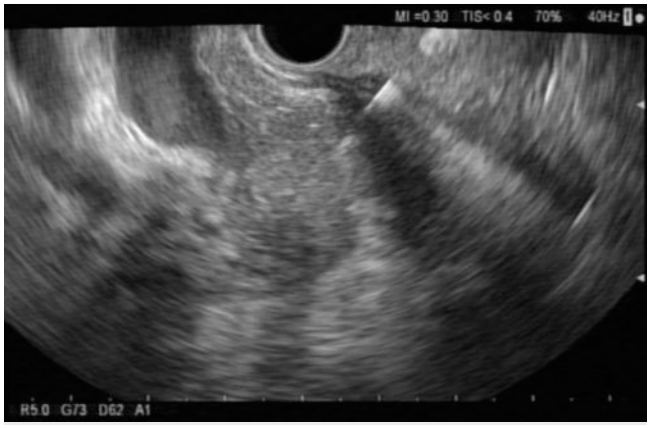
After 4–6 weeks (two doses of chemotherapy), patients underwent ^{32}P brachytherapy following which a further six doses of chemotherapy were administered.

EUS-guided ^{32}P implantation

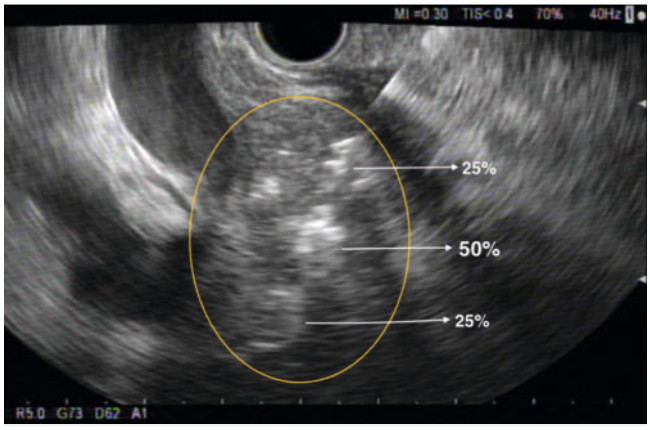
All procedures were performed with a consultant anesthetist using either monitored anesthesia care or general anesthesia. All proceduralists and assisting nurses wore a gown, face shield, mask, and cytotoxic gloves. Using a curvilinear echoendoscope (Olympus GF-UCT180; Olympus, Tokyo, Japan), connected to a Hitachi Prosound F75 machine, the pancreatic lesion was identified. Contrast EUS was performed using Definity contrast agent (Lantheus Medical Imaging, Billerica, Massachusetts, USA), which generates microbubbles to outline the microvasculature of the tumor and pancreas. A 22-gauge fine-needle aspiration (FNA) needle (Cook Echotip Ultra; Cook Medical, Bloomington, Indiana, USA) was used to puncture the lesion under EUS visualization under standard B-mode with Doppler to avoid injection into blood vessels (▶ **Fig. 1**). Upon puncture, the stylet was removed from the needle and a prepared syringe with the desired amount of ^{32}P was attached by a nuclear medicine physician. In relation to the echoendoscope head, for tumors > 2 cm in maximal diameter, OncoSil was distributed with 25 % at the distal edge, 50 % in the center, and 25 % at the proximal edge within the tumor (▶ **Fig. 2**). A total of 1 mL of saline was injected to ensure that no residual ^{32}P remained within the dead space of the needle (**Fig. 2 s**). The needle was then withdrawn from the tumor without retraction of the sheath into the scope channel, by pulling back the echoendoscope into the gastric antrum, to avoid contamination of the scope with ^{32}P. The needle was further flushed with 5 mL of saline to remove any remaining radioactive material and subsequently retracted into the sheath. The entire complex was then removed from the patient and disposed of in a radioactive hazard disposal container along with used needles, syringes, and gauze. The lumens of both the FNA needle and working channel of the echoendoscope were further flushed with 50 mL of water, to avoid any contamination of the echoendoscope. The endosonographer, medical and nursing assistants, as well as the endoscopy suite were checked for any ^{32}P contamination by a nuclear medicine safety officer using a Geiger counter.

Post-implantation assessment

At 4 hours post-procedure, patients underwent SPECT and Bremsstrahlung scans to confirm the localization of ^{32}P implantation and to check for dissemination of the material within the abdomen. These scans were repeated 7 days post-procedure to assess retention of ^{32}P within the tumor. The tumor size was reassessed at 12 weeks after the commencement of treatment.



▶ **Fig. 1** Identification of the pancreatic lesion followed by puncture using a 22-guage fine-needle aspiration needle.



▶ **Fig. 2** Injection of ^{32}P in a 25 %–50 %–25 % distribution.

Following brachytherapy, patients were advised to isolate themselves in a similar way to that required for radioiodine treatment (1 week of sleeping in a separate bed, using a separate toilet).

Outcomes

The primary outcome was the rate of tumor downstaging allowing surgical resection. Secondary outcomes included changes in tumor size and volume, SPECT activity, technical success, retention of ^{32}P, pain score, serious and nonserious adverse effects, and survival. Adverse effects were graded according to US National Cancer Institute Common Terminology Criteria for Adverse Events from grade 1 to 4 (mild to life threatening).

Definitions

Successful tumor downstaging was defined as a reduction in tumor size that resulted in no vascular involvement and allowed surgical resection. Tumor size and volume were determined from CT scans by a centralized radiology center, using a standardized program. Technical success was defined as the ability to inject ^{32}P into the cancer mass without any leak to the surrounding organs as assessed by Bremsstrahlung scans. Pain scores were assessed using a visual analog scale from 0 to 10.

▶ **Table 1** Baseline characteristics of the patient cohort (n = 12) and details of ^{32}P intratumoral implantation.

Sex, n (%)	
▪ Female	4 (33)
▪ Male	8 (66)
Tumor location, n (%)	
▪ Uncinate	3 (25)
▪ Head	6 (50)
▪ Neck	3 (25)
Chemotherapy regimen, n (%)	
▪ FOLFIRINOX	4 (33)
▪ Gem/Nab	8 (66)
Route of injection, n (%)	
▪ Descending duodenum	3 (25)
▪ Duodenal bulb	9 (75)
Volume of ^{32}P implanted, median (IQR), mL	1.6 (1.0–2.0)
Amount of radiation implanted, median (IQR), MBq	10.4 (7.3–13.9)

FOLFIRINOX, folinic acid, fluorouracil, irinotecan, oxaliplatin; IQR, interquartile range.

Data analysis

Data were expressed as median with interquartile range (IQR) for skewed data or mean with standard error of the mean (SEM) for normally distributed data. Outcomes were compared using Prism 8.4.2 (GraphPad Software, San Diego, California, USA), using Wilcoxon Rank Sum testing to compare median values, Fisher's exact test for binary data, and Student's *t* test for continuous variables. A *P* value of <0.05 was considered statistically significant.

Results

A total of 12 patients (mean age 69 years [IQR 61.5–73.3]; 8 male) with LAPC completed the treatment protocol (**Table 2 s**). Eight patients received gemcitabine/nab-paclitaxel and four received FOLFIRINOX. All patients underwent EUS-guided ^{32}P implantation after the second chemotherapy cycle. Patient demographics, location and size of the lesion, calculated tumor volume, and volume of ^{32}P implanted are summarized in ▶ **Table 1**.

EUS-guided ^{32}P implantation

Technical success was 100 % and there were no intra- or postprocedural complications, such as intravascular injection, pain, bleeding, or pancreatitis. All injections were performed using the transduodenal route either from the duodenal bulb (9/12 [75 %]) or second part of the duodenum (3/12 [25 %]) for tu-

mors involving the neck/head or uncinate process, respectively (▶ **Table 1**). CT-SPECT Bremsstrahlung scans confirmed the localization of the radioactive signal to the cancer seen on pre-implantation CT imaging in all patients on the day of implantation (▶ **Fig. 3**) and in 100 % of patients 7 days after implantation. Two patients (16.7 %) had some activity in the liver and duodenum at Day 7 post-implantation, as residual amounts of ^{32}P were eliminated via the liver and gut.

Impact on tumor growth

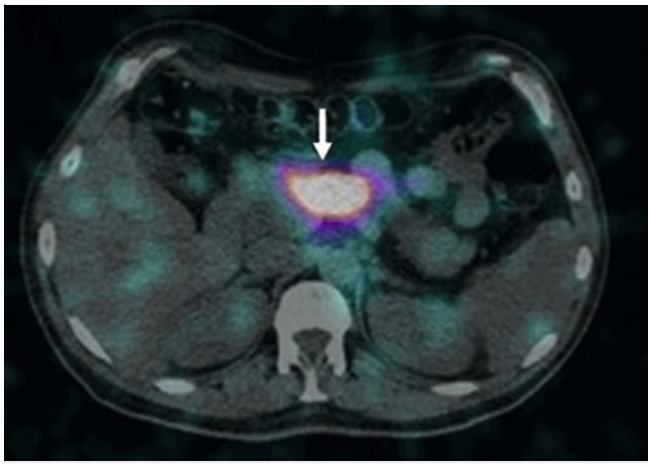
After 12 weeks of combination treatment, there was a significant median reduction in tumor size from 31 mm (IQR 25.3–43.8) to 28.5 mm (IQR 20.0–36.5; P = 0.003), and tumor volume from 17.7 cm^3 (IQR 12.3–27.9) to 10.6 cm^3 (IQR 3.7–16.9; P = 0.003), with a median reduction of 8.2 cm^3 (95 % confidence interval [CI] 4.95 to 10.85) in tumor volume (▶ **Table 2**). Similarly, there was a marked reduction in median serum cancer antigen 19–9 level, from 78.0 U/L (IQR 7.8–467.5) to 21.5 U/L (IQR 8.0–78.0; P = 0.007) (▶ **Table 2**). Follow-up PET-CT showed minimal or no ^{18}FDG uptake in nine patients (75 %).

Impact on tumor staging and surgical resection

In six patients (50 %), vascular involvement was no longer observed on cross-sectional imaging, resulting in tumor downstaging (▶ **Fig. 4**). Of these, one patient had severe chronic obstructive airway disease that precluded surgical resection. The remaining five patients (42 %) underwent Whipple's resection, with four patients (80 %) undergoing R0 resection with clear margins on histology.

Impact on clinical outcomes and survival

The overall median survival was 15.0 months, with all five patients who underwent surgery surviving compared with only 3/6 patients who did not achieve tumor downstaging (100 % vs. 50 %; P < 0.05). Although there was a numerical difference in pain scores before and after combined chemotherapy and ^{32}P treatment, this was not statistically significant (3.0 [SEM 0.9] to 1.7 [SEM 0.5] ; P = 0.10).



▶ **Fig. 3** Bremsstrahlung single photon emission computed tomography scan 4 hours post ^{32}P injection showing localization into the pancreatic cancer (white arrow).

Adverse effects

Two patients developed lower limb cellulitis and one patient had diarrhea, both of which were probably related to chemotherapy. There were no immediate or long-term serious adverse effects attributable directly to EUS-guided implantation of ^{32}P.

Discussion

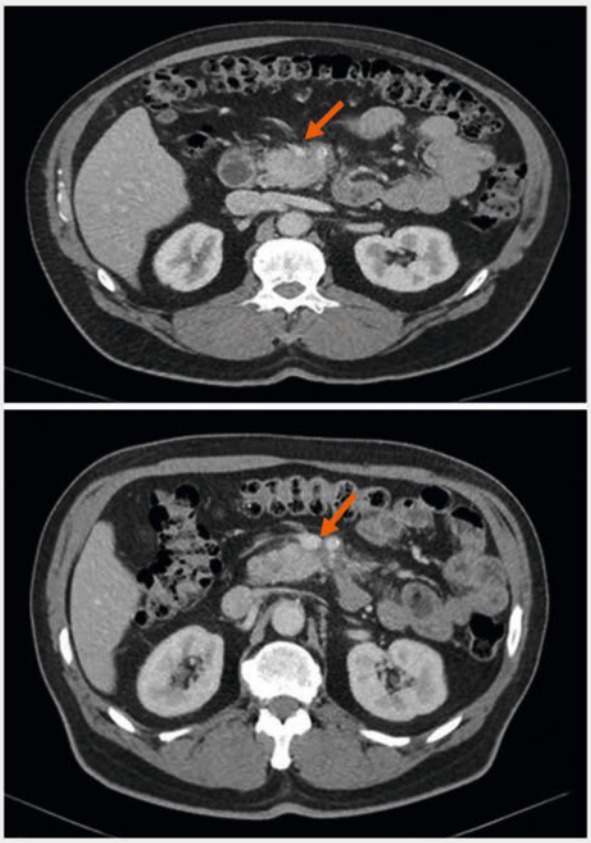
For patients diagnosed with pancreatic ductal adenocarcinoma, surgical resection improves median survival from 6 months to 18 months [10, 11]. The PanCO study reported a 24 % rate of surgical resection; however, we reported a rate of 42 % [8].

Possible reasons for this positive result in both studies include an increase in tumor vascularity due to a low dose of sustained radiation as opposed to larger intermittent doses with external beam radiotherapy, which can cause destruction of vascular beds. This potentially allows more efficient delivery of

▶ **Table 2** Outcomes of combined chemotherapy and intratumoral implantation of ^{32}P.

	Baseline (n = 12)	Week 12 after treatment (n = 12)	*P* value
Tumor size, median (IQR), mm	31.0 (25.3–43.8)	28.5 (20.0–36.5)	0.003
Tumor volume, median (IQR), cm^3	17.7 (12.3–27.9)	10.6 (3.7–16.9)	0.003
CA 19–9 level, median (IQR), U/L	78.0 (7.8–467.5)	21.5 (8.0–78.0)	0.007
PET positivity, n (%)	12/12 (100)	3/12 (25)	<0.001
Vascular involvement, n (%)	12/12 (100)	6/12 (50)	0.02
Resectability by imaging, n (%)	0/12 (0)	6/12 (50)	0.02
Surgical resection of mass after 16 weeks of treatment, n (%)	0/12 (0)	5/12 (42)	0.04
Pain score (VAS), mean (SD)	3.0 (0.9)	1.7 (0.5)	0.10

IQR, interquartile range; CA, cancer antigen; PET, positron emission tomography; VAS, visual analog scale; SD, standard deviation.



▶ **Fig. 4** Computed tomography images of a pancreatic head lesion in the same patient: **a** before ^{32}P injection; **b** after ^{32}P injection. Note the superior mesenteric vein (arrowhead) encasement of the lesion in the first image and a clear plane seen around the same vessel 12 weeks after treatment.

chemotherapeutic agents to a tumor that is characteristically hypovascular [12, 13].

Another possibility is an increase in cytotoxic T-cell infiltration into the tumor and subsequent immunogenic apoptosis. Previous animal studies support this theory showing greater tumor antigen presentation in concurrent versus sequential chemoradiotherapy. Hence, the timing of therapy along with a low dose of sustained radiation may lead to a better clinical response to FOLFIRINOX [14].

The potential challenges in implementation of ^{32}P brachytherapy include a skilled endosonographer, an established nuclear medicine department, and the high costs and labor-intensive nature of ^{32}P manufacture and preparation. However, there are two potential benefits of using this liquid medium for brachytherapy: 1) the ability to use a more flexible 22-gauge needle rather than a 19-gauge needle; 2) a more accurate dose of radiation, matching tumor volume to dose required.

The limitations of this study were the small sample size, the use of two different chemotherapy regimens, and the fact that our study was conducted in a single tertiary institution. However, our data provide real-world experience, with findings similar to those of the PanCO study, and offer a framework for further randomized, multicenter studies.

Conclusion

This pilot study is the first to report the use of EUS-guided intratumoral implantation of ^{32}P in combination with standard chemotherapy for the treatment of LAPC. The treatment was feasible, safe, and contributed to a 50 % rate of tumor downstaging, and 42 % rate of surgical resection, of which 80 % were R0 resections. Although these results are promising, a randomized study with a control chemotherapy group would be crucial in determining the additional effect of brachytherapy in patients with LAPC.

Competing interests

The authors declare that they have no conflict of interest.

Clinical trial

Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT 03003078 | Type of study: Prospective, Single Centre

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