THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Intra-Tumoral Infusion of P-32 Radiolabeled Microspheres for Localized Radiotherapy of Pancreatic Tumors

William D. Erwin, MS, FAAPM
Senior Medical Physicist
Department of Imaging Physics

Financial Disclosure

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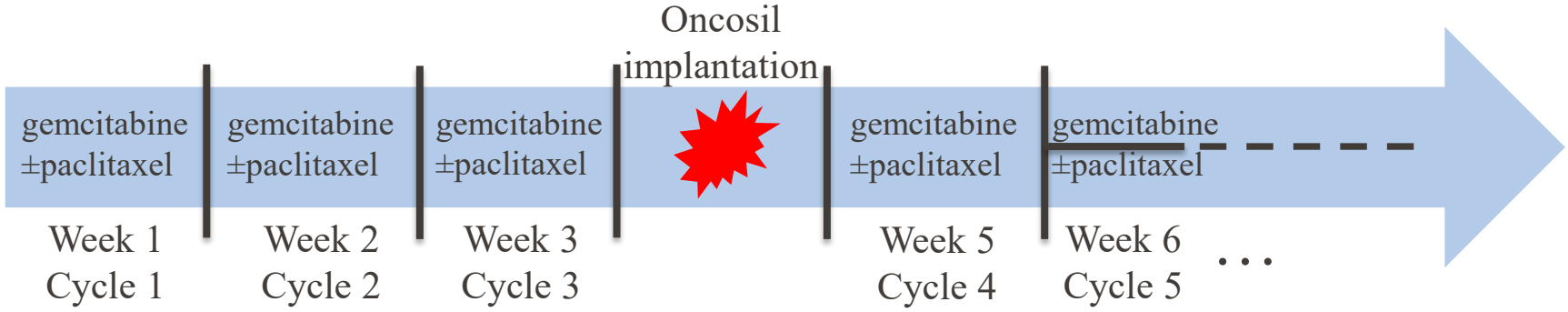
Oncosil™ (Oncosil Medical Ltd.)

Single-use brachytherapy device

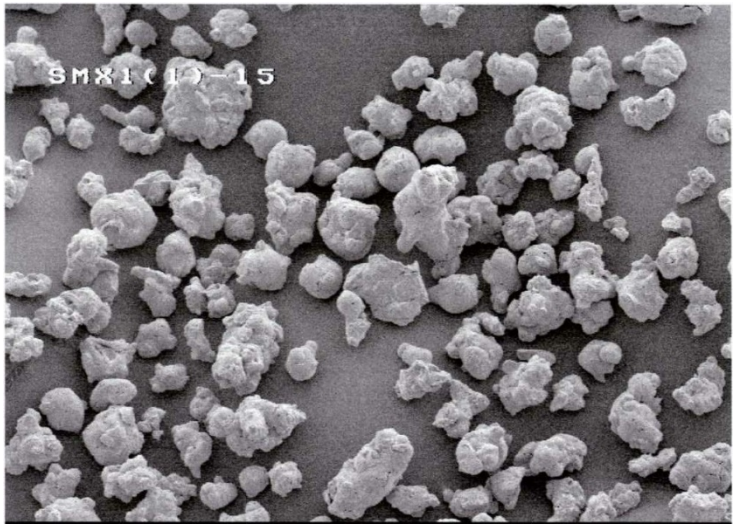
- indicated for treatment of locally advanced unresectable pancreatic cancer (LAPC)
- in combination with gemcitabine-based chemotherapy
- Approved in: EU, UK, Hong Kong, Singapore, Malaysia, New Zealand, Switzerland
- Clinical trials in the US completed



Oncosil

Silicon nanoporous microparticles (on the order of 30 μm, but variable)

- Highly-doped with phosphorous (^{31}P)
- Exposed to neutrons (nuclear reactor): $^{31}P(n,\gamma)^{32}P$



Phosphorus-32

- Pure β^- emitter
- E_{avg} = 0.695 MeV, E_{max} = 1.711 MeV
- Half-Life: 14.27 days
- β^- range (mm): 2.76 (E_{avg}), 8.14 (E_{max})

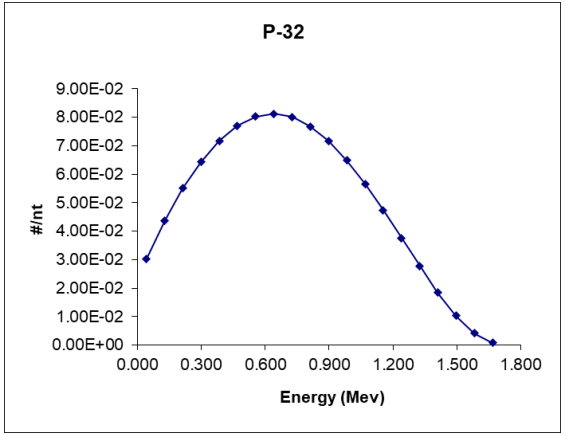
  (Cole A. Radiat Res. 1969;38:7–33, ICRP Report No. 37)
- ~100% (macroscopic) local energy deposition

  (1.11E-13 Gy-kg/Bq-s)

Parent Nucleus	Parent E(level)	Parent Jπ	Parent $T_{1/2}$	Decay Mode	GS-GS Q-value (keV)	Daughter Nucleus
$^{32}_{15}P$	0	1+	14.268 d 5	β^-: 100 %	1710.66 4	$^{32}_{16}S$

Beta-:

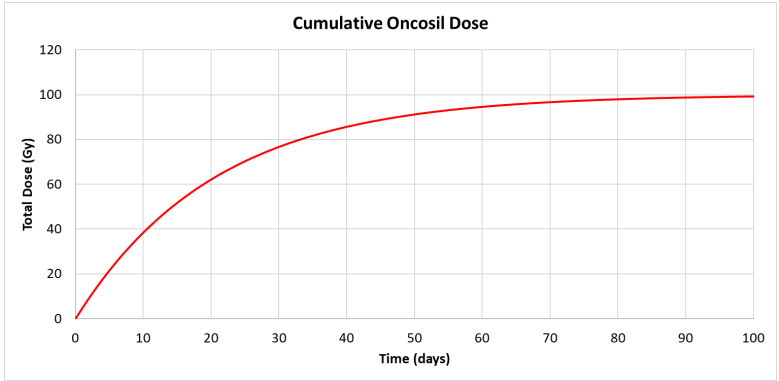
Energy (keV)	End-point energy (keV)	Intensity (%)	Dose (MeV/Bq-s)
695.03	1710.66 4	100 %	0.695



Sources: https://www.nndc.bnl.gov/nudat3/, https://www.doseinfo-radar.com

Oncosil Prescription

100 Gy (±20%)



- Assumptions
  - 100% local energy absorption and uniform dose (i.e., uniform microparticle distribution throughout tumor)
  - ^{32}P physical decay only (i.e., no biologic clearance)
  - 1.03 g/cc
  - Tumor volume: 14 to 113 cc (shortest diameter: 2 cm, longest diameter: 6 cm)

$$100\ \text{Gy} = 1.11\text{E-}04\ \text{Gy-g/MBq-s} \times \text{MBq}_{inj} \int_0^{\infty} e^{-\lambda t}\, dt \,/\, M_{tumor}(g);\ \lambda = 5.62\text{E-}07\ s^{-1}$$

$$\text{MBq}_{inj} = 0.5215 \times V_{tumor}(cc)\ (= 100 \times V_{tumor} \times 1.03 \times 5.62\text{E-}07 \,/\, 1.11\text{E-}04)$$

^{32}P concentration in diluent: 6.6 MBq/ml ($V_{Oncosil} = \text{MBq}_{inj} / 6.6$)

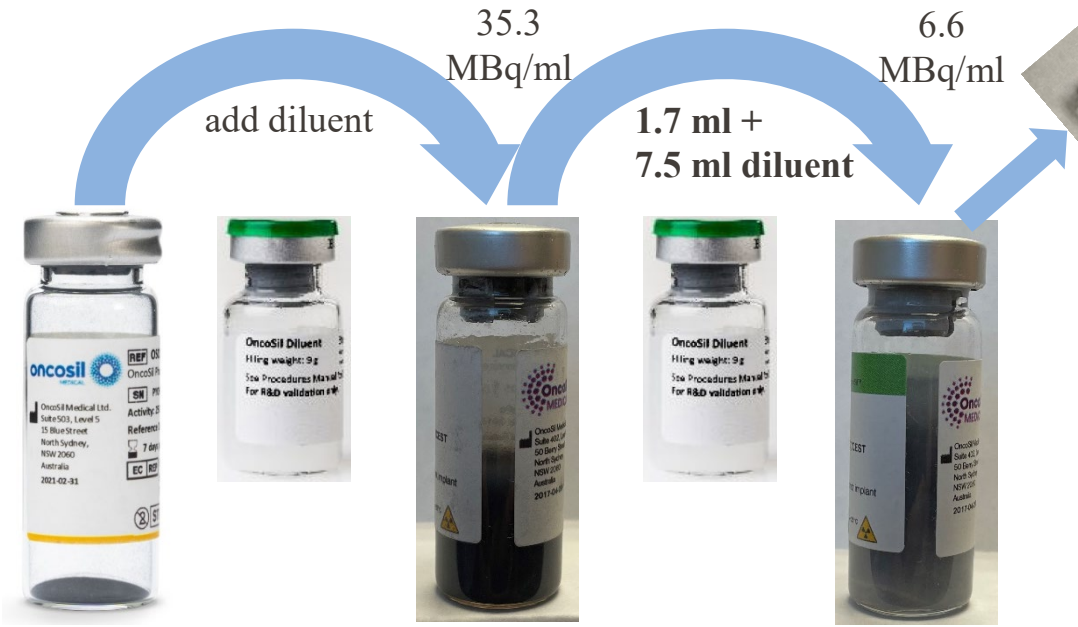
$V_{Oncosil}$ = 8% of V_{tumor} ($[\text{MBq}_{inj} / 6.6] / V_{tumor} = 0.079$ rounded off to 0.08)

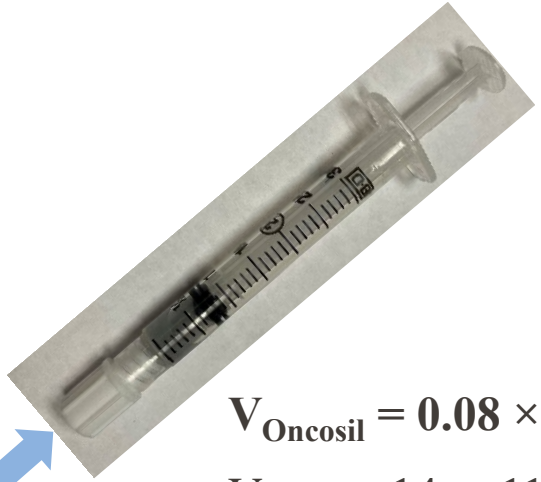
Oncosil Preparation

250 MBq ^{32}P calibrated on reference day (0)

Day of implantation (Di): -2 to +7

Diluent ml: $7.0e^{ln(2)Di/14.27}$





$$V_{Oncosil} = 0.08 \times V_{tumor}$$

V_{tumor} = 14 to 113 cc

$V_{Oncosil}$ = 1.1 to 9 ml

Oncosil Implantation (EUS-guided)

- echoendoscope (EES) guided to stomach or duodenum (whichever provides best access to the tumor)
- 22 gauge EUS guided FNA needle loaded into EES biopsy channel and advanced through gastric wall and into the tumor
- 3-way Luer lock tap and Oncosil syringe attached to FNA needle
- Slow infusion (visualized with EUS), followed by saline flush (1.5 ml)
- With EES in stomach, 3.5 ml saline flush
- EES + needle withdrawn, tip rinsed w/ water (50 ml) over radioactive waste bag, needle placed in radioactive waste container

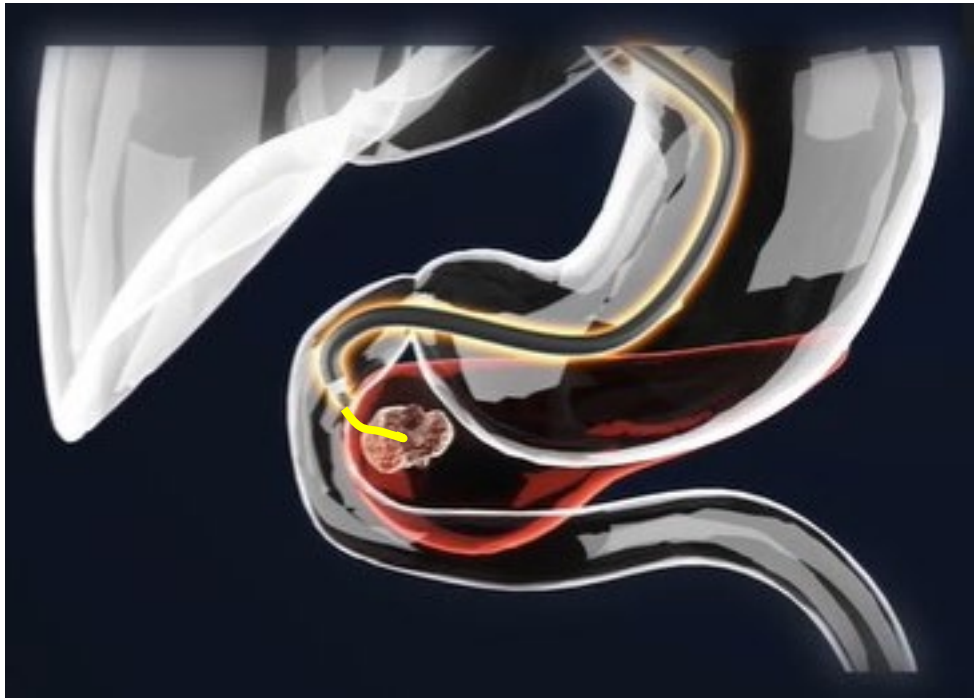
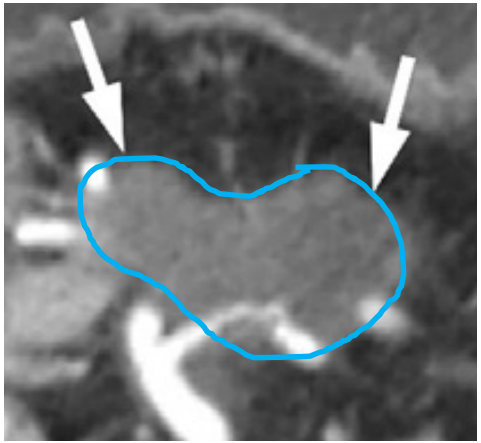


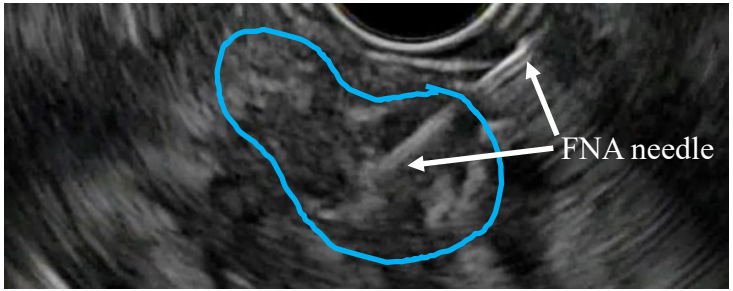
Image courtesy of Oncosil Medical Ltd.

Oncosil Implantation: Example Images

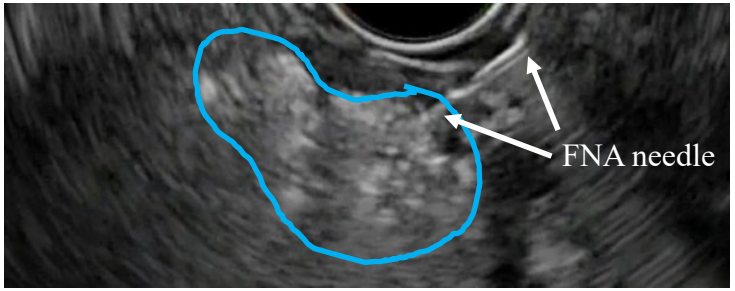
pre-Tx contrast CT of tumor



endoscopic US pre-infusion



endoscopic US post-infusion (Oncosil "blush")

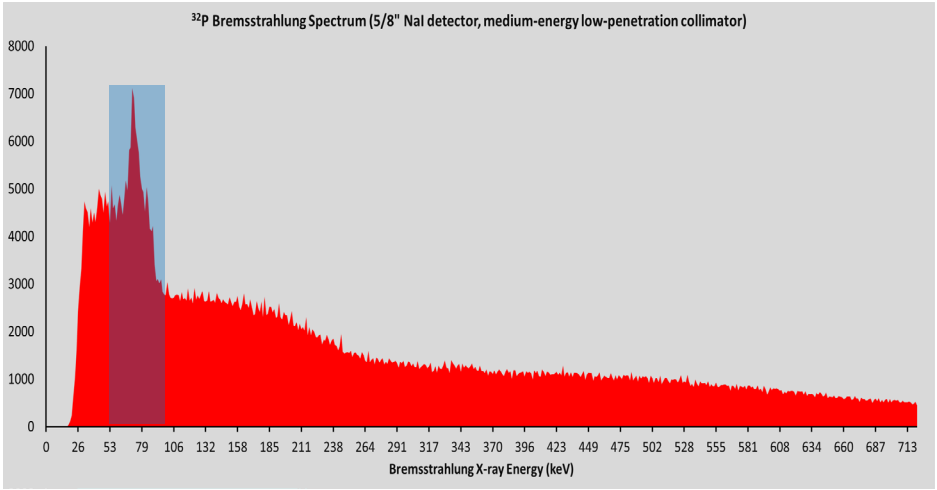


Images adapted from Bhutani et al. VideoGIE 2019; 4(5):223-5

Oncosil Post-Therapy Imaging

Secondary bremsstrahlung x-ray

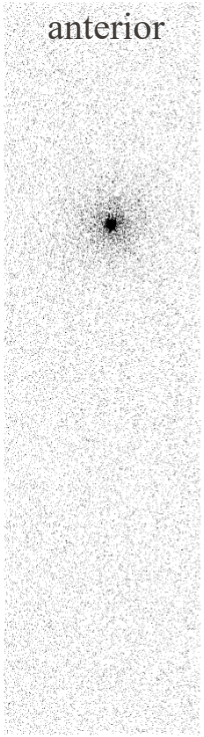
- ^{32}P is a pure beta emitter (no photon emissions)
- Manufacturer-recommended imaging
  - Post-implant time points: ≤ 4 hours and 7 days
  - Energy window: 75 keV±30% (52.5 – 97.5 keV)
  - Collimation: medium energy
  - Whole body planar (WB): 10 cm/min
  - SPECT: 90–120 views/360°, 30 sec/view, 128x128 matrix
  - CT: site's standard-of-care for SPECT/CT
- Tumor activity between time points should:
  - decrease over time according to ^{32}P T½ (14.27 d)
  - not redistribute (i.e., biodistribution should not change)

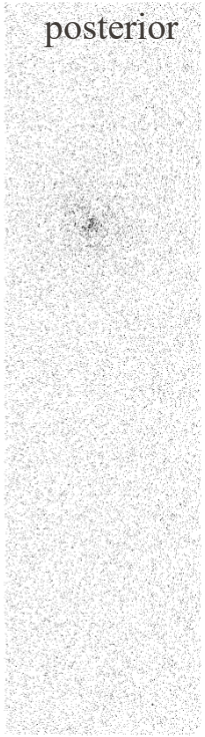


Oncosil Post-Therapy Imaging

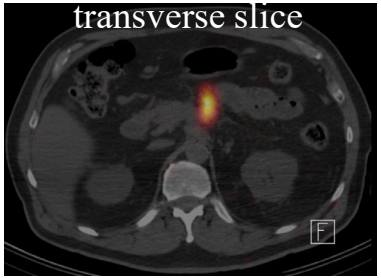
4-h post-implant

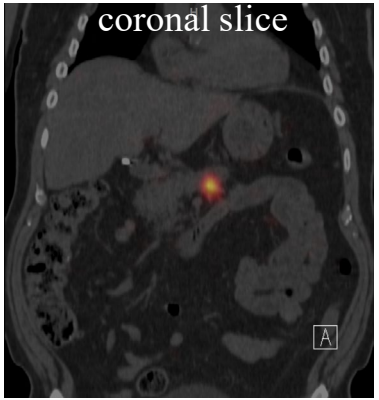
WB



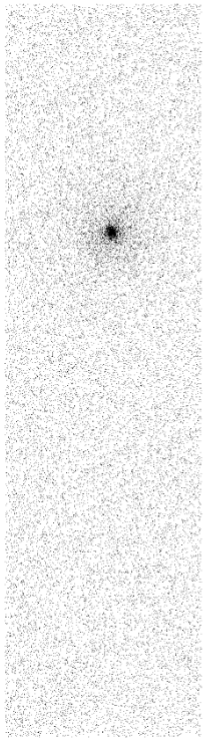


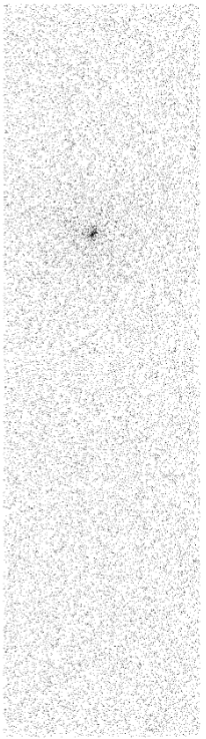
SPECT

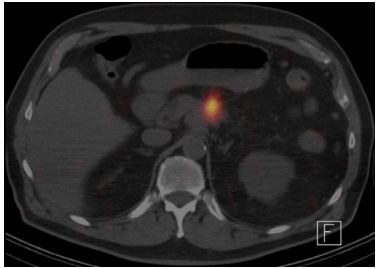




7-d post-implant







Oncosil Bremsstrahlung Imaging Limitations

- ^{32}P activity in the WB and SPECT images is a tiny "island" in an "ocean" of background (i.e., there is a complete lack of anatomical information and, thus, localization)
- Patient (e.g., breathing) motion
  - during WB and SPECT scanning, between the SPECT and CT scans, and during the CT scan
- Image registration is difficult and questionable
  - Single, small "island" in the SPECT, versus

    tumor + rest of pancreas (similar HU values) + a lot of other anatomy in the CT
  - Motion between SPECT and CT
- The SPECT images are low-count, and non-quantitative (i.e., counts, not Bq or Bq/ml)

A better method of imaging the Oncosil microparticle distribution is needed

Oncosil – our experience

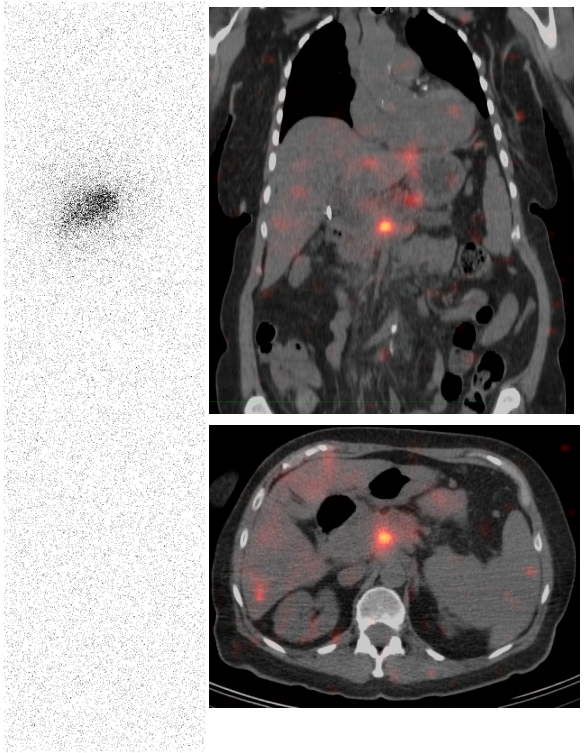
OncoPac-1 Pilot Study

In combination with gemcitabine or gemcitabine+nab-paclitaxel in subjects with unresectable LAPC

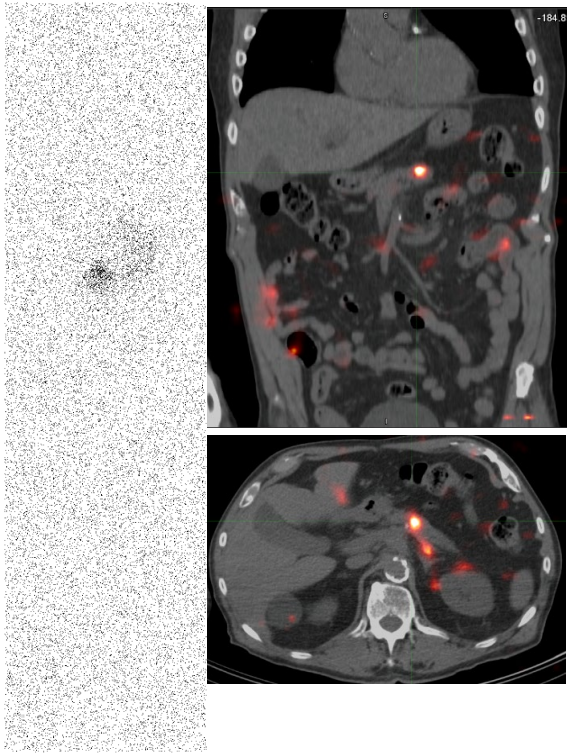
	Baseline Tumor Volume	Survival Post-Oncosil
Patient 1	23.2 cc	~1.5 y
Patient 2	31.5 cc	~6 m
Patient 3	8.44 cc	unknown (returned to S. Africa post-Tx)
Patient 4	52.5 cc	~2 y

Oncosil – our experience

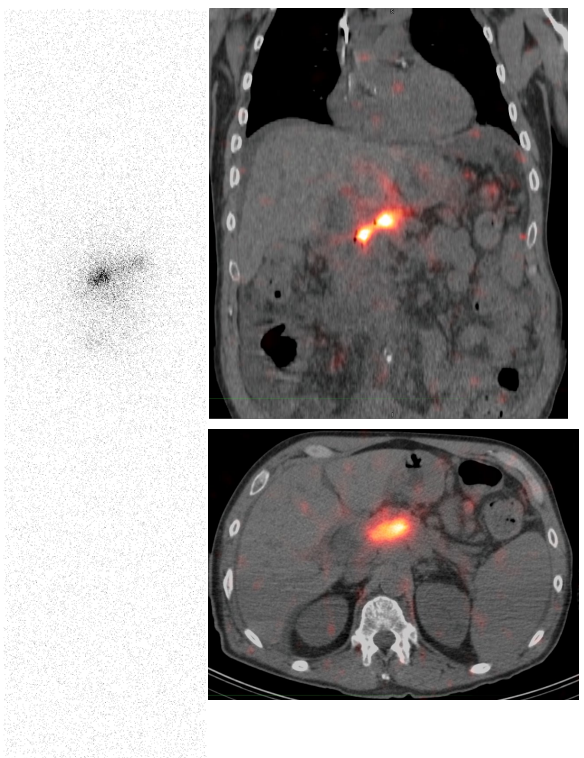
Patient 2 (31.5 cc)



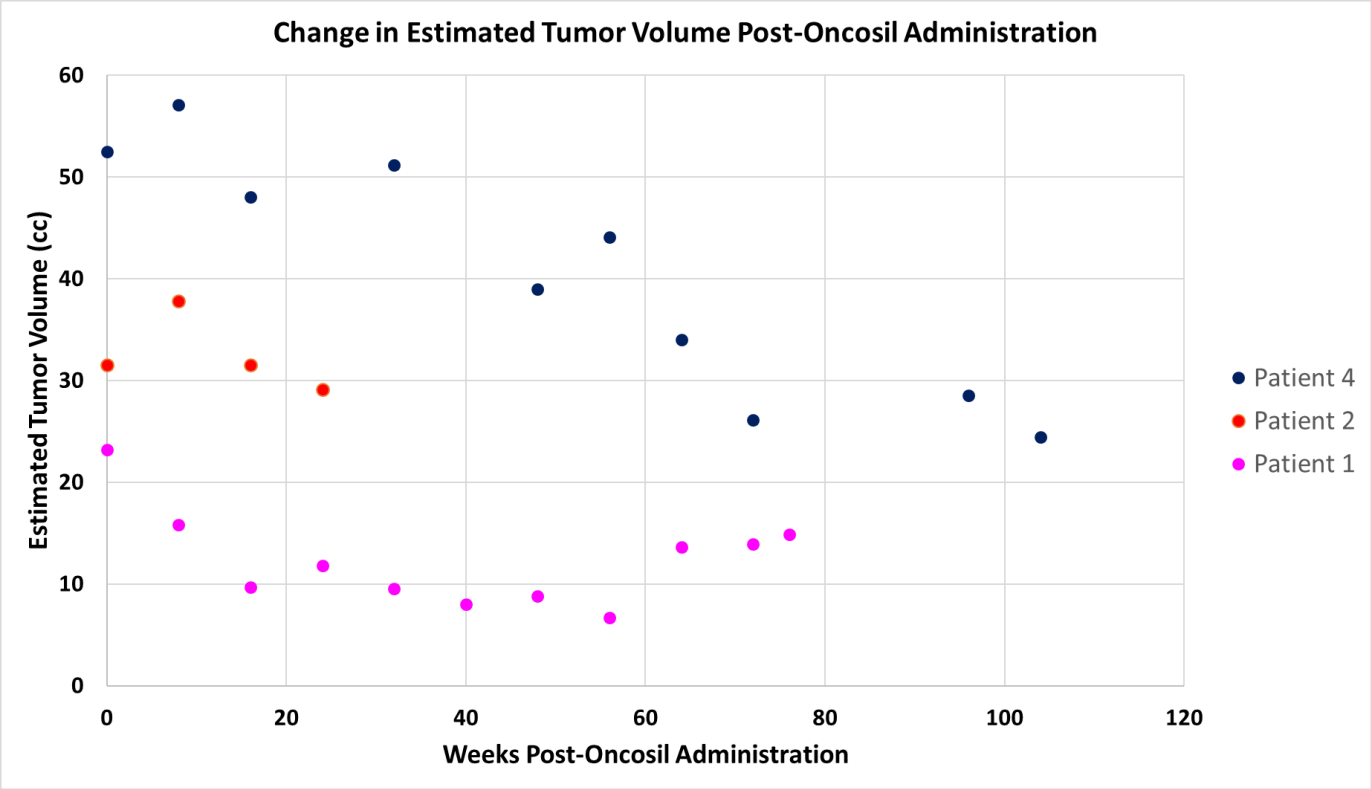
Patient 3 (8.44 cc)



Patient 4 (52.5 cc)



Oncosil – our experience



Week 0 volume is pre-treatment baseline

Oncosil – outcomes

PanCO international, multi-center, single-arm pilot study (3/2017 - 6/2018)

- 42 patients with unresectable LAPC (Australia, Belgium, UK)
- Oncosil with Gemcitabine+Nab-Paclitaxel (34) or FOLFIRINOX (8)

Median Baseline Tumor Volume	24.35 cc (range: 7.9–68.7)
Partial Response	13 (31%)
Stable Disease	29 (69%)
Overall Response Rate	13 (31%)
Local Disease Control at 16 weeks	38 (91%)
Median Progression-Free Survival	9.3 months (32.3% 1-year rate)
Median Overall Survival	16.0 months (64.0% 1-year rate)
Median tumor volume change from baseline	-52% (range: +11% to -90%)

Ross P et al. Abstract O-1, ESMO World Congress on Gastrointestinal Cancer 2020

Oncosil – outcomes

PanCO vs. state-of-the-art standard-of-care (literature review)

- SoC therapy: chemo (CT) or induction chemo (ICT) + consolidated chemoradio (CCRT)

	PanCO	CT	ICT+CCRT
Median PFS in months [95% CI]	9.3 [7.2, 12.2]	6.6 [6.2, 7.8] (27 trials) p=0.010	9.1 [7.6, 9.3] (16 trials) p=0.227
Median OS in months [95% CI]	16.0 [11.1, nc]	12.7 [11.9, 13.6] (34 trials) p<0.001	12.6 [12.2, 14.0] (20 trials) p<0.001
One-year % survival [95% CI]	64.0 [47.5, 76.5]	50.4 [45.3, 55.5] (34 trials) p=0.013	55.2 [49.4, 60.9] (20 trials) p<0.001

Allerdice S et al. Abstract P-260, ESMO World Congress on Gastrointestinal Cancer 2020

Oncosil – summary

- A novel, direct-infusion unsealed brachytherapy device for unresectable LAPC
- Feasibility of EUS-guided delivery has been demonstrated
- In combination with gemcitabine+nab-paclitaxel or FOLFIRINOX
  - appears to confer additional benefit compared to SoC CT alone and ICT+CCRT
- Limitations
  - Uniform distribution, and, thus, uniform dose, is assumed (not the case in reality)
    - Dose distribution corresponding to “uniform 100 Gy” will vary from tumor to tumor
  - Aside from live EUS, visualization of implant localization is difficult
    - “hot spot” SPECT/CT insufficient (weak bremsstrahlung signal, SPECT-CT misregistration)
    - method allowing actual particle distribution visualization (and voxel dosimetry?) is needed

References

Bhutani MS, Cazacu IM, Luzuriaga Chavez AA, et al. Novel EUS-guided brachytherapy treatment of pancreatic cancer with phosphorus-32 microparticles: first United States experience. VideoGIE 2019; 4(5):223-5 (https://www.videogie.org/article/S2468-4481(19)30047-5/fulltext) (includes a case report video)

Oncosil Medical Ltd. Web site (https://www.oncosil.com/)
(links to scientific meeting posters and publications found there)

Thank you!

Questions?

Contact: werwin@mdanderson.org