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Stereotactic body radiotherapy with or without selective dismutase mimetic in pancreatic adenocarcinoma: an adaptive, randomised, double-blind, placebo-controlled, phase 1b/2 trial

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- This trial was designed to establish the efficacy and toxicity afforded by the selective dismutase mimetic avasopasem manganese when combined with ablative SBRT for localised pancreatic ductal adenocarcinoma.
- In this adaptive, randomised, double-blind, placebo-controlled, phase 1b/2 trial, patients aged 18 years or older with borderline resectable or locally advanced pancreatic cancer who had received at least 3 months of chemotherapy and had an Eastern Cooperative Oncology Group performance status of 0–2 were enrolled.
- Eligible patients were randomly assigned (1:1), with block randomisation (block sizes of 6–12) with a maximum of 24 patients per group, to receive daily avasopasem (90 mg) or placebo intravenously directly before (ie, within 180 min) SBRT (50, 55, or 60 Gy in five fractions, adaptively assigned in real time by Bayesian estimates of 90-day safety and efficacy).
- The primary objective was to find the optimal dose of SBRT with avasopasem or placebo as determined by the late onset EffTox method.
- Between Jan 25, 2018, and April 29, 2020, 47 patients were screened, of whom 42 were enrolled (median age was 71 years [IQR 63–75], 23 [55%] were male, 19 [45%] were female, 37 [88%] were White, three [7%] were Black, and one [2%] each were unknown or other races) and randomly assigned to avasopasem (n=24) or placebo (n=18);
- The placebo group was terminated early after failing to meet prespecified efficacy parameters. At data cutoff (June 28, 2021), the avasopasem group satisfied boundaries for both efficacy and toxicity.
- In the placebo group, grade 3 adverse events within 90 days of SBRT were abdominal pain, acute cholangitis, pyrexia, increased blood lactic acid, and increased lipase (one [6%] each); no grade 4 events occurred.
- In the avasopasem group, grade 3–4 adverse events within 90 days of SBRT were acute kidney injury, increased blood alkaline phosphatase, haematoma, colitis, gastric obstruction,

lung infection, abdominal abscess, post-surgical atrial fibrillation, and pneumonia leading to respiratory failure (one [4%] each).

- SBRT that uses 50 or 55 Gy in five fractions can be considered for patients with localised pancreatic ductal adenocarcinoma. The addition of avasopasem might further enhance disease outcomes. A larger phase 2 trial (GRECO-2, NCT04698915) is underway to validate these results.

Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study

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- Most patients with metastatic cancer eventually develop resistance to systemic therapy, with some having limited disease progression (ie, oligoprogression).
- The study aims to evaluate whether stereotactic body radiation therapy (SBRT) targeted to oligoprogressive sites could improve patient outcomes.
- It is a phase 2, open-label, randomised controlled trial of SBRT in patients with oligoprogressive metastatic breast cancer or non-small-cell lung cancer (NSCLC) after having received at least first-line systemic therapy, with oligoprogression defined as five or less progressive lesions on PET-CT or CT.
- Patients aged 18 years or older were enrolled with a 1:1 randomisation between standard of care (standard-of-care group) and SBRT plus standard of care (SBRT group). Randomisation was done with a computer-based algorithm with stratification by number of progressive sites of metastasis, receptor or driver genetic alteration status, primary site, and type of systemic therapy previously received.
- The primary endpoint was progression-free survival, measured up to 12 months.
- From Jan 1, 2019, to July 31, 2021, 106 patients were randomly assigned to standard of care (n=51; 23 patients with breast cancer and 28 patients with NSCLC) or SBRT plus standard of care (n=55; 24 patients with breast cancer and 31 patients with NSCLC). 16 (34%) of 47 patients with breast cancer had triple-negative disease, and 51 (86%) of 59 patients with NSCLC had no actionable driver mutation. The study was closed to accrual before reaching the targeted sample size, after the primary efficacy endpoint was met during a preplanned interim analysis.
- The median follow-up was 11·6 months for patients in the standard-of-care group and 12.1 months for patients in the SBRT group. The median progression-free survival was 3.2 months (95% CI 2·0–4·5) for patients in the standard-of-care group versus 7.2 months (4·5–10·0) for patients in the SBRT group (hazard ratio [HR] 0·53, 95% CI 0·35–0·81; p=0·0035). The median progression-free survival was higher for patients with NSCLC in the SBRT group than for those with NSCLC in the standard-of-care group (10·0 months [7·2–not reached] vs 2.2 months [95% CI 2.0–4.5]; HR 0.41, 95% CI 0.22–0.75; p=0.0039), but no difference was found

for patients with breast cancer (4.4 months [2.5–8.7] vs 4.2 months [1.8–5.5]; 0.78, 0.43–1.43; p=0.43).

- The trial showed that progression-free survival was increased in the SBRT plus standard-of-care group compared with standard of care only.
- Oligoprogression in patients with metastatic NSCLC could be effectively treated with SBRT plus standard of care, leading to more than a four-times increase in progression-free survival compared with standard of care only.
- No benefit was observed in patients with oligoprogressive breast cancer.

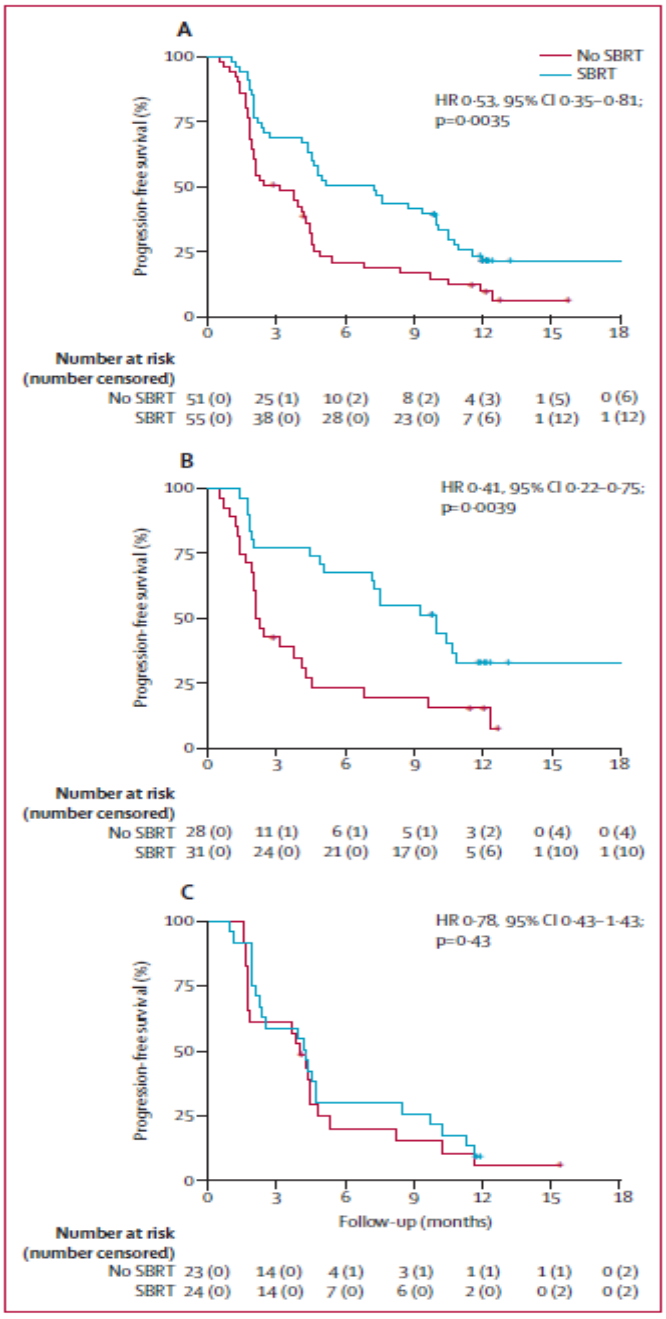

Figure 2: **Progression-free survival**
Progression-free survival in the entire cohort (A), patients with non-small-cell lung cancer (B), and patients with breast cancer (C). Tick marks indicate censored data. HR=hazard ratio. SBRT=stereotactic body radiotherapy.

Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: Meta-Analysis and International Stereotactic Radiosurgery Society Practice Guidelines

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- This systematic review was conducted according to criteria of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 statement. A literature search was performed using the Embase, MEDLINE, Cochrane, and Scopus databases. The following search terms were used: ("stereotactic body radiotherapy" OR "SBRT" OR "SABR" OR "stereotactic ablative radiotherapy") AND ("hepatocellular carcinoma" OR "HCC").
- An aggregated data meta-analysis was conducted to assess overall survival (OS) and local control (LC) using weighted random effects models. In addition, individual patient data analyses incorporating data from 6 institutions were conducted as their own subgroup analyses. Seventeen observational studies, comprising 1889 patients with HCC treated with ≤9 SBRT fractions, between 2003 and 2019, were included in the aggregated data meta-analysis.
- The 3- and 5-year OS rates after SBRT were 57% (95% confidence interval [CI], 47%-66%) and 40% (95% CI, 29%-51%), respectively. The 3- and 5-year LC rates after SBRT were 84% (95% CI, 77%-90%) and 82% (95% CI, 74%-88%), respectively.
- Tumor size was the only prognostic factor for LC. Tumor size and region were significantly associated with OS. Five-year LC and OS rates of 79% (95% CI, 0.74-0.84) and 25% (95% CI, 0.20-0.30), respectively, were observed in the individual patient data analyses.
- Factors prognostic for improved OS were tumor size <3 cm, Eastern Region, Child-Pugh score ≤ B7, and the Barcelona Clinic Liver Cancer stage of 0 and A.
- Late ≥grade 3 hepatic toxicity was reported in 3 studies and ranged from 0% to 9%. Toxicity data are summarized in Table 4.
- From this systemic review and meta-analysis key recommendations for SBRT to HCC (Table 5) on behalf of the International Stereotactic Radiosurgery Society (ISRS) were provided.

Table 4 Hepatic toxicity

	Acute hepatic toxicity			Late toxicity	
First author	Hepatic toxicity* grade ≥3 (%)	Classic RILD (%)	Nonclassic RILD (%)	Type of hepatic toxicity grade ≥3	%
Shin[17]			13		
Roquette[18]	2		18	0	0
Rordlamool[19]	30	4	7		
Ueno[20]					
Kibe[21]		0		LC progression	1
Mathew[22]	25†	0	16	Biliary toxicity	1
Fu[23]	0	0	0		
Park[24]	3	0	6	Biliary toxicity	9
Yoon[25]	0	0	2	0	0
Su[26]	1‡		10		
Sun[27]	0	3	5	0	0
Shen[28]		4§	20§		
Lee[29]	0	16	25	0	0
Kimura[30]	7			0	0
Hijazi[31]	0	0	4	0	0
Que[32]	16†	0	3		
Jang[33]	4	0	5	0	0

Abbreviations: LC = liver cirrhosis; RILD = radiation-induced liver disease.
* Defined according to Common Terminology Criteria for Adverse Events.
† Some patients had more than 1 kind of hepatic toxicity.
‡ This study reported only hepatic toxicity of grade 5.
§ Two patients had both classic RILD and nonclassic RILD.

Table 5 Key opinions for SBRT to HCC

Recommendations
Patient selection
1. Patients with HCC <3 cm can be considered for SBRT with favorable local control and survival outcomes. SBRT to HCC ≥3 cm can be performed with the expectation of durable long-term local control.
2. SBRT can be performed when the pretreatment liver function is CP class A or B7. SBRT to patients with CP class ≥B8 should be delivered with caution, particularly for CP class C patients.
Treatment
1. SBRT with 1-9 fractions is recommended for patients with liver-confined HCC. No specific recommendation for the optimal dose fractionation can be made.
Treatment outcome
1. Considering worse overall survival rates in patients from Western regions compared with those from Eastern regions, despite similar local control rates, different follow-up strategies according to the etiology of HCC may be needed.
2. Classic RILD is a rare event after SBRT to HCC with proper patient selection.
3. The incidence of classic RILD and nonclassic RILD should be separately recorded to facilitate comparisons with historical SBRT studies. The use of Common Terminology Criteria for Adverse Events is recommended to facilitate comparisons with other treatment modalities.

Abbreviations: CP = Child-Pugh; HCC = hepatocellular carcinoma; RILD = radiation-induced liver disease; SBRT = stereotactic body radiation therapy.

High dose proton and photon-based radiation therapy for 213 liver lesions: a multi-institutional dosimetric comparison with a clinical perspective

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- Stereotactic radiotherapy (SRT) and Proton therapy (PT) are both options in the management of liver lesions.
- Moreover, dose-constraint routinely used in liver PT and SRT considers only the liver spared, while optimization strategies to limit the liver damaged are poorly reported.
- Primary endpoint was to assess and compare liver sparing of four contemporary RT techniques. Secondary endpoints were freedom from local recurrence (FFLR), overall survival (OS), acute and late toxicity.
- Focal Liver Reaction (FLR) was delineated on follow-up MRI. A so-called Fall-off Volume (FOV) was defined as the area of healthy liver (liver-PTV) receiving more than the isotoxic dose.
- Fall-off Volume Ratio (FOVR) was defined as ratio between FOV and PTV.
- 213 lesions were identified. Mean best fitting isodose (isotoxic doses) for FLR were 18Gy, 21.5 Gy and 28.5 Gy for 3, 5 and 15 fractions.
- Among photons, an advantage in terms of healthy liver sparing was found for Vmat FFF with 5mm jaws ($p = 0.013$) and Cyberknife ($p = 0.03$).
- FOV and FOVR resulted lower for PT ($p < 0.001$). Three years FFLR resulted 83%. Classic Radiation induced liver disease (RILD, any grade) affected 2 patients.
- Cyberknife and V-MAT FFF with 5mm jaws spare more liver than V-MAT FF with 10 mm jaws.
- PT spare more liver compared to photons.
- FOV and FOVR allows a quantitative analysis of healthy tissue sparing performance showing also the quality of plan in terms of dose fall-off.

Skin dose-volume predictors of moderate-severe late side effects after whole breast radiotherapy

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- Toxicity after whole breast Radiotherapy is a relevant issue, impacting the quality-of-life of a not negligible number of patients.
- We aimed to develop a Normal Tissue Complication Probability (NTCP) model predicting late toxicities by combining dosimetric parameters of the breast dermis and clinical factors.
- The skin structure was defined as the outer CT body contour's 5 mm inner isotropic expansion. It was retrospectively segmented on a large mono-institutional cohort of early-stage breast cancer patients enrolled between 2009 and 2017 (n=1066).
- Patients were treated with tangential-field RT, delivering 40 Gy in 15 fractions to the whole breast
- Toxicity was reported during Follow-Up (FU) using SOMA/LENT scoring.
- The study endpoint was moderate-severe late toxicity consisting of Fibrosis-Atrophy-Telangiectasia-Pain (FATP G≥2) developed within 42 months after RT completion.
- A machine learning pipeline was designed with a logistic model combining clinical factors and absolute skin DVH (cc) parameters as output.
- The FATP G2+ rate was 3.8%, with 40/1066 patients experiencing side effects.
- After the preprocessing of variables, a cross-validation was applied to define the best-performing model. We selected a 4-variable model with Post-Surgery Cosmetic alterations (Odds Ratio, OR = 7.3), Aromatase Inhibitors (as a protective factor with OR = 0.45), V20 Gy (50% of the prescribed dose, OR = 1.02), and V42 Gy (105%, OR = 1.09). Factors were also converted into an adjusted V20Gy.
- The association between late reactions and skin DVH when delivering 40 Gy/15 fr was quantified, suggesting an independent role of V20 and V42. Few clinical factors heavily modulate the risk.

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