CLINICAL PRIORITIES ADVISORY GROUP
1 September 2021

Agenda Item No	2.1
National Programme	Cancer
Clinical Reference Group	Radiotherapy
URN	2011

Title
Stereotactic ablative body radiotherapy for patients with locally advanced, inoperable, non-metastatic pancreatic carcinoma (adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
The clinical commissioning policy statement recommends the use of stereotactic ablative body radiotherapy (SABR) as a treatment option for adults with locally advanced, inoperable, non-metastatic pancreatic carcinoma (LANPC) where the disease remains localised following ≥3 months of systemic chemotherapy and in accordance with the eligibility criteria. The use of SABR as an alternative treatment option to chemoradiotherapy , which is the current standard of care for these patients, means that patients will require fewer daily hospital visits for their radiotherapy and, as concurrent daily oral chemotherapy is not required, they are also spared the side effects of the chemotherapy.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy statement.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Cancer Programme confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary- 3 x Evidence Papers
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

Three papers included in the summary

Paper 1:

Tchelebi LT, Lehrer EJ, Trifiletti DM, Sharma NK, Gusani NJ, Crane CH, Zaorsky NG. Conventionally fractionated radiation therapy versus stereotactic body radiation therapy for locally advanced pancreatic cancer (CRiSP): an international systematic review and meta-analysis. Cancer. 2020;126(10):2120-2131. doi: 10.1002/cncr.32756.

- A systematic review and meta-analysis indirectly comparing the effectiveness of SABR (nine studies (n=277)) to conventionally fractionated radiation therapy (CFRT) with concurrent chemotherapy (11 studies (n=870)) in patients with locally advanced pancreatic cancer

Paper 2:

Suker M, Nuyttens JJ, Eskens FALM, Haberkorn BCM, Coene P-P LO, van der Harst E, Bonsing BA, Vahrmeijer AL, Mieog JSD, Swijnenburg RJ, Roos D, Koerkamp BG, van Eijck CHJ. Efficacy and feasibility of stereotactic radiotherapy after folfirinox in patients with locally advanced pancreatic cancer (LAPC-1 trial). EClinicalMedicine. 2019;17:100200. doi: 10.1016/j.eclinm.2019.10.013.

- A multi-centre phase II uncontrolled trial of sequential folfirinox and SABR in 50 patients with locally advanced pancreatic cancer

Paper 3:
Petrelli F, Comito T, Ghidini A, Torri V, Scorsetti M, Barni S. Stereotactic body radiation therapy for locally advanced pancreatic cancer: a system atic review and pooled analysis of 19 trials. International Journal of Radiation Oncology, Biology, Physics. 2017;97(2):313-322.

- A systematic review and meta-analysis of 1,009 patients with locally advanced pancreatic cancer reported in 19 non-comparative studies assessing SABR

Outcome	Evidence statement
Clinical effectiveness	
Overall survival **Certainty of evidence:** Not assessed for 3 paper summaries	Overall survival was reported in all 3 papers included in the summary. Tchelebi et al 2020 reported a statistically significant benefit for SABR (7 studies, n=239) compared to CFRT (11 studies[1], n=870) for two-year overall survival (not further defined) (random effects estimates: SABR 26.9% (95% confidence interval (CI) 20.6 to 33.6, I^2=23%); CFRT 13.7% (95%CI 8.9 to 19.3, I^2=77%); SABR vs CFRT no estimate reported (p=0.004)). There was no statistically significant difference between SABR (9 studies, n=277) and CFRT (11 studies1, n=870) for one-year overall survival (not further defined) (random effects estimates: SABR 53.7% (95%CI 39.3 to 67.9, I^2=83%); CFRT 49.3% (95%CI 39.3 to 59.4, I^2=88%); SABR vs CFRT no estimate reported (p=0.63)). In sensitivity analysis, excluding three SABR studies that were outliers in terms of dose/fractionation, there was a statistically significant difference favouring SABR for two-year overall survival and no statistically significant difference at one-year. Suker et al 2019 reported a one-year overall survival[2] rate of 64% (95%CI 50 to 76) in the intention-to treat population (n=50) with a median overall survival of 15 months (95%CI 11 to 18). Overall survival was also reported for subgroups of patients: • One-year overall survival rate for patients who had no disease progression after the completion of folfirinox and therefore received SABR (n=39): 79% (95%CI 65 to 89). • Median overall survival for patients who received SABR (n=39) vs patients who did not receive SABR (n=11): 17 months (95%CI 14 to 21) vs 7 months (95%CI 6 to 8), p<0.001. • Median overall survival after starting SABR (n=39): 10 months (95%CI 7 to 12) • Overall survival for patients who received curative resection following SABR (n=6): one-year overall survival 83% (95%CI 44 to 97); median overall survival 23 months (95%CI 13 to 34). Petrelli et al 2017 reported a pooled one-year overall survival rate[3] of 51.6% (95%CI 41.4 to 61.7) from 13 studies (n=668). Heterogeneity between the studies was described as 'substantial', and number of fractions was reported to explain 82.3% of the between-trial variance

[1] 12 results were pooled as one study included data for CFRT f rom 2 study arms
[2] Overall survival was calculated from the start of folfirinox to the date of death
[3] The review authors stated that 6 studies calculated outcomes from the diagnosis of pancreatic cancer and the remainder from the start of radiotherapy, chemotherapy or SABR

	in treatment effect. The authors reported that the exclusion of three studies that included patients with recurrent or metastatic disease (5% of overall population) did not change the median or one -year overall survival results (no further details reported). The pooled median overall survival from 18 studies (n not stated) was 17 months (range 5.7 to 47). The pooled median two-year overall survival rate from five studies (n not stated) was 18% (range 0 to 47). **One of the 3 included papers reported a statistically significant benefit for SABR compared to CFRT for two-year overall survival but not for one-year overall survival. The other 2 included papers reported one-year overall survival rates ranging from 52% to 79% for patients who received SABR.**
Progression-free survival **Certainty of evidence:** Not assessed for 3 paper summaries	Progression-free survival was reported in 2 of the 3 papers included in the summary. Suker et al 2019 reported a one-year progression-free survival[4] rate of 34% (95%CI 22 to 48) in the intention-to treat population (n=50) with a median progression-free survival of nine months (95%CI 8 to 10). Median locoregional progression-free survival was 17 months (95%CI 11 to 24) for all patients (n=50), 20 months (95%CI 14 to 28) for patients who received SABR (n=39) and 3 months (95%CI 2 to 4) for patients who did not receive SABR (n=11) (for SABR vs no SABR p<0.0001). Median distant progression-free survival was 11 months (95%CI 10 to 12) for all patients (n=50), 11 months (95%CI 9 to 13) for patients who received SABR (n=39) and 3 months (95%CI 2 to 4) for patients who did not receive SABR (n=11) (for SABR vs no SABR p<0.0001) (median follow-up 29 months). Petrelli et al 2017 reported that median progression-free survival[3] ranged from 4.8 to 27 months in 11 studies (n not stated). **Two of the included papers reported median progression-free survival. This ranged from 4.8 to 27 months for patients who received SABR.**
Disease control **Certainty of evidence:** Not assessed for 3 paper summaries	Disease control was reported in 2 of the 3 papers included in the summary. Suker et al 2019 reported that after folfirinox and SABR treatment, four of 39 patients (10%) showed local progression, 19 (49%) distant progression and four (10%) both local and distant progression (median follow-up 29 months, local and distant progression not further defined). Petrelli et al 2017 reported a pooled locoregional control rate[3] of 72.3% (95%CI 58.5 to 79, I^2=89%) at one year from 13 studies (n=889). The authors reported that total SABR dose delivered and higher number of fractions were statistically significantly associated with one-year locoregional control in multivariate analysis (p=0.03 and p=0.019 respectively).

[4] Progression-free survival was calculated from the start of folfirinox to the date of progression or death

	One of the included papers reported local and distant disease progression ranging from 10% to 49% for patients who received SABR. A second paper reported a pooled locoregional control rate of 72% for patients who received SABR.
Overall response rate **Certainty of evidence:** Not assessed for 3 paper summaries	Overall response rate was reported in 1 of the 3 papers included in the summary. Petrelli et al 2017 reported that overall response rate (not further defined) ranged from 25% to 70% in the three (of 19) included studies that reported this (n not stated, timeframe not stated). **One of the included papers reported an overall response rate ranging from 25% to 70% for patients who received SABR.**
Surgery following SABR **Certainty of evidence:** Not assessed for 3 paper summaries	Surgery following SABR was reported in 2 of the 3 papers included in the summary. Suker et al 2019 reported that six (of 39) patients underwent potentially curative resection after folfirinox and SABR treatment (timeframe not stated). Petrelli et al 2017 reported a resection surgery rate ranging from 0% to 100% in the 14 (of 19) included studies that reported this (n not stated). In the four studies reporting resection surgery according to (pre-SABR) operability, unresectable locally advanced pancreatic cancer was resected in 0% to 20% of cases and borderline resectable pancreatic cancer in 50% to 56% of cases (n not stated). **Two of the included papers reported resection surgery rates. These ranged from 0% to 100% for patients who received SABR.**
Safety	
Toxicity **Certainty of evidence:** Not assessed for 3 paper summaries	Toxicity was reported in all 3 of the papers included in the summary. Tchelebi et al 2020 reported a statistically significant benefit for SABR (9 studies, n=277) compared to CFRT (7 studies, n=409) for acute grade 3/4 (severe/life threatening) toxicity[5] (random effects estimates: SABR 5.6% (95%CI 0.0 to 20, I^2=93%); CFRT 37.7% (95%CI 24.0 to 52.5, I^2=89%); SABR vs CFRT no estimate reported (p=0.013)). There was no statistically significant difference between SABR (9 studies, n=277) and CFRT (6 studies, n=329) for late grade 3/4 toxicity[6] (random effects estimates: SABR 9.0% (95%CI 3.3 to 17.1, I^2=75%); CFRT 10.1% (95%CI 1.8 to 23.8, I^2=91%); SABR vs CFRT no estimate reported (p=0.85)). In sensitivity analysis, excluding three SABR studies that were outliers in terms of dose/fractionation, there was a statistically significant difference favouring SABR for acute grade 3/4 toxicity and no statistically significant difference for late grade 3/4 toxicity. Suker et al 2019 reported grade 3 (severe) to 5 (death) adverse events in four of 39 patients who received SABR, occurring within three months after completing SABR. One patient had grade 3

[5] The authors stated that the included studies most commonly defined acute toxicity as occurring within 3 months of completion of radiation

[6] The authors stated that the included studies most commonly defined late toxicity as occurring from 3 months after completion of radiation

	vomiting, one patient had grade 4 gastro-intestinal bleeding and two patients had grade 5 gastro-intestinal bleeding. Suker et al 2019 also reported 30 grade 3 or 4 adverse events during folfirinox treatment (n=50) prior to SABR. Petrelli et al 2017 reported that the rates of acute severe toxicity for the 19 included studies (n=1,009) ranged from 0% to 36%, with only three studies detecting grade 3/4 (severe/life threatening) gastrointestinal toxicity rates of >10%. The proportion of chronic (late) grade 3/4 events ranged from 9% to 11%, with six studies reporting a toxicity rate of 0%. No definition or timeframe was provided for acute and chronic toxicity. **One of the 3 included papers reported a statistically significant benefit for SABR compared to CFRT for acute grade 3/4 toxicity but not for late grade 3/4 toxicity. The other included 2 papers reported severe toxicity rates ranging from 0% to 36% for patients who received SABR.**

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** Patients have moderate problems in walking about • **ability to provide self-care:** Patients have moderate problems in washing or dressing • **undertaking usual activities:** Patients have moderate problems in doing their usual activities • **experience of pain/discomfort:** Patients have severe pain or discomfort • **experience of anxiety/depression:** Patients are severely anxious or depressed
Further details of impact upon patients: Patients diagnosed with LANPC often experience symptoms of depression and anxiety, they experience pain, weight loss, cachexia which impact on their quality of life. They have an increased propensity for blood clots. The cancer can cause obstruction of the bile duct (causing jaundice) as well as gastric or duodenal obstruction. **Further details of impact upon carers:** Carers experience anxiety about the inoperable diagnosis of their loved one. They support them as they experience the symptoms of inoperable pancreatic cancer and are impacted by the limitations the disease causes on the patient's quality of life, which in turn impacts the carers quality of life

Considerations from review by Rare Disease Advisory Group
Not applicable

Pharmaceutical considerations
Not applicable

Considerations from review by National Programme of Care
The proposal received the full support of the Cancer Programme of Care (PoC) on 1st July 2021.