MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
07 October 2020

Agenda Item No	2.1
National Programme	Cancer
Clinical Reference Group	Radiotherapy
URN	1909

Title
Stereotactic ablative radiotherapy (SABR) for patients with previously irradiated, locally recurrent primary pelvic tumours (All ages).

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

Proposition
The policy proposition recommends that SABR be made routinely available as a treatment option for the treatment of previously irradiated, locally recurrent primary pelvic tumours as a treatment alternative to systemic therapy (e.g. chemotherapy), where curative surgery is not an option or has been declined. The policy proposition has been developed following the completion of a Commissioning through Evaluation (CtE) programme relating to SABR to treat pelvic, spinal and para-aortic tumours previously treated with radiotherapy. While the scope of the CtE was broader and included indications that are anatomically close, this policy proposition relates solely to the pelvic tumour group. This policy proposition has been developed by a Policy Working Group established in line with standard processes and involved clinical members, Public Health England and patient and public voice representatives. This policy proposition is being treated as cost neutral as funding is being provided via the service development monies and not from the CPAG prioritisation reserve. Importantly, this policy proposition is one of two that are currently progressing through the policy development process; the other (URN 1918) relates to para-aortic tumours and recommends a not for routine commissioning position. Should both policies be approved, work will be undertaken to update an existing Clinical Commissioning Policy (Ref 16021/P): The use of Stereotactic ablative radiotherapy (SABR) in the treatment of previously irradiated tumours of the pelvis, spine and nasopharynx, published in 2016, to reflect the new commissioning position.

Collectively, these three policies will address all clinical indications covered by the CtE.

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

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 and a Public Health England Report
4.	Clinical Panel Report x3
5.	Equality and Health Inequalities Impact Assessment

The Benefits of the Proposition (only non-comparative studies are included)		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Median overall survival (OS) is the length of time from either the date of diagnosis or the start of treatment, that half of the patients in a group of patients diagnosed with the disease are still alive. The best evidence for patients undergoing pelvic re-irradiation came from a systematic review by Murray et al. (2017) that included 205 patients from 17 studies and reported a median OS of 11-14.5 months.

		Non-comparative studies do not show a clear clinical benefit. Various doses were used in different studies, which also limits validity. It is difficult to draw any firm conclusions due to the non-comparative, largely retrospective nature of the evidence, the variability in the makeup of the patients and the study design of the different studies. Overall, there is considerable uncertainty about this outcome and additional randomised controlled studies will need to verify this finding. **CtE** In the CtE scheme, it was not possible to calculate median overall survival due to the length of follow-up.
2.	Progression free survival	Progression free survival (PFS) is the length of time during which the disease does not worsen, or the proportion of patients without worsening disease at a defined follow-up point after beginning treatment. PFS was defined based on biochemical control of a blood-circulating biomarker in some studies (for example, prostate studies report the prostate-specific antigen levels as a measure of biochemical response). The best evidence for this outcome is provided by the retrospective cohort study by Loi et al (2018) that analysed 50 patients with prostate cancer and found that the 1-year biochemical relapse free survival was 80% in prostate cancer patients. Non-comparative studies do not show a clear clinical benefit. Loi et al (2018) found failure was significantly associated with tumour stage ≥3a (high risk) and ongoing androgen-deprivation therapy (p=0.014 and p=0.025 respectively). It is difficult to draw any firm conclusions due to the non-comparative, largely retrospective nature of the evidence, the variability in the makeup of the patients and the study design of the different studies. Overall, there is considerable uncertainty about this outcome and additional randomised controlled studies will need to verify this finding. **CtE** The CtE scheme did not include progression free survival as one of its outcomes.
3.	Mobility	The studies did not report any quality of life outcomes, with the exception of pain outcomes. Most studies reported the proportion of patients in whom pain was under control, or had worsened or got better.
4.	Self-care	

5.	Usual activities	The best evidence for patients undergoing pelvic re-irradiation came from a systematic review by Murray et al. (2017) that included 205 patients from 17 studies and reported pain improvement in 50-100% of patients. None of the studies compared SABR with another form of treatment so it is impossible to ascertain if it has a clinical benefit. It is difficult to draw any firm conclusions due to the non-comparative, largely retrospective nature of the evidence, the variability in the makeup of the patients and the study design of the different studies. Overall, there is considerable uncertainty about this outcome and additional randomised controlled studies will need to verify this finding. **CtE** In the CtE scheme, the majority of patients did not report pain at baseline it is therefore, difficult to draw any conclusions for this outcome. Quality of life remained stable for the majority of patients recruited in the scheme.
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	*Not directly assessed*
9.	Dependency on care giver / supporting independence	*Not directly assessed*
10.	Safety	The definition of safety is based on the number and severity of adverse events a patient can experience after undergoing treatment. Treatment-related toxicity in patients with cancer is usually recorded and graded according to the Common Toxicity Criteria Adverse Events (CTCAE). Studies reported acute and late toxicities although not consistently throughout the studies. There was not always a distinction made between radiotherapy and non-radiotherapy related morbidities. The best evidence for patients undergoing pelvic re-irradiation came from a systematic review by Murray et al. (2017) that included 205 patients from 17 studies and reported that 7.3% of patients suffered grade 3-4 events. Although none of the studies compared SABR to another treatment, the number of severe (grade 3-4) events was low and there were no grade 5 events reported in these studies.

		It is difficult to draw any firm conclusions due to the non-comparative, largely retrospective nature of the evidence, the variability in the makeup of the patients and the study design of the different studies. Overall, there is considerable uncertainty about this outcome and additional randomised controlled studies will need to verify this finding. **CtE** In the CtE, for patients with pelvic tumours, 3.8% suffered a grade 3-4 event (7 of 185 patients).
11.	Delivery of intervention	*Not directly assessed*

The Benefits of the Proposition (only non-comparative studies are included)		
No	*Outcome measures*	*Summary from evidence review*
1.	Local control	Local control (LC) is usually reported as the proportion of patients for which the treated cancer lesion does not increase in size at a defined follow-up point after beginning treatment. Local control was reported in different ways depending on the tumour site (for example, prostate studies report prostate-specific antigen levels as a measure of biochemical response). The best evidence for patients undergoing pelvic re-irradiation came from a systematic review by Murray et al. (2017) that included 205 patients from 17 studies and showed 1-year local control rates of 51.4-100%. These outcomes show that local control is highly variable. Although Murray et al (2017) identified a clinical benefit when using doses of >60Gy, it is difficult to identify a clinical benefit from non-comparative studies. It is difficult to draw any firm conclusions due to the non-comparative, largely retrospective nature of the evidence, the variability in the makeup of the patients and the study design of the different studies. Overall, there is considerable uncertainty about this outcome and additional randomised controlled studies will need to verify this finding. **CtE** The Commissioning through Evaluation (CtE) scheme collected data on a number of outcomes, including LC. For patients with pelvic tumours (n=185), 1-year local control was 75.8%, which is within the range reported by Murray et al (2017). Two year local control in the CtE was 46.7%, an important outcome that was not reported elsewhere in the literature.
2.	1 year survival	This outcome was reported as a proportion of patients surviving at 1-year follow-up from re-irradiation. The best evidence for patients undergoing pelvic re-irradiation came from a systematic review by Murray et al. (2017) that included 205 patients from 17 studies and that at 1-year follow-up 46-52% of patients survived. None of the studies compared SABR with another form of treatment so it is impossible to tell if it has a clinical benefit.

		It is difficult to draw any firm conclusions due to the non-comparative, largely retrospective nature of the evidence, the variability in the makeup of the patients and the study design of the different studies. Overall, there is considerable uncertainty about this outcome and additional randomised controlled studies will need to verify this finding. **CtE** In the CtE scheme, for patients with pelvic tumours actuarial overall survival was 92% at 1-year and 71.9% at 2-years. This suggests that overall survival in the CtE scheme was better than that reported in the literature.
3.	Cost-effectiveness	*No applicable studies were found during the evidence review.* **CtE** Using data from the CtE scheme, a cost-effectiveness analysis was performed, which compared SABR to pelvic exenteration in patients with pelvic tumours. Probabilistic sensitivity analysis showed that SABR is likely to be cost-effective over pelvic exenteration in 99.94% of cases. SABR 'dominates' pelvic exenteration due to its significantly lower risk of serious adverse events, as well as a lower cost.

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **Mobility:** Patients have no problems in walking about.
- **Ability to provide self-care:** Patients have slight problems in washing or dressing.
- **Undertaking usual activities:** Patients have slight to moderate problems doing their usual activities.
- **Experience of pain/discomfort:** Patients have moderate to severe pain or discomfort.
- **Experience of anxiety/depression:** Patients are moderately to severely anxious or depressed

Further details of impact upon patients:
Primary pelvic tumours cover a wide range of cancers including prostate cancer, gynaecological cancers and rectal cancer. The impact will depend on the type of cancer the patient has; however, pelvic tumours can have a severe impact on a patient's quality of life. Some patients will have residual continence problems as a result of their cancer or may be managing a stoma, impacting their daily life. For

other patients, sexual dysfunction may also be an issue. These issues can have a moderate to severe impact on the anxiety experienced by patients.

Further details of impact upon carers:
The impact on a carer will be a broad range and depend on the actual relationship. For example, a formal partner may be affected by the patient's sexual dysfunction. Relatives and carers are more often the ones who worry about the health of their loved ones and have high anxiety levels. They at least will share the practical and financial problems that are worsened with a cancer recurrence.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
The proposition received the full support of the Cancer PoC on the 11th September 2020.