CLINICAL PRIORITIES ADVISORY GROUP
05 02 2019

Agenda Item No	02.2
National Programme	Cancer
Clinical Reference Group	Cancer Diagnostics
URN	1704

Title
18F-flourodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) as part of radical radiotherapy treatment planning for oesophageal cancer (all ages).

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

Proposition
This policy recommends that 18F-flourodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) as part of radical radiotherapy treatment planning for oesophageal cancer should not be routinely commissioned. PET-CT for radiotherapy treatment planning in this indication is not currently commissioned and therefore this policy proposition does not alter the current commissioning position.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a not for 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 Acute Programmes confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board 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.	Consultation Report
3.	Evidence Summary and evidence report
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Overall survival was measured from the end of radiotherapy to the date of death. In the study with the larger sample size and longest median follow-up (Ng et al 2017), 4- year overall survival was 37% (95%CI 24 to 57). One-year survival (76%, 95%CI 64 to 91), 2-year survival (57%, 95%CI 43 to 76) and 3-year survival (40%, 95%CI 26 to 60) were also reported. The median follow-up in this study was 4 years (range 2.7 to 6.8). A 4-year overall survival of 37% could be considered within the context of the poor prognosis for oesophageal cancer (published 5-year survival rate 15%, Cancer Research UK). However, the confidence intervals around the overall survival rates are wide, reducing confidence in the result. The PET-CT scan only was used to determine the subsequent radiotherapy so no comparison with survival following radiotherapy planned without PET-CT was available. This uncontrolled prospective study had a small sample size (n=41) with patients recruited from an unknown number of centres over a 5-year period and clinical analysis available for 38 patients who commenced radiotherapy. The lack of comparator limits the strength of the conclusions that can be drawn.
2.	Progression free survival	Event-free survival (progression free survival) was determined from the date of commencing radiotherapy to the date of loco-regional, systemic cancer recurrence or secondary primary cancer. In patients who did not have surgery, event was determined at time to tumour progression or metastases. In 1 study (Lertbutsayanukul et al, 2013) 1- year event-free

		survival was 59%, and median event-free survival was 15.5 months. The median follow-up in this study was 12 months (range 4 to 25.8). The PET-CT scan only was used to determine the subsequent radiotherapy so no comparison with event-free survival following radiotherapy planned without PET-CT was available. This uncontrolled prospective study had a small sample size (n=17) with patients recruited from 1 centre over a 12-month period. The lack of comparator limits the strength of the conclusions that can be drawn.
3.	Safety	Safety outcomes reported by Lertbutsayanukul et al (2013) included adverse effects, and dose to critical normal tissues. Adverse effects were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events1. This has 5 grades: grade 1 'mild'; grade 2 'moderate', grade 3 'severe or medically significant but not immediately life threatening; grade 4 'life-threatening consequences'; grade 5 'death'. Lertbutsayanukul et al (2013) reported the number of ≥grade 3 adverse events. The most common was leucopenia2 (59%) followed by vomiting (24%), pulmonary toxicity (12%), dysphagia (12%), weight loss (12%) and cardiovascular toxicity (6%). One patient died from oesophageal fistula 186 days after the 1st day of radiation. Grade 1-2 adverse effects included anaemia (100%), platelet decrease (100%), cardiovascular toxicity (94%), dysphagia (88%), pulmonary toxicity (88%), weight loss (88%), vomiting (76%) and leucopenia (41%). Lertbutsayanukul et al (2013) also reported the percentage of normal tissue receiving radiation: 26% normal lung tissue received 20Gy; 48% of normal lung tissue received 10Gy; the average maximum dose to the spinal cord was 40.6Gy and the median dose to the heart was 30.8Gy. High levels of grade 1-2 (mild to moderate) adverse effects were observed with all patients experiencing anaemia and platelet decrease. No figure was provided for the proportion of patients who experienced any grade 3 or higher adverse effect, but more than half of patients experienced ≥grade 3 leucopenia. Patients in this study received 64Gy to high risk areas and 54Gy to low risk areas. Without a comparator for treatment planned using a different scanning method it is difficult to interpret the clinical significance of this result. This uncontrolled prospective study had a small sample size (n=17) with patients recruited from 1 centre over a 12-month period. The lack of comparator limits the strength of the conclusions that can be drawn.

Other health outcome measures determined by the evidence review		
No	*Outcome measure*	*Summary from evidence review*
1.	Assessment of tumour length	Gross tumour volume (GTV) was contoured using a planning CT scan and a planning FDG PET-CT scan. The GTV determined by FDG PET-CT was assumed to represent the true extent of disease. Both over and under-estimates of the cranial and caudal extent of the tumour using CT compared with PET-CT were reported. Overestimation of GTV may result in radiotherapy being delivered to a greater area than necessary. Underestimation of GTV may result in insufficient coverage of the treatment area. Ng et al (2017) reported GTV based on planning scans using CT and PET-CT for 38 patients. Compared to PET-CT, GTV planned using CT overestimated the cranial extent of the tumour in 29% of cases and overestimated the caudal extent of the tumour in 50% of cases. The median overestimate in the cranial extent was 1.28cm (range 0.33 to 3.40). The median overestimate in the caudal extent was 0.66cm (range 0.3 to 5.52). Compared to PET-CT, GTV planned using CT underestimated the cranial extent of the tumour in 36% of cases and underestimated the caudal extent in 26% of cases. The median underestimate in the cranial extent was 1.14cm (range 0.3 to 2.85) and the median underestimate in the caudal extent was 1.03cm (range 0.4 to 4.25). A different GTV area was contoured using the two planning scans. The findings suggested that planning based on CT scan alone would have missed tumour in some cases and delivered treatment to a wider area than was necessary in others. In this study the FDG PET-CT was a combined diagnostic and planning scan. The PET-CT scan only was used to determine the subsequent radiotherapy so no comparison with outcomes for radiotherapy planned without PET-CT was available and adverse effects were not reported. This uncontrolled prospective study had a small sample size (n=41) with patients recruited from an unknown number of centres over a 5-year period and planning analysis available for 38 patients who completed PET-CT. The lack of comparator for treatment outcomes limits the strength of the conclusions that can be drawn.
2.	Comparison of treatment plans	Gross tumour volume (GTV) was contoured using a planning CT scan and a planning PET-CT scan. Planning target volume (PTV) was defined as GTV plus 1cm volumetric margin. A grade 1 geographic miss was defined as any PET-avid disease not included in the CT PTV. A grade 2 geographic miss was defined as <95% of the PET PTV receiving at least 95% of the prescription dose based on planning with CT data alone. Ng et

		al (2017) reported GTV based on planning scans using CT and PET-CT for 38 patients. GTV determined by PET-CT was not included in GTV determined by CT in 29 patients (76%, median percentage volume excluded 17%, range 1 to 100). Grade 1 geographic misses occurred in 5 patients (13%) and grade 2 geographic misses occurred in 8 patients (21%). For the grade 1 misses the median percentage volume of PET-avid disease excluded was 6% (range 2 to 92). For the grade 2 misses the median percentage volume of PET PTV receiving ≥95% prescription dose was 82% (range 63 to 92). The study authors reported that there would have been no clinically significant differences in radiation dose to the lungs, liver and spinal cord between CT and PET-CT treatment plans (figures not reported). It was assumed that the PET-CT represented the true extent of disease. GTV determined by CT scan would have missed GTV determined by PET-CT for approximately three quarters of patients. In this study the FDG PET-CT was a combined diagnostic and planning scan. The PET-CT scan only was used to determine the subsequent radiotherapy so no comparison with outcomes for radiotherapy planned without PET-CT was available and adverse effects were not reported. This uncontrolled prospective study had a small sample size (n=41) with patients recruited from an unknown number of centres over a 5-year period and planning analysis available for 38 patients who completed PET-CT. The lack of comparator for treatment outcomes limits the strength of the conclusions that can be drawn.
3.	Treatment response	In the study with the larger sample size (Ng et al 2017), treatment response was presented as 4 categories: clinical complete response, partial response, stable disease and progressive disease. No further definition of these categories was provided. For 36 patients, assessed 3-months after completion of radiotherapy a clinical complete response was observed for 18 (50%, 95%CI 34 to 66); a partial response for 14 (39%, 95%CI 25 to 55); stable disease for 3 (8%) and progressive disease for 1 (3%). Confidence intervals were not reported for stable disease and progressive disease. A complete or partial response was seen in 89% of patients assessed, with only 1 patient showing progressive disease. Data was missing from 2 patients due to refusal of follow-up (n=1) and death prior to response assessment (n=1). The PET-CT scan only was used to determine the subsequent radiotherapy so no comparison with treatment response for radiotherapy planned without PET-CT was available. This

		uncontrolled prospective study had a small sample size (n=41) with patients recruited from an unknown number of centres over a 5-year period and clinical analysis available for 38 patients who commenced radiotherapy. The lack of comparator limits the strength of the conclusions that can be drawn.
4.	Patterns of treatment failure	In the study with the larger sample size (Ng et al 2017), loco-regional failures were defined as a failure at the primary site and/or regional node and were within the radiation treatment field. Distant failure was considered a censoring event. 21 patients relapsed post-treatment (55%). Local and/or regional failures only were observed in 7 patients. A combination of local, regional and/or distant failures were observed in 4 patients. Distant failure only was observed in 10 patients. The median follow-up in this study was 4 years (range 2.7 to 6.8). Some locoregional failure (within the radiation treatment field) occurred in 11 patients; 29% of the 38 patients treated with radiotherapy. The PET-CT scan only was used to determine the subsequent radiotherapy so no comparison with treatment failure for radiotherapy planned without PET-CT was available. This uncontrolled prospective study had a small sample size (n=41) with patients recruited from an unknown number of centres over a 5-year period and clinical analysis available for 38 patients who commenced radiotherapy. The lack of comparator limits the strength of the conclusions that can be drawn.
5.	Relapse free survival	Relapse free survival was measured from the end of radiotherapy to the date of first relapse (any site) or date of death for patients that did not relapse. In Ng et al (2017) 4-year relapse free survival was 30% (95%CI 18 to 49). One year relapse free survival (58%, 95%CI 44 to 76), 2-year relapse free survival (39%, 95%CI 26 to 58) and 3-year relapse free survival (33%, 95%CI 21 to 52) were also reported. The median follow-up in this study was 4 years (range 2.7 to 6.8). Approximately one third of patients survived 4 years without some form of relapse at any site. The confidence intervals around the relapse free survival rates are wide, reducing confidence in the result. The PET-CT scan only was used to determine the subsequent radiotherapy so no comparison with relapse free survival for radiotherapy planned without PET-CT was available. This uncontrolled prospective study had a small sample size (n=41) with patients recruited from an unknown number of centres over a 5-year period and clinical analysis available for 38 patients who commenced radiotherapy. The lack of comparator limits the strength of the conclusions that can be

		drawn.
6.	Loco-regional failure free survival (local control)	Loco-regional failure free survival is length of survival without recurrence at the primary site and/or regional node (within the field of treatment). Loco-regional failure was measured from the end of radiotherapy to the date of first loco-regional failure. In the study with the larger sample size and longest median follow-up (Ng et al 2017), 4-year loco-regional failure free survival was 65% (95%CI 47 to 90). One-year locoregional failure free survival (86%, 95%CI 75 to 99), 2-year loco-regional failure free survival (72%, 95%CI 56 to 93) and 3-year loco-regional failure free survival (72%, 95%CI 56 to 93) were also reported. The median follow-up in this study was 4 years (range 2.7 to 6.8). Approximately two thirds of patients survived 4 years without recurrence within the field of treatment. The confidence intervals around the locoregional failure free survival rates are wide, reducing confidence in the result. The PETCT scan only was used to determine the subsequent radiotherapy so no comparison with loco-regional failure free survival for radiotherapy planned without PET-CT was available. This uncontrolled prospective study had a small sample size (n=41) with patients recruited from an unknown number of centres over a 5-year period and clinical analysis available for 38 patients who commenced radiotherapy. The lack of comparator limits the strength of the conclusions that can be drawn.
7.	Metabolic response	Patients were re-evaluated 3 months after completion of chemoradiotherapy with an FDG PET-CT scan to assess metabolic response. Tumours were classified as responding or non-responding using Positron Emission Tomography Response Criteria in Solid Tumours (PERCIST), using maximum standard uptake value3 (SUVmax). The PERCIST rules define when tumours in cancer patients improve, stay the same or worsen during treatment. Lertbutsayanukul et al (2013) assessed metabolic response in 15 patients. All patients had a partial response to therapy with a mean percent SUVmax reduction of 61.7% (range 36.5 to 82.3). A reduction in measurable tumour was achieved in all patients, ranging from 36.5% to 82.3% reduction. The definition for a partial response to therapy also includes no new lesions being identified. Without a comparator for treatment planned using a different scanning method it is difficult to interpret the clinical significance of this result. This uncontrolled prospective study had a small sample size (n=17) with patients recruited from 1 centre over a 12-month period. The lack of comparator limits the strength of the conclusions that can be drawn.

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 PoC Board on Thursday 10th January 2019.

SECTION 2 – IMPACT REPORT

No	Item	N/Cost £K	Level of uncertainty
1.	Number of patients affected in England	3,600	
2.	Total cost per patient over 5 years	£0	This policy is not for routine commissioning.
3.	Budget impact year 1	£0	See above.
4.	Budget impact year 2	£0	See above.
5.	Budget impact year 3	£0	See above.
6.	Budget impact year 4	£0	See above.
7.	Budget impact year 5	£0	See above.
8.	Total number of patients treated over 5 years	0	
9.	Net cost per patient treated over 5 years	£0	
Key additional information:			
This intervention is not currently commissioned for this indication and this is policy is for not routine commissioning; as a result, no financial model has been completed.			