

NHS England

Evidence review: 18F-fluoro-deoxyglucose (FDG) positron emission tomography (PET-CT) planned radiotherapy treatment for oesophageal cancer



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1 Introduction

Introduction

- Cancer can develop in any part of the oesophagus. Cancers in the upper and middle part of the oesophagus tend to be squamous cell carcinomas, whereas cancers in the lower part of the oesophagus tend to be adenocarcinomas. Gastro-oesophageal junction cancers are found where the lower end of the oesophagus joins the stomach (CRUK 2018a).
- The most common symptoms of oesophageal cancer include dysphagia (difficulty swallowing), persistent indigestion or heartburn, weight loss, pain and persistent cough (CRUK 2018a).
- Surgical resection is the treatment of first choice, but surgery alone generally results in poor loco-regional tumour control and survival (Lu et al 2013).
- Radical radiotherapy, as a neo-adjuvant strategy prior to surgery or as a definitive treatment, could form part of the treatment plan for 40%-50% of oesophageal cancer cases where radical, curative treatment may be possible (NHS England, 2018).
- The accurate delineation and irradiation of the gross tumour volume is key to the successful treatment of oesophageal cancer with radiotherapy (Muijs et al 2010).
- Positron emission tomography computed tomography (PET-CT) using 18F-fluoro-deoxy-glucose (FDG) can potentially contribute to the care of people with oesophageal cancer by more accurately determining the extent of the radiotherapy treatment field (NHS England 2018).

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- NICE have produced guidance on the assessment and management of oesophago-gastric cancer in adults (NICE, 2018).
- The NICE guideline considered the question “what are the optimal staging investigations to determine suitability for curative treatment of oesophageal or gastro-oesophageal junction cancer after diagnosis with endoscopy and whole-body CT scan?” (NICE 2018).
- With regards to FDG PET-CT, NICE concluded that this: “was moderately useful to identify if disease involved regional lymph nodes or not, (N+ or N0 disease), and could also identify the presence or absence of metastases (M+ from M0 disease). F-18 FDG PET-CT would therefore be useful in all people with oesophageal cancer, except those with very early stage disease (T1a) who were unlikely to have nodal or metastatic involvement” (NICE, 2018).
- The NICE guideline did not consider evidence relating to the use of FDG PET-CT in determining the extent of the radiotherapy treatment field.

The indication and epidemiology

- Oesophageal cancer is the 13th most common cancer in the UK with 9,211 new cases in 2015 (CRUK 2018b).
- About 70% of oesophageal cancer cases in England are diagnosed at a late stage (CRUK 2018b). The prognosis for oesophageal cancer remains poor with a five-year survival of 15% and a ten-year survival of 12% (CRUK 2018b).

Standard treatment and pathway of care

- There is an established role for FDG PET-CT in the staging of disease to accurately determine whether people with oesophageal cancer are suitable for radical treatment with

curative intent or whether the disease is too advanced for such treatment (NHS England, 2018). This use of FDG PET-CT is recommended by NICE (NICE 2018).

- Accurate determination of the tumour volume is essential to facilitate radical radiotherapy (NHS England 2018). CT scans can be used to define gross tumour volume for radiotherapy, combined with information from other diagnostic processes such as endoscopic ultrasonography (EUS) (Muijs et al 2014). However, the discriminative power of CT is generally poor and it remains difficult to relate EUS information to CT images (Muijs et al 2014).

The intervention (and licensed indication)

- 18F FDG uses the increased glucose metabolism that occurs during cell reproduction as a measure of tumour cell proliferation (Lu et al 2013).
- Adding the functional information of FDG PET to the anatomical information provided by CT may improve tumour visualisation and therefore tumour delineation (Muijs et al 2010).

Rationale for use

- A second FDG PET-CT scan (after the first staging FDG PET-CT scan) with the patient in treatment position could more accurately determine the extent of the radiotherapy treatment field compared with CT (NHS England 2018).
- A more accurate determination of the radiotherapy treatment field using FDG PET-CT can result in the delivery of a higher dose of radiotherapy to areas that require treatment and reduce radiotherapy dose to adjacent normal structures (NHS England 2018). It is hoped that this will improve outcomes and quality of life by reducing the side effects of treatment (NHS England 2018).
- This review considers whether performing an FDG PET-CT scan with the patient in treatment position as part of oesophageal cancer radiotherapy treatment planning improves treatment safety and increases the chance of cure with fewer side effects compared to radiotherapy without direct FDG PET-CT planning (NHS England 2018).

2 Summary of results

- No controlled studies matching the PICO inclusion criteria were identified. No evidence was identified comparing the effectiveness of radiotherapy directly planned with FDG PET-CT to radiotherapy without direct FDG PET-CT planning.
- Three prospective uncontrolled studies were included in which patients received an FDG PET-CT scan in the treatment position and outcomes from radiotherapy using the FDG PET-CT treatment plan were reported.

Clinical effectiveness

- Three uncontrolled studies used FDG PET-CT to delineate **gross tumour volume** (GTV). In one study (Ng et al 2017) two potential treatment plans were generated for all patients, one using a CT scan and one an FDG PET-CT scan. Differences between the two treatment plans were reported, based on the assumption that the FDG PET-CT plan represented the true extent of the disease. In most patients the two scanning methods resulted in differences in estimated tumour size and areas identified as requiring treatment, but these differences were not consistent in magnitude or direction. The study did not compare the effectiveness of plans or treatment using different scanning methods. All patients received treatment using the FDG PET-CT treatment plan. In two studies (Yu et al 2015; Lertbutsayanukul et al 2013) the delineation of GTV using FDG PET-CT was

used to deliver different levels of radiation dose to different tumour areas (with reduced dose to margins).

- In one study (Ng et al 2017) a clinical complete **response to treatment** was seen in 50% (95%CI 34 to 66) of 36 patients assessed three months after completion of radiotherapy and a partial response in a further 39% (95%CI 25 to 55). In another study (Lertbutsayanukul et al 2013) pathologic response to neo-adjuvant chemotherapy was assessed in seven patients undergoing surgery. A complete response (on histological examination) was seen in 57% of patients and a further 29% had microscopic residual disease.
- In Ng et al (2017) loco-regional **treatment failures** (within the radiation treatment field) were observed in 29% of 38 patients who received radiotherapy (median follow-up four years). Regional failure was observed in one of 14 surviving patients in Lertbutsayanukul et al (2013) (median follow-up 12 months).
- One-year overall **survival** ranged from 69% to 87% in the three studies (Ng et al 2017; Yu et al 2015; Lertbutsayanukul et al 2013). The study with the longest median follow-up (Ng et al 2017) reported four-year overall survival as 37% (95%CI 24 to 57). Ng et al also reported loco-regional failure free survival as 86% (95%CI 75 to 99) at one year and 65% (95%CI 47 to 90) at four years; and relapse free survival¹ as 58% (95%CI 44 to 76) at one year and 30% (95%CI 18 to 49) at four years. In addition Lertbutsayanukul et al (2013) reported one-year event-free survival² as 59% and Yu et al (2015) reported one-year progression free survival (not further defined) as 52%.
- In Lertbutsayanukul et al (2013) 15 patients assessed three months after the completion of radiotherapy all had a partial **metabolic response** with a mean maximum standard uptake value³ reduction of 62% (range 37 to 82).

Safety

- The most common severe **adverse events** in Lertbutsayanukul et al (2013) were leucopenia⁴ (59%) and vomiting (24%), and one patient died from oesophageal fistula 186 days after the first day of radiation. In Yu et al (n=25) severe adverse events occurring during treatment were acute oesophagitis (40%), hematologic toxicity (28%) and nausea and vomiting (24%), and one patient died from oesophageal haemorrhage. The most commonly reported mild to moderate adverse effects were anaemia, platelet decrease, cardiovascular toxicity, dysphagia, pulmonary toxicity, weight loss, vomiting and leucopenia.
- In Lertbutsayanukul et al (2013) the percentage of **normal tissue receiving radiation** was reported: 26% of 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.
- In Yu et al (2015) there was uninterrupted **completion of radiotherapy** for 23 of 25 patients. In two patients radiotherapy was interrupted due to bronchiectasis hemoptysis and cold and fever respectively.

¹ Measured from the end of radiotherapy to the date of first relapse at any site or date of death for patients that did not relapse

² Measured 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

³ Standard uptake value is the ratio of the image derived radioactivity concentration and the whole body concentration of the injected radioactivity

⁴ A reduction in the number of white blood cells

Cost-effectiveness

- No studies assessing the cost or cost-effectiveness of radiotherapy planned with FDG PET-CT or the cost or cost-effectiveness of combined compared to separate staging and planning PET-CT scans were identified.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: PubMed, Embase and Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1st January 2008 and 20th March 2018.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- No controlled studies matching the PICO inclusion criteria were identified. Therefore, three uncontrolled studies were included where patients received radiotherapy planned with FDG PET-CT with the patient in the treatment position and outcomes of radiotherapy using the FDG PET-CT treatment plan were reported.
- The decision to include uncontrolled studies in the absence of controlled studies was confirmed with NHS England during the production of the review. It was also confirmed that the following studies are out of scope: dosimetric studies, studies that used FDG PET-CT as a staging scan rather than a radiotherapy treatment planning scan and studies that compared target volume determined using different scanning methods but did not go on to report any outcomes from radiotherapy.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using the National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8).

4 Results

No controlled studies matching the PICO inclusion criteria were identified. Three prospective uncontrolled studies were included in which patients received an FDG PET-CT scan in the treatment position and radiotherapy outcomes were reported following implementation of the FDG PET-CT treatment plan. These were Ng et al (2017) (n=41); Yu et al (2015) (n=25) and Lertbutsayanukul et al (2013) (n=17). Follow-up periods in these studies ranged from a median of 8.9 months to four years. Full details of the study designs and outcomes are summarised in the evidence tables in section 7.

Clinical effectiveness

The first two of the three clinical effectiveness questions relate to the calculation of gross tumour volume (GTV). These are:

1. Compared to radiotherapy planned without FDG PET-CT, what is the effect of FDG PET-CT planned radiotherapy (and chemoradiotherapy) on gross tumour volume among patients with established oesophageal cancer due to be treated in a neo-adjuvant or radical fashion?
2. What is the effect of reduced gross tumour volume on adverse effects from radiotherapy and does it allow treatment completion?

The interpretation of question 2 was confirmed with NHS England as follows: If radiotherapy planning with FDG PET-CT leads to a reduced calculation of GTV, what is the effect of this on adverse effects from radiotherapy and on treatment completion (as a consequence of reductions in treatment dose and/or field)?

The third clinical effectiveness question relates to patient outcomes following radiotherapy. The evidence relating to these three questions is presented below.

- 1. Compared to radiotherapy planned without FDG PET-CT, what is the effect of FDG PET-CT planned radiotherapy (and chemoradiotherapy) on gross tumour volume among patients with established oesophageal cancer due to be treated in a neo-adjuvant or radical fashion?**

No studies compared outcomes for radiotherapy planned with FDG PET-CT to radiotherapy planned without FDG PET-CT. Three uncontrolled studies used FDG PET-CT to plan and deliver radiotherapy, including the delineation of GTV.

One uncontrolled study (Ng et al 2017) produced separate treatment plans for the same cohort of patients based on FDG PET-CT and CT scans. The FDG-PET CT was used as both a diagnostic and planning scan, and the radiotherapy treatment was delivered based on the FDG PET-CT scan findings. This study therefore does not compare the impact of radiotherapy planned without FDG PET-CT to FDG PET-CT planned radiotherapy.

Ng et al described differences in GTV determined by CT scan and FDG PET-CT scan, based on the assumption that the FDG PET-CT scan findings represented the true extent of disease. The GTV delineated by CT scan was determined to be an overestimate in some cases and an underestimate in others. The cranial extent of tumour was overestimated in 29% of cases and the caudal extent was overestimated in 50% of cases. The cranial extent of the tumour was underestimated in 36% of cases and the caudal extent was underestimated in 26% 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). The median underestimate in the cranial extent was 1.14cm (range 0.3 to 2.85) and the median underestimate in the caudal extent in 1.03cm (range 0.4 to 4.25).

Ng et al also compared the areas which would have been treated using the different treatment plans. GTV determined by PET-CT was not included in GTV determined by CT in 76% of patients (median percentage volume excluded 17%, range 1 to 100). Grade 1 geographic misses occurred in 13% of patients (defined as PET-avid disease not included in the CT planning target volume (PTV); median percentage volume excluded 6%, range 2 to 92). Grade 2 geographic misses occurred in 21% of patients (defined as <95% of the PET-CT PTV receiving at least 95% of the prescription dose based on planning with CT data alone). The median percentage volume of PET-CT PTV receiving $\geq 95\%$ prescription dose was 82% (range 63 to 92). They also 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).

Two of the uncontrolled studies (Yu et al 2015; Lertbutsayanukul et al 2013) focused on using FDG PET-CT to plan different levels of radiation dose to different areas based on the GTV, but there was no comparison with planning or delivery of treatment without FDG PET-CT.

In Yu et al (2015) three treatment areas were defined:

- GTV at risk (the volume with a standard uptake value (SUV⁵) of more than 50% of the maximum SUV which was delineated automatically plus a uniform 1cm expansion margin); these areas were treated with 70Gy
- Planning target volume (PTV) GTV (any visible primary tumour and involved nodes); these areas were treated with 62.5-64Gy
- Planning target volume clinical target volume (GTV of primary tumour plus 2cm margin craniocaudally without lateral margins and GTV of involved nodes without expansion in all directions); these areas were treated with 50-50.4Gy.

In Lertbutsayanukul et al (2013) two areas were defined:

- High risk PTV (GTV plus a lateral margin of 1cm and a longitudinal margin of 3cm); these areas were treated with 64Gy
- Low risk PTV (GTV plus a lateral margin of 1.5cm and a longitudinal margin of 5cm); these areas were treated with 54Gy.

2. If radiotherapy planning with FDG PET-CT leads to a reduced calculation of GTV, what is the effect of this on adverse effects from radiotherapy and on treatment completion (as a consequence of reductions in treatment dose and/or field)?

No studies compared differences in adverse effects associated with differences in calculated GTV when radiotherapy was planned with or without FDG PET-CT.

Two uncontrolled studies (Yu et al 2015; Lertbutsayanukul et al 2013) reported adverse effects following radiotherapy planned using FDG PET-CT. Both studies reported adverse events using the five-grade level National Cancer Institute Common Terminology Criteria for Adverse Events⁶. The most common severe adverse events (grade three and above) affecting more than 20% of the study population in Lertbutsayanukul et al (n=17) were leucopenia⁷ (59%) and vomiting (24%), and one patient died from oesophageal fistula 186 days after the first day of radiation. In Yu et al (n=25) severe adverse events occurring during treatment were acute oesophagitis (40%), hematologic toxicity (28%) and nausea and vomiting (24%), and one patient died from oesophageal haemorrhage. Lertbutsayanukul et al reported high levels of grade one and two adverse events (mild to moderate), the most common including anaemia (100%), platelet decrease (100%), cardiovascular toxicity (94%), dysphagia (88%), pulmonary toxicity (88%), weight loss (88%), vomiting (76%) and leucopenia (41%). Grade one and two toxicities reported by Yu et al occurred at much lower rates (4% to 16% of the study population).

One uncontrolled study (Lertbutsayanukul et al 2013) reported the percentage of normal tissue receiving radiation: 26% of 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

⁵ Standard uptake value is the ratio of the image derived radioactivity concentration and the whole body concentration of the injected radioactivity

⁶ https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8_5x11.pdf

⁷ A reduction in the number of white blood cells

heart was 30.8Gy.

No studies compared differences in treatment completion associated with differences in calculated GTV when radiotherapy was planned with or without FDG PET-CT. One uncontrolled study (Yu et al 2015) reported uninterrupted completion of radiotherapy for 23 of 25 patients who had had radiotherapy planned using FDG PET-CT. Radiotherapy was interrupted for two patients, one due to bronchiectasis hemoptysis and one to cold and fever.

3. Compared to radiotherapy planned without FDG PET-CT, does FDG PET-CT planned radiotherapy result in improved outcomes for patients with oesophageal cancer?

No studies compared outcomes for radiotherapy planned with FDG PET-CT to radiotherapy planned without FDG PET –CT.

Outcomes from radiotherapy planned with FDG PET-CT were reported in three uncontrolled studies. These included treatment response, patterns of treatment failure, survival and metabolic response.

Treatment response

Treatment response was reported in two uncontrolled studies (Ng et al 2017; Lertbutsayanukul et al 2013) which used different categories to determine treatment response. Ng et al (2017) presented treatment response results for 36 patients, assessed three months after the completion of radiotherapy, as four categories (which were not defined): clinical complete response (50%, 95%CI 34 to 66); partial response (39%, 95%CI 25 to 55); stable disease (8%) and progressive disease (3%)⁸. Lertbutsayanukul et al (2013) reported pathologic response to neo-adjuvant chemoradiotherapy for seven patients who subsequently underwent surgery as complete response (absence of any residual viable tumour cells on histological examination) (57%); microscopic residual disease (residual tumour <10%) (29%) and macroscopic residual disease (residual disease >10%) (14%).

Patterns of treatment failure

Patterns of treatment failure were reported in two uncontrolled studies (Ng et al 2017; Lertbutsayanukul et al 2013). In Ng et al, loco-regional failures were defined as failure at the primary site and/or regional node which were within the radiation treatment field. Some form of loco-regional failure was observed in 29% of the 38 patients treated with radiotherapy (median follow-up four years). Regional failure was observed in one of 14 surviving patients in Lertbutsayanukul et al (median follow-up 12 months). Distant failure was observed in 26% of patients in Ng et al and 29% of patients in Lertbutsayanukul et al 2013.

Survival

Overall survival was reported by three uncontrolled studies. (Ng et al 2017; Yu et al 2015; Lertbutsayanukul et al 2013). The studies had different lengths of follow-up, but all three reported one-year survival which ranged from 69% to 87%. Ng et al (n=38 for radiotherapy outcomes) also reported two-year survival as 57% (95%CI 43 to 76); three-year survival as 40% (95%CI 26 to 60) and four-year survival as 37% (95%CI 24 to 57).

Three uncontrolled studies additionally reported some form of relapse or progress free survival.

Ng et al (2017) reported loco-regional failure free survival which was measured from the end of radiotherapy to the date of first loco-regional failure (recurrence within the field of treatment). One-year loco-regional failure free survival was 86% (95%CI 75 to 99); two-year and three year

⁸ Confidence intervals not reported for stable disease and progressive disease

survival were both 72% (95%CI 56 to 93) and four-year survival was 65% (95%CI 47 to 90). Yu et al (2015) (n=25) reported one-year local control (not further defined) as 77%.

Ng et al also reported relapse free survival, which was measured from the end of radiotherapy to the date of first relapse at any site or date of death for patients that did not relapse. Relapse free survival was 58% (95%CI 44 to 76) at one year; 39% (95%CI 26 to 58) at two years; 33% (95%CI 21 to 52) at three years and 30% (95%CI 18 to 49) at four years.

Lertbutsayanukul et al (2013) (n=17) reported event-free survival, which was measured 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. One-year event-free survival was 59%. Yu et al (2015) (n=25) reported one-year progression-free survival (not further defined) as 52%.

Metabolic response

Metabolic response was reported in one uncontrolled study. Lertbutsayanukul et al (2013) assessed metabolic response in 15 patients three months after completion of chemoradiotherapy. Tumours were classified as responding or non-responding using Positron Emission Tomography Response Criteria in Solid Tumours (PERCIST), using maximum standard uptake value⁹ (SUV_{max}). All 15 patients had a partial response to therapy with a mean percent SUV_{max} reduction of 61.7% (range 36.5 to 82.3).

Cost-effectiveness

4. **Compared to radiotherapy planned without FDG PET-CT, what is the evidence of cost-effectiveness of radiotherapy directly planned with FDG PET-CT?**
 - 4a. **Is there evidence that combined FDG PET-CT for staging/ diagnosis and for radiotherapy planning is more cost-effective compared to separate FDG PET-CT for these two purposes?**

No studies were identified assessing the cost or cost-effectiveness of radiotherapy planned with FDG PET-CT or the cost or cost-effectiveness of combined compared to separate staging and planning PET-CT scans.

5 Discussion

No controlled studies matching the PICO inclusion criteria were identified. Three prospective uncontrolled studies were included in which patients received an FDG PET-CT scan in the treatment position and radiotherapy outcomes based on the FDG PET-CT treatment plan were reported.

The three studies included 17, 25 and 41 patients with median follow-up periods of 8.9 months, 12 months and four years respectively. They reported a number of clinical outcomes including treatment response, patterns of failure (i.e. recurrence), survival and metabolic response. In the largest study with the longest follow-up (Ng et al 2017), 50% of patients had a clinical complete treatment response and 39% had partial response 3 months after completion of radiotherapy; there was some form of loco-regional treatment failure in 29% patients and distant failure in 26%. Overall one-year survival ranged from 69-87% across the three studies and Ng et al reported four-

⁹ Standard uptake value is the ratio of the image derived radioactivity concentration and the whole body concentration of the injected radioactivity

year survival as 37%. However these results represent the outcomes of treatment following radiotherapy planned with FDG PET-CT and provide no evidence on how these might compare with outcomes following radiotherapy planned using a different treatment planning method.

One study performed both FDG PET-CT and CT scans in the same patients for planning purposes. Differences were found between tumour delineation using FDG PET-CT and CT scan in the majority of patients, but these were not consistent in magnitude or direction. All patients received treatment based on the FDG PET-CT scan. This study therefore does not provide any evidence on the effectiveness of radiotherapy treatment planned with FDG PET-CT compared to radiotherapy planned by other means.

High numbers of severe adverse events were reported in the two studies that reported safety outcomes, but mild to moderate adverse events were much more common in one study than the other. The one study which reported on this found that over 90% of patients had uninterrupted treatment completion. However the studies provide no evidence on whether adverse events of radiotherapy or treatment completion might vary depending on the method used to plan the radiotherapy.

Different radiotherapy dosing strategies were used in different studies. Almost all patients in the studies received concurrent chemotherapy. The proportion that also underwent surgery varied.

The prospective design of these studies reduces the possibility of selection bias in the study population. However, they were not designed to compare the effectiveness of radiotherapy planned with FDG PET-CT and radiotherapy without direct FDG PET-CT planning.

Given the high level of adverse effects of radiotherapy and poor longer term outcomes for patients with cancer of the oesophagus, approaches to the planning and delivery of treatment which improve its effectiveness and reduce unwanted effects would be welcomed. However there is currently uncertainty about the value of an FDG PET-CT scan to plan radiotherapy treatment for this patient group. Well-designed comparative studies would be required to address this, including assessment of the outcomes of treatment delivered based on different treatment planning methods, and an evaluation of costs and cost-effectiveness.

6 Conclusion

No evidence was identified comparing the effectiveness of radiotherapy directly planned with FDG PET-CT to radiotherapy without direct FDG PET-CT planning for patients with cancer of the oesophagus. Three prospective uncontrolled studies reported radiotherapy outcomes for patients who received an FDG PET-CT scan in the treatment position and received radiotherapy based on the FDG PET-CT treatment plan. While these studies provide some information about outcomes up to four years after this treatment, they do not allow any conclusions to be drawn about the effectiveness of using an FDG PET-CT scan with patients in the treatment position to plan radiotherapy treatment, compared with any other method for radiotherapy treatment planning.

7 Evidence Summary Table

For abbreviations see list after each table

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Ng et al (2017)	P1 – Prospective cohort study Patients recruited between June 2003 and May 2008 (number of centres not reported) The aim of this study was to determine the impact of PET-CT on radiotherapy planning	Patients with localised oesophageal cancer suitable for definitive chemoradiotherapy Patients with metastatic disease were excluded 97% patients had concurrent chemotherapy 32% patients had surgery	n = 41 All patients had an FDG PET-CT scan in the radiotherapy treatment position. This acted as a diagnostic and planning scan 2 blinded radiologists contoured GTV using either the planning CT scan or planning PET-CT scan PTV plans ¹⁰ were generated from CT data alone and from combined PET-CT data	Clinical effectiveness	Assessment of tumour length	Gross tumour volume (GTV) determined by FDG PET-CT was assumed to represent the true extent of the disease GTV by CT scan: <ul style="list-style-type: none"> Overestimated cranial extent in 11 (29%) cases (median 1.28cm, range 0.33 to 3.40) Overestimated caudal extent in 19 (50%) cases (median 0.66cm, range 0.3 to 5.52) Underestimated cranial extent in 14 (36%) cases (median 1.14cm, range 0.3 to 2.85) Underestimated caudal extent in 10 (26%) cases (median 1.03cm, range 0.4 to 4.25) 	6	Direct	This uncontrolled prospective study had a small sample size with a median 4-year follow-up period 57 patients were initially recruited for the study. 13 were excluded due to metastatic disease detected by FDG PET-CT scan, 2 had gastric cancer determined and 1 patient did not tolerate planning scans or radical radiotherapy Separate treatment plans were produced using PET-CT and CT scans. However all treatment was conducted using the PET-CT planning scan 3 patients were excluded from the planning analysis due to lost data (n=1) or did not tolerate PET-CT in the treatment position (n=2) 3 patients were excluded from the clinical analysis because they did not commence radical radiotherapy No information on adverse effects from radiotherapy were reported Confidence intervals around the results are wide, reducing confidence in the results The prospective design of the study reduces the possibility of selection bias in the study population. Patients were recruited over a 5-year period and it is not clear how many centres patients were recruited
				Clinical effectiveness	Comparison of treatment plans	PET GTV was not included in CT GTV in 29 patients (76%) (median percentage volume excluded 17%, range 1 to 100) Grade 1 geographic miss ¹¹ : 5 (13%) (median percentage volume of PET-avid disease excluded was 6%, range 2 to 92) Grade 2 geographic miss ¹² : 8 (21%) (median percentage volume of PET PTV receiving \geq 95%			

¹⁰ GTV plus 1cm volumetric margin

¹¹ Defined by the study authors as any PET-avid disease not included in the CT planning target volume (PTV)

¹² Defined by the study authors as less than 95% of the PET PTV receiving at least 95% of the prescription dose based on planning with CT data alone

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	and outcomes		<p>Patients were treated using the PET-CT treatment plan</p> <p>Patients were treated to a dose of 50-50.4 Gy in 25-28 fractions, 5 per week for 5 weeks</p> <p>Median follow-up 4 years (range 2.7 to 6.8)</p>			<p>prescription dose for these patients was 82%, range 63 to 92)</p> <p>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)</p>			from. Differences in practices between centres may introduce a potential source of bias
				Clinical effectiveness	Treatment response	<p>36 patients were assessed at 3 months follow-up using imaging (CT and/or PET) with/without gastroscopy</p> <ul style="list-style-type: none"> Clinical complete response: 18 (50%, 95%CI 34 to 66) Partial response: 14 (39%, 95%CI 25 to 55) Stable disease: 3 (8%, CI not reported) Progressive disease: 1 (3%, CI not reported) 			
				Clinical effectiveness	Patterns of treatment failure	<p>21 patients relapsed post-treatment</p> <ul style="list-style-type: none"> Local: 5 Regional: 1 Distant: 10 Loco-regional: 1 Local & distant: 2 Regional & distant: 0 Loco-regional & distant: 2 <p>Loco-regional failures are within the radiation treatment field</p>			
				Clinical effectiveness	Overall survival	<ul style="list-style-type: none"> 1-year: 76% (95%CI 64 to 91) 2-year: 57% (95%CI 43 to 76) 3-year: 40% (95%CI 26 to 60) 4-year: 37% (95%CI 24 to 57) 			

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
				Clinical effectiveness	Relapse free survival	<ul style="list-style-type: none"> 1-year: 58% (95%CI 44 to 76) 2-year: 39% (95%CI 26 to 58) 3-year: 33% (95%CI 21 to 52) 4-year: 30% (95%CI 18 to 49) 			
				Clinical effectiveness	Loco-regional failure free survival	<ul style="list-style-type: none"> 1-year: 86% (95%CI 75 to 99) 2-year: 72% (95%CI 56 to 93) 3-year: 72% (95%CI 56 to 93) 4-year: 65% (95%CI 47 to 90) 			
Yu et al (2015)	<p>P1 – Prospective cohort study</p> <p>Patients recruited between April 2012 and February 2014 at 1 centre</p> <p>The aim of this study was to observe the feasibility and safety of selective dose boost to high</p>	<p>Patients with histologically or cytologically proven oesophageal squamous cell carcinoma with tumours ≥ 10cm and $SUV_{max} > 5.0$ in PET scan</p> <p>Inclusion criteria included: age ≥ 18; ECOG performance status 0-1; no prior malignancy for ≥ 5 years; ability to swallow semifluid diet; adequate</p>	<p>n=25</p> <p>All patients had an FDG PET-CT scan for radiotherapy planning in the treatment position</p> <p>GTV was delineated using all available information including diagnostic CT, FDG PET-CT, barium esophagram and endoscopic reports</p> <p>Treatment areas were defined as PTV-GTV¹³;</p>	Clinical effectiveness	Overall survival	1 year overall survival: 69%	5	Direct	<p>This uncontrolled prospective study had a small sample size and a short follow-up period</p> <p>An FDG PET-CT planning scan was used to deliver radiotherapy</p> <p>The main focus of the study was to assess the safety of higher doses of radiotherapy to selected areas identified by treatment planning FDG PET-CT</p> <p>Adverse effects were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events¹⁶. 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'</p> <p>The authors did not include confidence intervals or other measure of the precision of the results</p> <p>The prospective design of the study reduces the possibility of selection bias in the study population. Patients were recruited from 1 centre over a 2-year period which reduces the risk of bias from differing practices</p>
				Clinical effectiveness	Progression-free survival	<p>1 year progression-free survival: 52%</p> <p>Median progression-free duration: 13 months</p>			
				Clinical effectiveness	Local control	1 year local control: 77%			
				Safety	Adverse events	<p>Grade 3 acute toxicity (during concurrent treatment):</p> <ul style="list-style-type: none"> Acute oesophagitis: 10 (40%) Hematologic toxicity: 7 (28%) Nausea and vomiting: 6 (24%) <p>Grade 3 late toxicities:</p> <ul style="list-style-type: none"> Oesophageal perforation: 1 (4%) Pericardial effusion: 1 (4%) <p>Grade 1 and 2 late toxicities:</p> <ul style="list-style-type: none"> Pulmonary fibrosis: 4 (16%) Oesophageal ulcer: 3 (12%) Oesophageal stenosis: 2 (8%) Oesophageal pain: 2 (8%) Oesophageal haemorrhage: 1 (4%) <p>6 patients died:</p>			

¹³ Derived from the GTV (any visible primary tumour and involved nodes)

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	FDG uptake areas defined prior to treatment	bone marrow reserve; normal renal and liver function; no prior thoracic radiation or chemotherapy Patients were excluded if they had radiological indications of deep ulcer or perforation of the oesophagus ; evidence of visceral metastases; weight loss ≥10% within 6 months; cachexia All patients had concurrent chemotherapy	PTV-CTV ¹⁴ and PTV-GTV ¹⁵ Radiation was delivered at different dose levels to 3 defined areas. PTV-CTV areas received 50 – 50.4 Gy; PTV-GTV areas received 62.5-64Gy; PTV-GTVR areas received 70Gy A minimum of 5 patients were treated at each dose level. Maximum-tolerated dose was defined as the dose level below that which induces a dose-limiting toxicity or Grade 5 toxicity in 2 patients	Safety	Interruption of radiotherapy	<ul style="list-style-type: none"> • Oesophageal haemorrhage: 1 • Persistent disease: 2 • Local recurrence: 3 2 patients had interruption of radiotherapy: <ul style="list-style-type: none"> • Bronchiectasis hemoptysis: 1 • Cold and fever: 1 23 patients completed radiotherapy without interruption			

¹⁶ https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

¹⁴ GTV of primary tumour plus 2cm margin craniocaudally without lateral margins and GTV of involved nodes without expansion in all directions

¹⁵ The volume with an SUV of more than 50% of the SUV_{max} which was delineated automatically plus a uniform 1cm expansion margin

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
			Median follow-up 8.9 months (range 2.3 to 20.7)						
Lertbut sayanu kul et al (2013)	P1 – Prospective cohort study Patients recruited between August 2009 and July 2010 at 1 centre in Thailand The aim of this study was to determine if PET-CT as a tool to delineate tumour extent with	Patients with potentially curable, locally advanced oesophageal cancer Inclusion criteria included: clinical stage I to IVa disease; age 15 to 75 years; ECOG performance status 0-1; adequate bone marrow reserve; normal renal function Patients with documented distant	n = 17 All patients had an FDG PET-CT scan for radiotherapy planning with arms positioned above the head (treatment position) GTV was delineated using all information from oesophagogastric endoscopy reports, PET and CT with contrast images High risk PTV and low risk	Clinical effectiveness	Treatment response	For 7 patients who underwent surgery pathologic response to neo-adjuvant chemoradiotherapy was: <ul style="list-style-type: none"> • Complete response (absence of any residual viable tumour cells on histological examination): 4 (57%) • Microscopic residual disease (residual tumour <10%): 2 (29%) • Macroscopic residual disease (residual disease >10%): 1 (14%) 	6	Direct	This uncontrolled prospective study had a small sample size and a short follow-up period An FDG PET-CT planning scan was used to plan treatment Results relating to surgical outcomes are not reproduced here Adverse effects were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events ¹⁶ . 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' The authors did not include confidence intervals or other measure of the precision of the results The prospective design of the study reduces the possibility of selection bias in the study population. Patients were recruited from 1 centre over a 12-month period which reduces the risk of bias from differing practices
				Clinical effectiveness	Patterns of treatment failure	5 of 14 surviving patients relapsed post-treatment <ul style="list-style-type: none"> • Regional: 1 • Distant metastases: 4 			
				Clinical effectiveness	Overall survival	1-year overall survival: 87% Median overall survival was 14 months in patients who did not have surgery Median survival time was not reached for surgical patients			
				Clinical effectiveness	Event-free survival	1-year event-free survival: 59% Median event-free survival was			

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	IMRT ¹⁷ to conform the maximum dose to target volumes would result in better tumour response	metastases were excluded All patients had concurrent chemotherapy 41% patients had surgery	PTV were calculated ¹⁸ Patients received IMRT to the primary tumour site and pathologic lymph nodes to a planned 64Gy in 30 fractions using a simultaneous integrated boost technique, 5 days per week High risk PTV areas were treated to 64Gy and low risk PTV to 54Gy 3 months after chemoradiotherapy, patients were re-evaluated with PET-CT to assess			15.5 months			
				Clinical effectiveness	Metabolic response	Metabolic response was assessed in 15 patients who received a 2 nd PET-CT after treatment All patients had a partial response to therapy with a mean percent SUV _{max} reduction: 61.7% (range 36.5 to 82.3)			
				Safety	Adverse effects	Acute ≥grade 3 adverse effects: <ul style="list-style-type: none"> • Leucopenia: 10 (59%) • Vomiting: 4 (24%) • Pulmonary toxicity: 2 (12%) • Dysphagia: 2 (12%) • Weight loss: 2 (12%) • Cardiovascular toxicity: 1 (6%) 1 patient died from oesophageal fistula 186 days after 1 st day of radiation Grade 1-2 adverse effects: <ul style="list-style-type: none"> • Anaemia: 17 (100%) • Platelet decrease: 17 (100%) • Cardiovascular toxicity: 16 (94%) • Dysphagia: 15 (88%) • Pulmonary toxicity: 15 (88%) • Weight loss: 15 (88%) • Vomiting: 13 (76%) • Leucopenia: 7 (41%) 			

¹⁷ Intensity modulated radiotherapy (IMRT) is used to administer patients the maximum dose while keeping dose to the surrounding tissues at a minimum (Lertbutayanukul et al 2013)

¹⁸ High risk PTV applied a lateral margin of 1cm and a longitudinal margin of 3cm to the GTV. Low risk PTV applied a lateral margin of 1.5cm and a longitudinal margin of 5cm

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
			therapeutic response Median follow-up 12 months (range 4 to 25.8)	Safety	Dose to critical normal tissues	Percentage of normal lung receiving a total dose of 20Gy: 26% Percentage of normal lung tissue receiving a total dose of 10Gy: 48% Average maximum dose to the spinal cord: 40.6Gy Median dose to the heart: 30.8Gy			

CI – Confidence Interval; CT – Computed Tomography; CTV – Clinical Target Volume; ECOG – Eastern Cooperative Oncology Group; FDG- 18F Fluoro-deoxyglucose; GTV – Gross Tumour Volume; GTVR –Gross Tumour Volume at Risk; Gy – Gray; IMRT – Intensity Modulated Radiotherapy; PET - Positron Emission Tomography; PTV- planning target volume; SUV – Standard Uptake Value

8 Grade of Evidence Table

For abbreviations see list after each table

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Assessment of tumour length	Ng et al 2017	6	Direct	C	<p>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.</p> <p>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).</p> <p>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.</p> <p>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.</p>

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Comparison of treatment plans	Ng et al 2017	6	Direct	C	<p>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.</p> <p>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 \geq95% 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).</p> <p>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.</p> <p>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.</p>
Treatment response	Ng et al 2017	6	Direct	B	<p>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.</p> <p>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.</p> <p>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).</p> <p>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.</p>
	Lertbutsayanukul et al 2013	6	Direct		

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Patterns of treatment failure	Ng et al 2017	6	Direct	B	<p>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.</p> <p>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.</p> <p>The median follow-up in this study was 4 years (range 2.7 to 6.8). Some loco-regional failure (within the radiation treatment field) occurred in 11 patients; 29% of the 38 patients treated with radiotherapy. Without a comparator for treatment planned using a different scanning method it is difficult to interpret the clinical significance of this result.</p> <p>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.</p>
	Lertbutsayanukul et al 2013	6	Direct		
Overall survival	Ng et al 2017	6	Direct	B	<p>Overall survival was measured from the end of radiotherapy to the date of death.</p> <p>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.</p> <p>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.</p> <p>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.</p>
	Lertbutsayanukul et al 2013	6	Direct		
	Yu et al 2015	5	Direct		
Relapse free survival	Ng et al 2017	6	Direct	C	<p>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.</p> <p>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.</p> <p>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.</p> <p>This uncontrolled prospective study had a small sample size (n=41) with patients recruited</p>

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					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.
Loco-regional failure free survival (local control)	Ng et al 2017	6	Direct	B	<p>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.</p> <p>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 loco-regional 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.</p> <p>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 loco-regional failure free survival rates are wide, reducing confidence in the result. Without a comparator for treatment planned using a different method it is difficult to interpret the clinical significance of this result.</p> <p>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.</p>
	Yu et al 2015	5	Direct		
Event-free survival (progression-free survival)	Lertbutsayanukul et al 2013	6	Direct	B	<p>Event-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.</p> <p>In 1 study (Lertbutsayanukul et al, 2013) 1-year event-free survival was 59%, and median event-free survival was 15.5 months.</p> <p>The median follow-up in this study was 12 months (range 4 to 25.8). Without a comparator for treatment planned using a different scanning method it is difficult to interpret the clinical significance of this result.</p> <p>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.</p>
	Yu et al 2015	5	Direct		
Metabolic response	Lertbutsayanukul et al 2013	6	Direct	C	<p>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 value¹⁹ (SUV_{max}). The PERCIST rules define when tumours in cancer patients improve, stay the same or worsen during treatment.</p> <p>Lertbutsayanukul et al (2013) assessed metabolic response in 15 patients. All patients had</p>

¹⁹ Standard uptake value is the ratio of the image derived radioactivity concentration and the whole body concentration of the injected radioactivity

Use of FDG PET-CT planned radiotherapy for oesophageal cancer (No Comparator)

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					<p>a partial response to therapy with a mean percent SUV_{max} reduction of 61.7% (range 36.5 to 82.3).</p> <p>A reduction in measureable 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.</p> <p>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.</p>
Safety	Lertbutsayanukul et al 2013	6	Direct	B	<p>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 Events²⁰. 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'.</p> <p>Lertbutsayanukul et al (2013) reported the number of ≥grade 3 adverse events. The most common was leucopenia²¹ (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.</p> <p>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.</p> <p>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.</p>
	Yu et al 2015	5	Direct		

CI – Confidence Interval; CT – Computed Tomography; CTV – Clinical Target Volume; FDG- 18F Fluoro-deoxyglucose; GTV – Gross Tumour Volume; Gy – Gray; PET - Positron Emission Tomography; PTV- planning target volume; SUV – Standard Uptake Value

²⁰ https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

²¹ A reduction in the number of white blood cells

9 Literature Search Terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	All patients with confirmed oesophageal carcinoma scheduled for radiotherapy or chemoradiotherapy
I – Intervention Which intervention, treatment or approach should be used?	Radiotherapy directly planned with FDG PET-CT
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Radiotherapy without direct FDG PET-CT planning
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	<u>Critical to decision making:</u> Accuracy in delineation of primary tumour and nodal spread Size of treatment fields Radiation side effects Completion of treatment courses <u>Important to decision-making:</u> Lower gross tumour volume Improved survival Improved response rates Increased time to relapse Cost-effectiveness
Assumptions / limits applied to search	
Include: Peer reviewed publication published in the last 10 years, English language only Exclude: Uncontrolled studies, dosimetric studies, abstracts, conference papers, posters, commentaries, letters	

10 Search Strategy

We searched PubMed, Embase and Cochrane Library limiting the search to papers published in England from 1st January 2008 to 20th March 2018. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 20th March 2018

Embase search:

- 1 Positron Emission Tomography Computed Tomography/
- 2 ((fluoro-deoxyglucose or fluorodeoxyglucose or 18f or fdg) adj3 (pet or positron emission tomogra*)).ti,ab.
- 3 ((pet or positron emission tomogra*) adj3 (ct or computed tomogra*)).ti,ab.
- 4 1 or 2 or 3
- 5 Esophageal Neoplasms/
- 6 ((oesophag* or esophag*) adj3 (cancer* or carcinoma* or neoplas* or malignan* or tumour* or tumor*)).ti,ab.
- 7 5 or 6
- 8 exp RADIOTHERAPY/

- 9 (radiotherap* or irradiat* or radiation therap* or radiation treatment or chemoradi* or chemo-radi*).ti,ab.
- 10 8 or 9
- 11 7 and 10
- 12 Esophageal Neoplasms/rt [Radiotherapy]
- 13 11 or 12
- 14 4 and 13
- 15 limit 14 to (english language and yr="2008 -Current")

11 Evidence Selection

- Total number of publications reviewed: 38
- Total number of publications considered potentially relevant: 19
- Total number of publications selected for inclusion in this briefing: 3

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