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Overview

The Application of Functional Imaging Techniques to Personalise Chemoradiotherapy in Upper Gastrointestinal Malignancies

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Abstract

Functional imaging gives information about physiological heterogeneity in tumours. The utility of functional imaging tests in providing predictive and prognostic information after chemoradiotherapy for both oesophageal cancer and pancreatic cancer will be reviewed. The benefit of incorporating functional imaging into radiotherapy planning is also evaluated. In cancers of the upper gastrointestinal tract, the vast majority of functional imaging studies have used ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). Few studies in locally advanced pancreatic cancer have investigated the utility of functional imaging in risk-stratifying patients or aiding target volume definition. Certain themes from the oesophageal data emerge, including the need for a multiparametric assessment of functional images and the added value of response assessment rather than relying on single time point measures. The sensitivity and specificity of FDG-PET to predict treatment response and survival are not currently high enough to inform treatment decisions. This suggests that a multimodal, multiparametric approach may be required. FDG-PET improves target volume definition in oesophageal cancer by improving the accuracy of tumour length definition and by improving the nodal staging of patients. The ideal functional imaging test would accurately identify patients who are unlikely to achieve a pathological complete response after chemoradiotherapy and would aid the delineation of a biological target volume that could be used for treatment intensification. The current limitations of published studies prevent integrating imaging-derived parameters into decision making on an individual patient basis. These limitations should inform future trial design in oesophageal and pancreatic cancers.

Key words: Functional imaging; oesophageal cancer; pancreatic cancer; radiotherapy treatment planning; response assessment; target volume delineation

Statement of Search Strategies Used and Sources of Information

Four separate searches were completed on Ovid MEDLINE® in-process and other non-indexed citations and Ovid MEDLINE® 1994 to present. The searches targeted literature on: (i) oesophageal cancer, chemoradiotherapy (CRT) and functional imaging; (ii) pancreatic cancer, CRT and functional imaging; (iii) oesophageal cancer, functional imaging and target volume definition; (iv) pancreatic cancer, functional imaging and target volume definition. All English language abstracts were reviewed and unrelated articles were excluded. Trials of neoadjuvant chemotherapy alone or mixed cohorts of chemotherapy and CRT were excluded if separate analyses of these treatment modalities were not described. Studies were grouped into those that carried out functional imaging before CRT, before and during CRT, pre- and post-CRT and post-CRT only.

Introduction

The utility of functional imaging to predict chemoradiotherapy (CRT) treatment response and prognosis or to define target volumes for radiotherapy for upper gastrointestinal tumours remains uncertain. Functional imaging can provide information about the heterogeneity of physiological properties within tumours. Correlating functional imaging-derived parameters with treatment response and long-term treatment outcome may offer a means of risk-stratifying patients and ultimately guide treatment

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decisions. Certain physiological parameters are associated with resistance to radiotherapy.

Physiological processes that can be assessed with imaging techniques include glucose metabolism, cell proliferation, hypoxia, perfusion and water diffusion. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), which reflects glucose uptake and retention, is by far the most commonly used functional imaging test.

Both neoadjuvant CRT and definitive CRT are treatment options in oesophageal cancer. Definitive CRT has a 2 year local failure rate of around 50% [1–3] and most local failures occur within the gross tumour volume (GTV) [4]. A pathological complete response (pCR) is seen in 30% of cases after CRT [5–7]. If rates of pCR could be improved by image-guided treatment intensification, CRT followed by selective salvage oesophagectomy may become the preferred treatment. The early identification of non-responders would also define a group of patients who should proceed to early surgery.

Locally advanced pancreatic cancer (LAPC) has a poor prognosis, with a median survival ranging from 5 to 19 months [8]. The LAP07 trial has recently reported that CRT after induction chemotherapy confers no survival advantage compared with continuing with chemotherapy alone (overall survival 15.2 and 16.4 months, respectively) [9]. The failure of CRT to improve treatment outcome is, perhaps, a little surprising, given that for 25–29% of patients with LAPC, the first site of disease progression is at the site of the original tumour [10,11]. Escalating the radiotherapy dose to the pancreas seems attractive, but is limited by normal tissue toxicity, particularly in the duodenum [12]. If a method of identifying patients who have a high risk of local failure could be identified, a dose-escalation regimen that allows a higher rate of treatment-associated toxicity may be seen as worthwhile. After neoadjuvant CRT, those with $<$10% of viable tumour cells have a median overall survival of 39 months compared with only 15 months in those who have $>$10% of viable tumour cells remaining [13].

Accurate GTV definition is essential in radiotherapy planning to reduce geographical misses and limit the involvement of normal tissues in the treatment volume. Incorporating functional imaging into GTV delineation is attractive for a number of reasons – not least to reduce intra- and interobserver variability. It may allow an automation of the target delineation process and identify areas that may benefit from radiotherapy dose boosting. Computed tomography is usually used in target volume delineation for radiotherapy planning. Computed tomography has its limitations – most notably in defining mediastinal lymph node involvement in oesophageal cancer, which is improved with FDG-PET.

The utility of functional imaging tests in providing predictive and prognostic information after CRT for both oesophageal cancer and pancreatic cancer will be reviewed. A separate review of the benefit of incorporating functional imaging into radiotherapy treatment planning will be included. The limitations of the evidence will be discussed and recommendations as to how the integration of functional imaging into the risk stratification of patients with locally advanced oesophageal and pancreatic cancers will be made.

Methods

Four separate searches were completed on Ovid MEDLINE® in-process and other non-indexed citations and Ovid MEDLINE® 1994 to present. The searches targeted literature on: (i) oesophageal cancer, CRT and functional imaging; (ii) pancreatic cancer, CRT and functional imaging; (iii) oesophageal cancer, functional imaging and target volume definition; (iv) pancreatic cancer, functional imaging and target volume definition.

All English language abstracts were reviewed and unrelated articles were excluded. Trials of neoadjuvant chemotherapy alone or mixed cohorts of chemotherapy and CRT were excluded if separate analyses of these treatment modalities were not described. Studies were grouped into those that carried out functional imaging before CRT, before and during CRT, pre- and post-CRT and post-CRT only.

Results

The database search to identify studies concerned with treatment response prediction in oesophageal cancer returned 181 results and three additional studies were identified from the references of these studies. Of these, 141 were excluded after full-text review, leaving 43 studies for review. Eighty-one studies concerning target volume definition in oesophageal cancer were identified by the database search. After full-text review, only 13 were included. The numbers in pancreatic cancer were lower – the database search identified 66 studies concerning functional imaging as a means of predicting CRT response, only six of which were eligible after full-text review. Only one study using functional imaging to guide target volume definition in pancreatic cancer was identified by this search strategy. Apart from one series that used diffusion-weighted magnetic resonance imaging (MRI) [14] and another that used a putative hypoxia PET tracer (^{18}F-fluoroerythronitromidazole) [15], all series used FDG-PET as the imaging modality of choice. Although other functional imaging modalities, such as dynamic contrast enhanced MRI, have been shown to be feasible in cancers of the upper gastrointestinal tract [16], they have not been used in response prediction or target volume definition studies.

Tables 1–4 summarise the data that showed a positive correlation with treatment outcome or prognosis. Many studies that carried out imaging at more than one time point commented upon the usefulness of the imaging at each time point. A clear trend immediately becomes apparent; imaging before CRT, when analysed independently, offers little to no predictive or prognostic information [26,33,38,41]. Recent studies that have gleaned as much information as is possible from pre-CRT FDG-PET by carrying out a textural analysis have improved upon this to a degree: one series reported an area under the received