Positron Emission Tomography in Staging of Esophageal Cancer
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2005

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
SUMMARY AND FUTURE PERSPECTIVES
SUMMARY

Curative treatment of patients with esophageal cancer mainly depends on the stage of disease. Until now, surgical resection is the only curative option in patients with locoregional stage of the disease, but is accompanied by substantial morbidity and even mortality. Patients with distant metastases (M1) or local invasion of adjacent vital structures by the primary tumor (T4) are beyond cure. These patients may benefit from less invasive methods, including stenting, external radiation and/or brachytherapy for palliation.

The primary aim in staging of esophageal cancer is to assess the prognosis in order to select those patients who may benefit from surgery. Therefore, several techniques are employed to stage these patients. During the last decade, preoperative noninvasive staging modalities have improved. Computed tomography (CT) of thorax and abdomen has been the first-line method to determine local resectability and metastatic spread for many years. Later, endoscopic ultrasound (EUS) was introduced and has become the most reliable method of identifying the depth of primary tumor invasion and to assess regional and distant lymph node involvement, particularly in combination with fine-needle aspiration (FNA). Recently, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been gaining acceptance in the detection of distant metastatic disease.

This thesis discusses several aspect of PET in staging patients with cancer of the esophagus or gastroesophageal junction.

In chapter 2, the literature concerning staging esophageal cancer with FDG-PET was systematically reviewed. FDG-PET was found to have moderate sensitivity and specificity in the detection of locoregional lymph node metastases, with considerable heterogeneity across the included studies. In the detection of distant nodal and hematogenous metastases, FDG-PET has reasonable sensitivity and specificity, with a lower degree of heterogeneity. As M stage determines patient management, we feel that the potential contribution of FDG-PET to staging should carry more weight than its role in N staging when deciding whether or not to implement FDG-PET in the standard preoperative work-up of patient with esophageal cancer.

Chapter 3 describes a systematic review of CT, EUS and FDG-PET for the response assessment to neoadjuvant therapy in patients with esophageal cancer. Single slice CT scanning to assess the response to neoadjuvant therapy in esophageal cancer is inaccurate and therefore not recommended. EUS and FDG-PET have equivalent accuracy. EUS can identify patients who have achieved a pathological response, but is not always feasible during or shortly after chemoradiation and therefore not routinely used for therapy response assessment. FDG-PET, measuring alterations in tissue metabolism, seems a promising noninvasive tool for neoadjuvant therapy response assessment in esophageal cancer.

In chapter 4, the impact of FDG-PET on the rate of unnecessary surgical explorations is investigated. This study shows a substantial rate of unnecessary surgery in patients suitable for curative treatment mainly because of distant metastases. Improvement of preoperative staging, especially by implementation of FDG-PET, may have reduced the rate of unnecessary surgery to approximately 20%.

Chapter 5 describes the additional value of FDG-PET after a state-of-the-art conventional staging and the additional costs related to FDG-PET. FDG-PET improves the selection for potentially curative surgery, especially in stage III-IV esophageal cancer patients.
However its yield after extensive conventional staging including EUS-FNA and multidetector CT is limited. The additional costs of FDG-PET were not compensated by the cost reduction of prevented surgery.

Chapter 6 discusses the clinical importance of synchronous neoplasms, which are detected on FDG-PET that was obtained for the preoperative staging of esophageal cancer patients. FDG-PET may detect unexpected synchronous primary neoplasms in patients with esophageal cancer. Sites of suspected metastases should be confirmed histologically before treatment, as synchronous neoplasms can mimic metastatic disease.

In chapter 7, the possible pitfalls of FDG-PET are described. This study demonstrates the pitfalls of staging esophageal cancer with FDG-PET due to the occurrence of false-positive results. We should remember that FDG is not a tumor-specific substance, and that false-positive results may occur as a result of increased glucose metabolism in benign lesions. This study shows that PET still has to be used complementary to conventional staging methods. From these observations, it is clear that positive findings on FDG-PET must be confirmed by pathological examination, whenever possible, before denying patients from surgery with curative intent.

Besides imaging, FDG-PET offers the opportunity for quantification of FDG uptake in the primary tumor. Chapter 8 discusses the role of the standardized uptake value (SUV) in the assessment of prognosis in esophageal cancer. SUV analysis should be performed because a high SUV seems to be related with advanced stages of esophageal carcinoma, irresectability and therefore with poorer prognosis. However, SUV is not useful as an independent predictor of survival in patients with esophageal cancer. Since esophagectomy is the only potentially curative option, survival is strongly predicted by the eligibility for surgery.

In chapter 9, the new tracer $^{18}$F-fluoro-3’deoxy-3’-L-fluorothymidine (FLT) is investigated in a feasibility study. At present, $^{18}$F-FDG is the tracer of choice for the staging of esophageal cancer. FLT seems to be more tumor specific. Despite the lower incidence of false-positive results with $^{18}$F-FLT, false-negative results will increase by using $^{18}$F-FLT, which is a major disadvantage for the staging of esophageal cancer.

**FUTURE PERSPECTIVES**

The last decades have been characterized by the development of high-resolution imaging techniques such as FDG-PET but also the multidetector CT. Further improvements of several techniques are expected and they will play a role in increasing the accuracy for the staging of several types of cancer. This paragraph describes some new techniques that will be implemented in the management of esophageal cancer patients.

**Multidetector CT**

As is discussed in chapter 5, the role of CT has increased for staging esophageal cancer by use of a multidetector technique. The spatial resolution of this type of CT will further increase by the currently available 64-row multidetector CT. The reliability of the CT in detecting distant metastases will increase but also the assessment of tumor invasion into surrounding structures will be improved. Therefore, multidetector CT will have a key role for the initial staging of esophageal cancer.
PET/CT
Recently, dual-modality PET/CT tomographs have become available. PET/CT is currently the fastest growing imaging technology worldwide. The PET/CT machines combine morphological CT and functional PET imaging within one system served by a single examination table. CT and PET images are obtained in series with the patient remaining in the same table position thereby providing accurately fused morphological and functional data. Initial experience has amply demonstrated, that PET and CT information are highly synergistic in identifying and specifying lesions such as tumor metastases. The interaction of high lesion sensitivity as afforded by PET with precise anatomic referencing as provided by CT appears very relevant. In addition, there are technical synergies for PET/CT, which translate into shorter imaging times than when PET is used alone: transmission correction of PET data can be done with the CT data, abbreviating imaging data taking by of the order of 25%. This translates into improved patient comfort and into more efficient use of FDG. For colorectal cancer, PET/CT leads to a significant improvement of the TNM-staging results as compared to both imaging modalities alone as well as CT and PET viewed side by side. For esophageal cancer, PET/CT may have advantages especially for the assessment of lymph node metastases in the cervical region and in the abdomen. However, studies are not yet available on this topic.

MR-USPIO
Recently, magnetic resonance (MR) with ultrasmall superparamagnetic iron oxide (USPIO) is gaining acceptance as a noninvasive method for detection of lymph node metastases in several tumors. MR provides images with excellent anatomical detail and soft tissue contrast but is relatively insensitive for lymph node metastases due to limited sensitivity of current nodes size criteria in differentiating benign from malignant nodes. However, the MR results can be improved by using a superparamagnetic contrast using USPIO.

After intravenous administration, USPIO particles reach lymph nodes by two distinct pathways. The major pathway is that of direct transcapillary passage through high endothelial venules within individual lymph nodes. Once within the nodal parenchyma, phagocytic cells of the mononuclear phagocyte system engulf the particles. The second pathway is via nonselective endothelial transcytosis across permeable capillaries throughout the body into the interstitium. USPIO particles are subsequently taken up from then interstitium by lymphatic vessels and transported to regional lymph nodes. A lymph node with normal phagocytic function takes up a substantial amount of USPIO and therefore markedly reduces the signal intensity following intravenous administration of iron oxide agents secondary to the magnetic susceptibility and T2 shortening effects of the iron oxide particles.

In metastatic lymph nodes, tumor cells replace the normal cells. This results in a decrease in the number of macrophages and can therefore result in a decrease in the uptake of a lymph node-specific tracer and maintains a relatively high signal intensity. As well as high sensitivities ranging from 81% to 92% as specificities, ranging from 80% to 98%, have been reported for different types of tumors. These encouraging results warrant further investigation especially in tumors like esophageal cancer which an early and whimsical pattern of nodal spread.

Response assessment
The best option for curative treatment is radical surgery for patients with esophageal cancer,
with a long-term survival of only 25%. Therefore, various forms of neoadjuvant or adjuvant multimodality therapy have been evaluated in an effort to improve these survival results. Neoadjuvant therapy aims at eradication of lymphatic and/or hematogenous metastases with improvement of survival and at shrinkage of the primary tumor with an improved radical resectability rate. However, in a large proportion of patients insufficient objective response is achieved. These patients do not benefit from neoadjuvant therapy, but do suffer from toxic side effects, while appropriate surgical therapy is delayed. For this reason, a diagnostic test that can accurately predict tumor response early in the course of neoadjuvant therapy is of crucial importance.

As described in chapter 3, FDG-PET is a promising noninvasive tool for the identification of responders to neoadjuvant therapy. FDG-PET reflects alterations in tissue metabolism that generally precede anatomic change. Therefore, FDG-PET will be implemented early during neoadjuvant therapy schedules for a proper selection of patients. In 2005, a prospective multicenter trial started in The Netherlands to investigate the exact role of FDG-PET in identifying responders to neoadjuvant therapy. Furthermore, the cost-effectiveness of implementing FDG-PET for early response assessment will be investigated.