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Review

European Organisation of Research and Treatment of Cancer (EORTC) Gastrointestinal Group: Workshop on the role of metabolic imaging in the neoadjuvant treatment of gastrointestinal cancer

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ABSTRACT

Metabolic imaging and early response assessment by positron emission tomography (PET) are gaining importance in guiding treatment of localised and metastatic gastrointestinal tumours. During a workshop organised by the European Organisation of Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Group the most relevant research questions, methodological aspects and unmet clinical needs in this disease were discussed. Potential future trials were drafted. This paper reviews the lectures and discussions held during this workshop and summarises the action points for the further investigation of metabolic imaging to guide treatment in gastrointestinal tumours.

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1. Introduction

Tumours originating from the gastrointestinal tract organs are amongst the most prevalent cancers worldwide with a particularly high incidence rate of colorectal cancer in the West and of stomach cancer in Asia. The incidence of oesophageal adenocarcinoma is dramatically increasing in countries with a western life style.

After recent studies, multimodal and especially neoadjuvant treatment strategies are now widely used. This is particularly true for localised oesophago-gastric cancers,[1–3] for liver metastases from colorectal cancer[4,5] and for locally advanced rectal cancer.[6,7] Soon after having implemented neoadjuvant treatment in clinical trials and into clinical routine, it became clear that some key issues in the context of neoadjuvant treatment are not yet understood and some relevant clinical problems are not yet solved.

First and foremost, the inaccuracy of clinical staging remains and becomes an even more relevant problem in the times of neoadjuvant treatment. This is because the selection of a patient for neoadjuvant treatment can only be based on clinical evaluation and not longer on histopathological staging. Therefore, it is now crucial to achieve a correct depiction of the TNM status and of other relevant prognostic and predictive factors. Novel imaging techniques such as positron emission tomography (PET) may help to achieve an accurate staging.

Second, in a variety of pre-operatively treated gastrointestinal tumours the response to neoadjuvant treatment appears determinant for the prognosis of patients who then undergo resection.[8–11] Traditionally, response has been determined post-operatively by pathological scoring of tumour regression. But this information comes late, when we aim at tailoring every patient's treatment according to individual tumour and patient characteristics. Novel imaging techniques may also be useful to determine the chemo-responsiveness of a tumour as early as possible in the course of specific treatment. This would allow altering the treatment by introducing novel or alternative drugs that may overcome chemotherapy resistance or changing the general treatment strategy for the patient.

Third, to accurately quantify the therapeutic response to pre-operative chemo- or radiotherapy is a key issue. Recent studies have shown that conventional pre-operative staging procedures cannot accurately define complete pathological responses.[12,13] However, accurate qualification of complete response is key in deciding on the extent of surgical resections. Sticking to the rule of operating in the limits of the initial tumour extension means that organ or sphincter preservation is often suboptimal even when the patient has achieved a good clinical responses to neoadjuvant treatment. Novel imaging techniques may help to more reliably and precisely define true complete responses to pre-operative treatment, which would allow to limit the radicality of the surgical resection and thus preserve organ function.

The European Organisation of Research and Treatment of Cancer (EORTC) Gastrointestinal (GI) Tract Cancer Group organised a multidisciplinary 2-day workshop in October 2007 to discuss the value of novel imaging techniques, in particular positron emission tomography/computed tomography (PET/CT) in the treatment of potentially curable GI cancer and to elaborate future clinical study concepts to assess the value of these novel imaging techniques.

2. The role of PET to characterise prognosis and response in the treatment of cancer (Lecture: Robert Downey, New York, USA)

The majority of patients with surgically treated lung and oesophageal cancer die from progression of micro-metastatic disease that is undetected pre-operatively. It is likely that the greatest benefit of surgery will be in those patients responding to induction chemotherapy. Currently imaging defines prognosis prior to induction therapy and measures response to therapy poorly.

The initial promise of PET imaging was that it would allow non-invasive determination of whether an indeterminate organ finding was likely to be malignant or not. At Memorial Sloan-Kettering Cancer Center, New York, PET has proven to be of limited use in this regard, and currently, PET is largely used in patients with newly diagnosed lung or oesophageal cancer to determine the probable extent of loco-regional and distant sites of disease. Again, PET has proven to be of more limited utility than had been hoped in this regard. Recently, completed large prospective trials have demonstrated that in patients with lung cancer[14] imaged with PET after standard imaging, PET will detect previously unsuspected sites of metastatic disease in 5.2% of patients (15 of 287), and in patients with oesophageal cancer,[15] PET after standard imaging detects additional site of metastatic disease in

4.8–9.5% of patients. Most recently, research has demonstrated that the standardised uptake value (SUV) of the primary site of thoracic malignancy correlates with prognosis,[16] and although further research is needed, it may be the most useful prognostic parameter available prior to resection. Further, recent reports have demonstrated that the change in SUV during induction therapy also predicts prognosis after subsequent resection.[17]

It is thus likely that PET SUV prior to treatment correlates with prognosis after resection and that changes in PET SUV during induction therapy correlate with biological response to therapy. Clinical trials evaluating the use of PET-defined prognosis before and after induction therapy to guide subsequent interventions are needed.

3. Nuclear medicine techniques for early prediction of response to chemotherapy and chemo-radiation in GI cancer (Lecture: Bernd Joachim Krause, Munich, Germany)

Therapy response assessment – especially in the neoadjuvant setting – is a major goal in oncology with an emphasis on assessments taking place early in the course of disease that carry potentially important implications for the therapeutic management of patients.

Amongst surrogate markers allowing therapeutic response assessment 18F-fluordeoxyglucose (FDG) uptake has been identified as a promising marker of response to treatment. The decrease of glucose utilisation during therapy correlates with the reduction of viable tumour cells as evident from comparison with pathological evaluation in the operative specimen [ref]. In responding tumours, a reduction of glucose utilisation occurs early after the initiation of therapy.

Tumour glucose utilisation – mostly represented by the standard uptake value (SUV) – can be assessed with FDG-PET and PET/CT with high reproducibility.[18] No significant difference was seen with respect to the reproducibility of SUV measurement and tracer kinetic approaches. For therapeutic response assessment changes of the SUV – rather than the absolute SUV values – have shown to be the most reliable parameter [ref]. No significant influence of methodological variations (imaging time after FDG injection, acquisition protocol, reconstruction algorithm, PET vs. PET/CT, SUV normalisation) on the response assessment could be found.[19,20] However, it is recommended to use highly standardised protocols.

In conclusion, response to therapy can be monitored with PET and PET/CT with high reproducibility. Changes of the SUV in the course of therapy represent a methodologically stable and validated response parameter. Provided that very standardised protocols are used, there are no major methodological constraints for using this technique in multi centre studies.

4. Current and new technological approaches when using PET-CT (Lecture: Hartwig Newiger, Erlangen, Germany)

The combination with CT-scans and other new technological advances enhance the precision of positron emission tomography (PET) images. Multi centre trials require precise and quantitative PET data sets.

Important parameters to the standardisation of quantitative PET are, e.g. sensitivity, correction methods and reconstruction algorithms. It is assumed that the system is perfectly normalised and cross-calibrated to a dose calibrator.

Sensitivity of PET systems has recently been improved by the use of very fast detectors and of extended axial coverage. These improved the performance by more than 70%. Metal artifacts caused by CT have been reduced by special algorithms, and the resolution of the images has been increased by a factor of two. With new reconstruction techniques, PET now provides a nearly 2-mm spatial resolution.

Recent advances in PET provide a higher sensitivity, better resolution, homogeneity and contrast, less artifacts and patient dependent uncertainties which result in more precise quantifications than with previous generations of PET/CT. The comparability of standard uptake values is now improved although absolute comparison is still very much dependent on the specific acquisition, reconstruction and processing parameters.

5. What can be the impact of response-guided pre-operative treatment on upper GI surgery? (Lecture: Katja Ott, Heidelberg, Germany)

Neoadjuvant chemo- or radiochemotherapy in locally advanced gastric (GC) – or distal oesophageal adenocarcinoma (AEG-type I) is now accepted as a standard of care. It is a fact, that patients who respond to induction therapy have a significantly improved prognosis compared to patients with non-responding tumours. No pre-therapeutically available molecular markers predicting response and/or prognosis are available so far.

In AEG-type I, FDG-PET was prospectively established as surrogate predicting response and prognosis.[21] The so-called MUNICON I study prospectively confirmed the value of early metabolic response evaluation and showed the feasibility of a PET-guided treatment algorithm.[17] These studies mark important steps towards tailoring multimodal treatment according to different biological tumour backgrounds.

In squamous cell oesophageal cancer (SCC), the FGD-PET signal after neoadjuvant therapy was shown to correlate with response and long-term prognosis. However, PET cannot predict a pathological complete response. Early response evaluation in SCC remains investigational.

In GC, FDG-PET was analysed prospectively. In GC, the issue is more complicated because using FDG as PET tracer, 30–40% of GC cannot be visualised with sufficient contrast for quantification. Insufficient FGD-uptake most often occurs with diffuse-type GC containing signet cells and mucus. In FDG-avid patients, FDG-PET can be used for response evaluation.[22] The prognosis of FDG-non-avid patients was shown to be similar to that of metabolic non-responders.[23] The addition of new tracers like fluorothymidine (FLT) might increase the sensitivity of PET in GC.[24]

PET-guided tailored therapy was not investigated in SCC so far. In GC, PET-guided tailored therapy could be established – even if it is more complex than in AEGI based on the available prospective data.

In conclusion, PET-guided treatment algorithms have proven feasible for AEG-I including cardia cancer (AEG-II) and

subcardial GC (AEG-III) and should now be evaluated in randomised prospective multi centre trials.

6. How can response to neoadjuvant treatment be assessed on the histopathological level? (Lecture Daniela E. Aust, Dresden, Germany)

It is now accepted that histopathological response to neoadjuvant treatment is a surrogate marker for treatment efficacy, which may predict local recurrence, overall- and disease-free survival and thus may help identify patients at high risk of recurrence or in need for more aggressive adjuvant treatment.

The parameters that can be assessed by post-operative histopathological examination are

(1) *Downstaging*: Reduction of tumour stage by at least one UICC-stage. Example: cT3,cN1,cM0 → ypT3,ypN0,ypM0 UICC-Stage 3 → UICC-stage 2.
(2) *Downsizing*: Reduction of tumour size (infiltration depth) by at least one T-stage. Example: c/uT3 → ypT2.
(3) Histological tumour response or 'tumour regression grade'.

The histopathological characteristics of tumour regression are plentifold and include the following parameters: tumour necrosis, fibrosis, granulation tissue, histiocytic infiltrate, lymphocytic infiltrate, granulocytic infiltrate, eosinophilic infiltrate and multinucleated giant cells[25] with fibrosis being the most indicative marker of response.[26]

Table 1 shows the examples of different regression grading systems and the cancers for which these regression grading systems are used. Examples of grades of tumour regression in oesophageal carcinomas are given in Fig. 1.

In order to assess the histopathological response of any given tumour, a thorough and standardised histopathological work-up has to be performed. If the tumour is visible macroscopically, a minimum of four tissue blocks, encompassing the maximal diameter of the tumour, should be investigated microscopically. If the tumour is not visible, the complete area of ulceration or mucosal flattening has to be investigated microscopically. If no viable tumour cells are visible on the tissue sections, serial sections and immunohistochemical analyses have to be performed in order to exclude residual vital tumour.

Table 1 – Regression grading systems for oesophagus, stomach and colorectal cancer

Regression grading for squamous oesophageal carcinoma[27]		
Grade 1	No residual cancer	Major tumour response
Grade 2	Rare residual tumour cells	
Grade 3	Fibrosis outgrowing residual cancer	Intermediate tumour response
Grade 4	Residual cancer outgrowing fibrosis	Minor tumour response
Grade 5	Absence of regressive changes	
Regression grading for adenocarcinoma of the oesophagus and the stomach[28]		
Grade 1a	Complete tumour regression, no vital tumour cells	Major tumour response
Grade 1b	Almost complete tumour regression, <10% vital tumour cells	
Grade 2	Partial tumour regression, >10% and <50% vital tumour cells	Minor tumour response
Grade 3	No or minimal tumour regression, >50% vital tumour cells	
Regression grading for colorectal adenocarcinomas[29]		
Grade 0	No regressive changes	Minor tumour response
Grade 1	Dominant residual tumour, less fibrosis	
Grade 2	Dominant fibrosis, less but easily detectable residual tumour	Intermediate tumour response
Grade 3	Dominant fibrosis, very little residual tumour (only detectable using high power)	Major tumour response
Grade 4	No residual tumour	

7. The emerging consensus on adjuvant therapy for oesophageal and gastric cancer. US perspective (Lecture: David Ilson, New York, USA)

There are sufficient data now from phase III trials to indicate that surgery alone is inadequate therapy for either oesophageal or gastric cancer.

Pre-operative treatment with cisplatin/5-FU-based chemotherapy improves survival in adenocarcinoma of the oesophagus and stomach, based on data from the recent MAGIC and FFCD trials, although the most convincing data support such therapy in gastric cancer.[2,30]

Adding radiotherapy to pre-operative chemotherapy in oesophageal adenocarcinoma achieves measurable rates of pathologic complete response, reduces local recurrence and improves survival, based on recent meta-analyses and the recent POET trial.[31]

The MUNICON trial indicates that assessment of response to induction chemotherapy with early PET scan may identify non-responders, who would benefit from earlier referral to surgery, or to treatment with alternative or investigational therapy.[17]

Given the more uncertain benefit for pre-operative chemotherapy without radiation in squamous cancer of the oesophagus, combined chemoradiotherapy as primary treatment without surgery, or chemoradiotherapy followed by surgery, is a therapy standard. With currently available systemic therapy, for squamous cancers of the oesophagus who respond to combined chemoradiotherapy, there is no clear survival benefit for the addition of surgery after chemoradiotherapy despite improvements in local tumour control with the addition of surgery.[32,33]

For gastric cancer, the role of radiation therapy has been questioned by the data from the MAGIC trial: pre- and post-operative therapy with ECF achieved an equivalent survival benefit without radiation therapy in gastric cancer, compared to the more complex and toxic use of post operative radiation and 5-FU.[2]

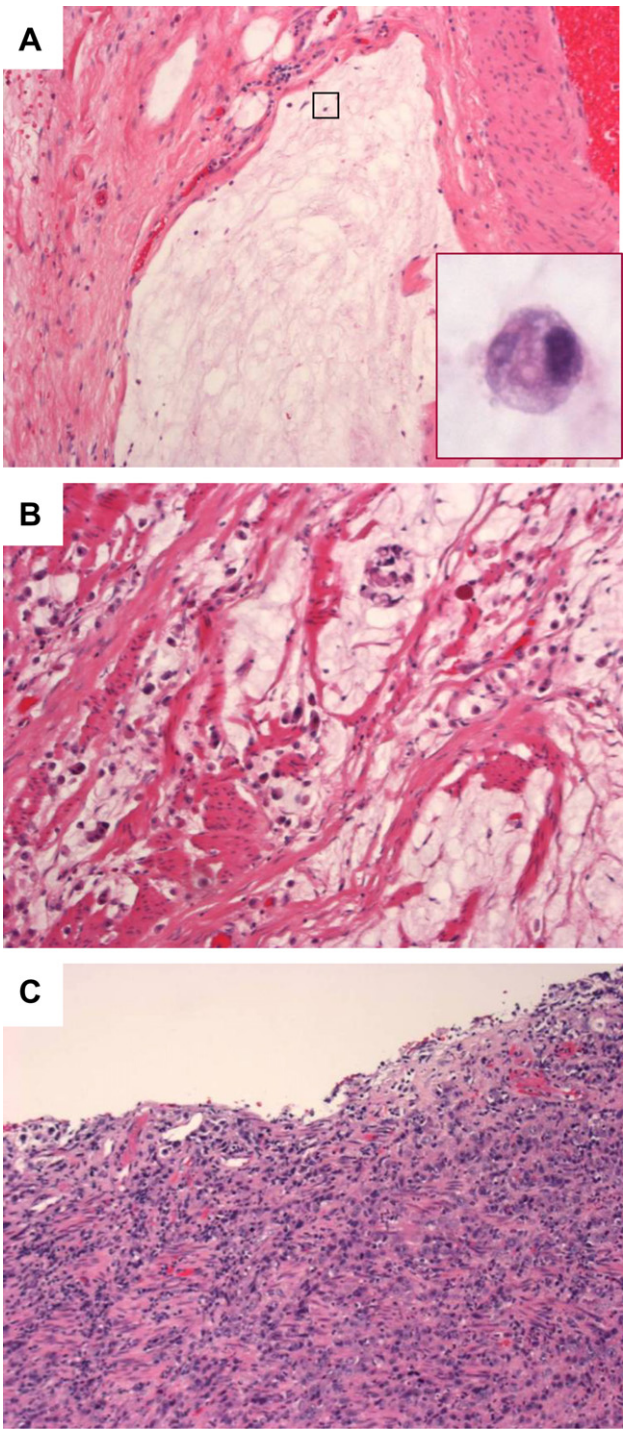


Fig. 1 – (A) Adenocarcinoma of the distal oesophagus with subtotal regression, grade 1b[28] < 10% vital tumour cells and large pools of extracellular mucin (10×, insert 40×), (B) Signet ring cell carcinoma of the distal oesophagus with partial regression, >10% and <50% vital tumour cells (20×), grade 2[26] (C) Adenocarcinoma of the distal oesophagus with minimal or no regression, grade 3[28] > 50% vital tumour cells (20×).

The CRITICS trial is now evaluating the role of post operative radiotherapy: patients with gastric cancer receive pre-operative chemotherapy with ECX (epirubicin, cisplatin, capecitabine) followed by surgery, and then patients are randomised to post-operative ECX, or to radiotherapy combined with CX.

The argument that a more aggressive D2 resection for gastric cancer will obviate a role for post-operative adjuvant therapy was recently ended, with publication of the JCOG S-1 trial, which treated 1000 patients with gastric cancer after D2 resection. A survival benefit was noted for treatment with adjuvant S-1, a well-tolerated oral 5-FU pro-drug administered without other chemotherapy agents and without radiotherapy.[34]

Targeted agents in phases II and III development in the adjuvant setting include agents targeting the VEGF pathway (bevacizumab) and the EGFR pathway (cetuximab, matuzumab, panitumumab, erlotinib). Studies tailoring therapy more precisely to individual patients, including PET scan response assessment, DNA array analysis and pharmacogenomic profiling for chemotherapy response and resistance, are ongoing.

In conclusion, pre-operative chemotherapy improves survival in oesophageal and gastric adenocarcinoma. In oesophageal adenocarcinoma, combined pre-operative chemoradiotherapy increases the rates of complete response, reduces local recurrence, and may further improve survival. Primary chemoradiotherapy, with or without surgery, is an appropriate therapy for squamous cell oesophageal cancer. Pre-operative chemotherapy, post-operative chemoradiotherapy and post-operative S-1 improve survival in gastric cancer. The contribution of radiotherapy, and the value of the addition of other chemotherapy agents to 5-FU, need to be validated in phase III trials.

8. What can be the next steps in the pre-operative treatment of oesophageal and gastric cancer? European perspective (Lecture: Eric Van Cutsem, Leuven, Belgium)

Despite progress in refining the indications for surgery and the improved outcome after primary surgery, a majority of patients with oesophageal and gastric cancer still die from metastases or from locoregional relapse. This has resulted in the exploration of combined therapeutic modalities. Over the last decade, the use of neoadjuvant (induction) protocols aiming at downsizing or downstaging oesophageal cancer and trying to improve the survival has been widely tested. Different trials unfortunately yielded conflicting results.

Surgery remains the mainstay of therapy, but the evidence is growing that a pre-operative chemotherapy or chemoradiotherapy improves the outcome of a subgroup of patients with oesophageal cancer. In gastric cancer, it is demonstrated that the outcome can be improved by strategy of either peri-operative chemotherapy or post-operative chemoradiotherapy.

8.1. *Oesophageal cancer*

Pre-operative radiotherapy alone has failed to improve the outcome of patients with oesophageal cancer compared with surgery alone. At least 5 randomised trials compared pre-operative radiotherapy followed by surgery with surgery and have shown no improvement in resectability nor in survival.

Several phase II and a few small phase III studies have shown interesting results with pre-operative chemotherapy (most often 5-FU/cisplatin based) in oesophageal cancer: they concluded that pre-operative chemotherapy is feasible, does not increase the post-operative morbidity and mortality, leads to lower distant failure rate, but does not influence the local failure rate. The pathologic complete response (pCR) rate after neoadjuvant chemotherapy is in the range of 10%. Two large randomised phase III trials, however, reported conflicting results. The US Intergroup study 0113 evaluating pre-operative chemotherapy followed by surgery compared to surgery alone in 467 patients did not show a difference in survival.[8] A United Kingdom Medical Research Council study in 802 patients with oesophageal cancer showed a significantly improved median survival (16.8 *versus* 13.3 months) and 2-year survival (43% *versus* 34%) in favour of the combined modality treatment.[1] The Cochrane meta-analysis including 11 trials with 2019 patients concludes that pre-operative chemotherapy may offer some survival advantage, but that the data are not completely conclusive.[35]

More than 50 phase II and several phase III studies evaluating the role of neoadjuvant chemoradiotherapy have been published. The phase II studies concluded that pre-operative chemoradiotherapy is feasible, but leads to slightly higher morbidity and mortality. In many of the trials, the chemotherapy combination was 5-FU/cisplatin-based and there was a wide variety of radiotherapy does, fractionation and fields. It is often concluded that patients with a pCR at surgery live longer than those who do not reach a pCR. Recurrence in these trials was more often metastatic than loco-regional.

The individual randomised phase III trials show often conflicting results. The studied patient population were often heterogeneous (different stages; squamous cell cancer and adenocarcinoma; proximal and distal tumours), the treatment regimens had a wide variety (different chemotherapy regimens; different radiotherapy schedules; synchronous chemoradiotherapy vs sequential chemoradiotherapy). Many of the trials were underpowered.

A meta-analysis of 9 randomised trials in 1116 patients of pre-operative chemoradiotherapy plus surgery *versus* surgery showed a pathologic complete response in 21% of patients, an improved 3 year survival (OR 0.66; $p = 0.01$), an improved R0 resection rate (OR 0.53; $p = 0.07$) and a lower locoregional recurrence rate (OR 0.38; $p = 0.0002$). There was, however, a trend towards an increased operative mortality (OR 1.63; $p = 0.053$).[36] These findings were confirmed in another meta-analysis.[37] However, post-operative morbidity and mortality remain a source of concern. The general conclusion is that pre-operative neoadjuvant chemoradiotherapy may improve survival of patients with resectable oesophageal cancer. It is, however, not clear who benefits most from a neoadjuvant chemoradiotherapy.

Across the different trials, approximately 20% of patients achieve a pathological complete response at surgery following neoadjuvant chemoradiotherapy. The patients who show a complete response at pathological examination benefit clearly, patients with a partial response benefit possibly, whereas non-responding patients and patients with progressive disease do not benefit from pre-operative chemoradiotherapy. The challenge is therefore to determine which patients will benefit most from the pre-operative chemoradiotherapy. There are actually no accurate ways to predict this before the start of the neoadjuvant treatment. No molecular or other markers were able to consistently and adequately predict for response. The emerging and promising role of FDG-PET in the early response prediction during or after chemoradiotherapy needs further validation.

The future strategies should therefore aim at improving the combined modality treatments, but also at better selecting patients who need and who will benefit from a combined modality treatment via molecular marker analysis and by defining strategies that allow response to be predicted early in the treatment course. Since no validated molecular markers are currently available or on the horizon to predict response to neoadjuvant chemoradiotherapy and since FDG-PET scan appears promising for that purpose, there is a need to explore this strategy in patients with oesophageal cancer.

8.2. *Gastric cancer*

Surgery is cornerstone in the management of patients with resectable gastric cancer. The standard recommendations for resectable gastric adenocarcinoma are free-margin surgery with at least D1 resection combined with removal of a minimum of 15 lymph nodes.[38,39] It has been shown that the outcome of patients with resectable gastric cancer can be improved by perioperative (pre- and post-operative) chemotherapy[2] or by post-operative chemoradiotherapy.[40] It has been recently shown in a Japanese study that adjuvant chemotherapy with S1 also improves the outcome in patients with resectable gastric cancer.[34] Other studies in the Western world did, however, not show a benefit from adjuvant chemotherapy.

In the future, we will have to determine which strategy is optimal in gastric cancer. In operable gastric cancer, especially in cancer localised at the gastro-oesophageal junction or in the upper stomach a strategy of neoadjuvant chemoradiotherapy should be explored.

Since it is unlikely that all patients with gastric cancer benefit from neoadjuvant chemotherapy or chemoradiotherapy, optimal selection strategies for patients exposed to multimodality treatments are also needed. Here as well predictive and prognostic molecular markers and ways of predicting response to treatment early *via* FDG-PET scan may be important tools for optimising the treatment strategy and need to be investigated further.

9. Reliability of imaging in the assessment of response to pre-operative chemotherapy in colorectal liver metastases (Lecture: Mostafa El Hajjam, Boulogne – Billancourt, France)

This update aims to determine the accuracy of imaging in the assessment of response to pre-operative chemotherapy.

Multi-detector CT is routinely used to monitor response to chemotherapy according to RECIST criteria. Volumetry of the metastasis may provide a more reliable assessment. Complete radiological response, considered as a good indicator

of treatment efficacy, is not correlated to complete pathological response and does not represent cure. Persistent macroscopic or microscopic residual disease or early recurrence *in situ* was observed in 83% of liver metastases having completely responded on CT.[12]

Liver steatosis induced by chemotherapy is a significant factor that decreases CT sensitivity.[41]

Magnetic resonance imaging (MRI) is probably the modality of choice in liver imaging. It enables liver study in a single breath-hold with high spatial resolution. Newly developing gadolinium-chelates or iron oxide contrast agents provide critical tumour characterisation. Reduction in tumour size is inappropriate for monitoring the effects of novel therapeutic agents that have a cytostatic mechanism of action. Measurement of metabolic response on PET/CT has been found more sensitive for early response. Similarly, contrast-enhanced ultrasound and diffusion-weighted MRI (DWI) are sensitive to changes in tumour environment occurring after treatment before reduction in size. DWI is evaluated quantitatively by the apparent diffusion coefficient (ADC). Pretreatment ADC can be used to predict response to chemotherapy and could be compared before and after treatment.[42]

In conclusion, morphologic and functional imaging is needed for an accurate assessment of response to novel therapeutic agents in colorectal liver metastasis.

10. Is there a way to assess complete response? The pathologist's perspective (Lecture Catherine Julié, Boulogne, France)

The pathological examination is supposed to be the gold standard for assessing tumour response. But even if the pathological features of response are now well described, this examination has also some limitations.

The pathological features of tumour response consist in the numeric decrease or disappearance of the tumour cells and an increase in fibrosis. The grading systems for tumour regression are based on the amount of tumour cells relative to the amount of fibrosis. Amongst them, the tumour regression grade (TRG), firstly described for oesophageal carcinoma Mandard[27], then applied to rectal carcinoma, was recently adapted to colorectal cancer liver metastases.[26] In this later study, pathological tumour regression of liver metastases corresponded to fibrosis and not to necrosis, and no correlation between the diameter of the metastasis and the TRG was observed: independent of the size, a metastasis can exhibit either good or poor response, showing the limits of imaging assessment mostly aimed at tumour shrinkage. In rectal carcinoma, colloid response was recently described in 20% of the cases, as predominant colloid changes with >80% of mucin pools (with or without tumour cells).[43]

Pathological examination is never complete: for each 3-mm thickness block one 4-μ slide is assessed. Thus, when the whole suspect area is embedded, in fact only a very small part is examined. Even if we increase the number of sections, small or few groups of residual tumour may be missed.

The pathological features of response are well described: these are predominantly fibrosis and colloid changes. Necrosis is not a feature of response. But our examination is just an approximation and the complete response as determined by pathology may sometimes not be really complete.

11. How to integrate PET-guided treatment algorithms into future studies in GI cancer (Chairs: Florian Lordick, Heidelberg, Germany and Theo Ruers, Amsterdam, Netherlands)

Several potentially interesting study scenarios were designed and discussed in two separate working groups, the other group focussing on oesophageal cancer and the other group focussing on colorectal cancer (Figs. 2–4).

Fig. 2 delineates a study design that randomises patients into one group that receives standard therapy without response monitoring by PET/CT and into one group that receives therapy with response monitoring by PET/CT. In the group with PET/CT-based response monitoring non-responders to standard therapy would switch to an alternative therapy, while PET-responders would continue with standard therapy. This study design would allow for an accurate validation of PET/CT-based response monitoring in a multi-centre setting. In addition this design would allow to study the influence of the PET/CT response on relevant outcome parameters (e.g. survival and morbidity) in an entire patient cohort. Furthermore, this design would allow for calculating treatment- and PET/CT-related costs in relation to the treatment outcome. These data are lacking thus far. Therefore, in most countries health systems PET/CT-based response monitoring is not yet routinely paid by the benefactors.

Fig. 3 outlines another phase III study design integrating PET-based response monitoring. Both PET-responders and

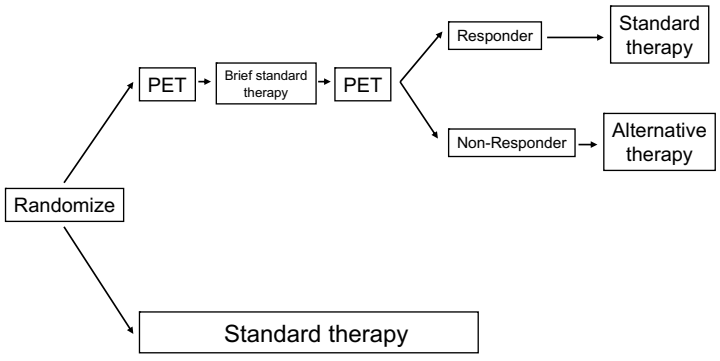


Fig. 2 – Design of a phase III trial integrating PET/CT into treatment of solid tumours as proposed by Weber and Figlin.[44]

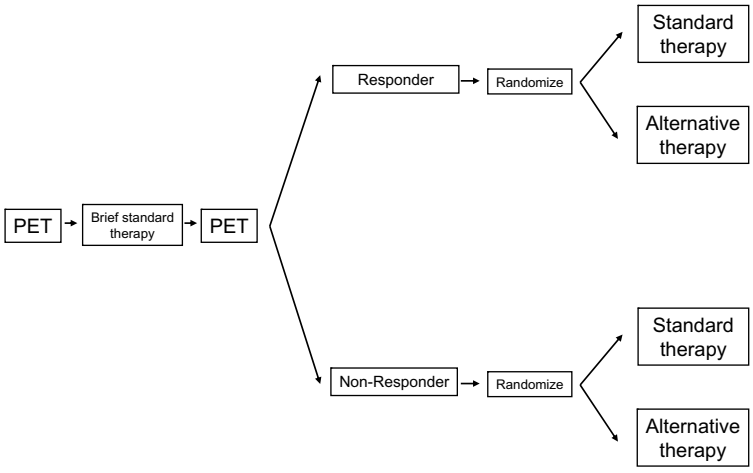


Fig. 3 – Design of a phase III trial integrating PET/CT into treatment of solid tumours.

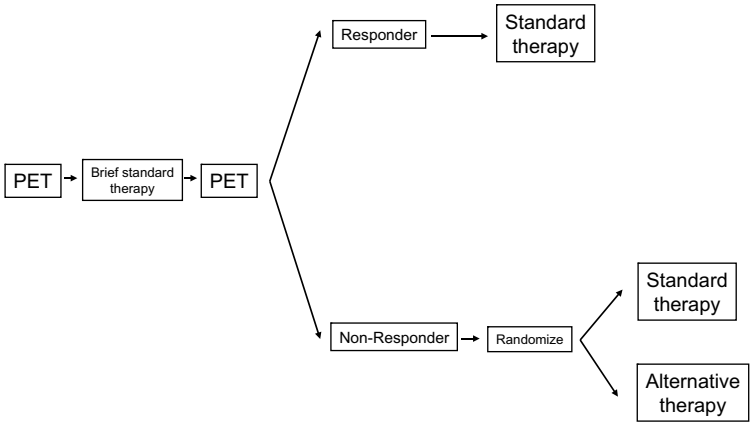


Fig. 4 – Design of a phase III trial integrating PET/CT into treatment of solid tumours.

PET non-responders are randomised to receive either a standard treatment or an alternative treatment. This design allows for assessing if either metabolic responders or non-responders take a greater advantage from an alternative treatment approach. Metabolic response can serve as a stratification criterion for a pre-planned subgroup analysis in such a design but both responders and non-responders undergo the same randomisation process.

Fig. 4 shows a study design that randomises only those patients who do not respond metabolically to the standard treatment between a standard treatment *versus* and alternative treatment. This approach allows for investigating potential improvements of specific outcome parameters in the subgroup with a poorer outcome, i.e. metabolic non-responders. At the same time, this approach allows for the validation of the accuracy of PET in predicting response to treatment. Depending on the chosen end-points (e.g. response or progression-free survival or overall survival), such a study can be designed as a phase II or phase III trial.

Fig. 5 illustrates a variant of the design shown in Fig. 4. In this study, two alternative treatments are randomised in those patients who do not respond metabolically to the standard treatment. This randomised phase II design is adequate when the negative predictive value of the PET test is believed to be sufficiently validated in a particular setting and when there is a clear need to find new treatment strategies in those patients who cannot benefit from standard treatment.

12. Working group A: Oesophageal cancer (Chairs: Florian Lordick, Heidelberg, Germany; Wolfgang A. Weber, Freiburg, Germany; Arnaud Roth, Geneva, Switzerland)

Ninety percent of oesophageal cancers are characterised by a high tumoural 18F-FDG uptake. They are therefore good target tumours for PET/CT studies. Extensive work has been done in the past to study the value of PET in monitoring early metabolic response to pre-operative chemotherapy in adenocarcinoma of the oesophagus (see lectures of Robert Downey and Katja Ott). The most convincing results of these trials were

(1) The lack of early metabolic changes measured by PET does negatively impact on later clinical and/or pathological response.[23,45,46]
(2) Early metabolic response clearly separates a group with a more favourable prognosis following neoadjuvant chemotherapy and resection from a group with an unfavourable prognosis.[17,23,45]

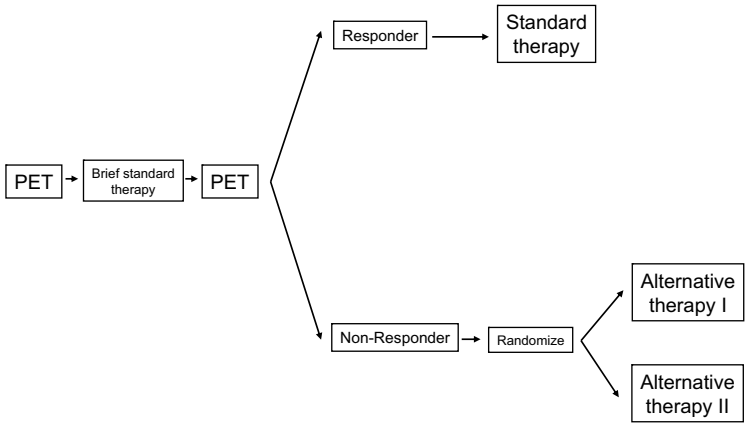


Fig. 5 – Design of a phase II trial integrating PET/CT into treatment of solid tumours.

(3) Relative changes in tumour FDG uptake are better predictors for treatment outcome than absolute SUVs. Metabolic changes within the first 2 weeks of therapy are at least as efficient for the prediction of pathologic response and patient survival as later changes.[47]
(4) Treatment algorithms based on PET-response are feasible and can be implemented into clinical practice.[17]

On the basis of these findings, the following topics were discussed:

(1) Target population for future studies:Current treatment algorithms often vary between patients with squamous cell cancer and patients with adenocarcinoma of the oesophagus (lectures David Ilson and Eric Van Cutsem). Thresholds for measuring PET response may also vary between these tumours. Therefore, separate trials for patients with adenocarcinoma and squamous cell cancer are warranted. The rate of R0 resection and the prognosis decreases with an increasing depth of tumour infiltration and with nodal involvement. Therefore, future studies should include patients with potentially resectable T3/4 tumours and/or nodal involvement (N+ status).
(2) Technique of measuring PET response:A consensus has been reached on how to measure PET response regarding the definition of SUVs, of the ROIs, of time points of measurement and of threshold decreases. (lectures of Bernd Joachim Krause and Wolfgang A. Weber). Highly standardised PET protocols should be used and all nuclear medicine physicians from participating centres should be centrally trained before a site is activated.
(3) Standard treatment of locally advanced adenocarcinoma of the oesophagus: Neoadjuvant treatment followed by transthoracic oesophagectomy is a standard of care for locally advanced adenocarcinoma of the oesophagus (lectures David Ilson and Eric Van Cutsem). Both chemotherapy alone and chemotherapy plus radiation therapy are accepted neoadjuvant treatment modalities. Preferences vary amongst centres. There was a consensus that based on currently available data neoadjuvant chemotherapy without radiation therapy can be accepted as treatment of choice in the pre-operative setting. A combination of a platinum salt and a fluoropyrimidine with or without anthracycline should be regarded as standard in this particular situation. The role of paclitaxel or docetaxel is less clear in the neoadjuvant setting and should be regarded as investigational.
(4) Selection of the primary end-point: Overall survival is the preferred end-point of trials in the curative setting. Trial designs as shown in Figs. 2–4 should preferentially be designed with either overall survival or relapse-free survival as primary end-points. However, calculation examples make clear that adequately powered randomised phase III trials with overall survival or relapse-free survival as clinical end-points would require approximately 400 to 800 randomised patients. As this goal is very difficult to achieve in oesophageal cancer, clinically relevant surrogate end-points were considered. Defining relevant surrogate parameters as study end-points would allow for a faster investigation of the value of PET-response-guided treatment algorithms in locally advanced adenocarcinoma of the oesophagus, although the results would be less convincing. Such surrogate end-points could be the pathological response rate, the local failure rate or the R0 resection rate.

13. Conclusions

Based on the discussion outlined above, several study designs were drafted and biometrically calculated. These designs were presented to the EORTC GI group at the autumn meeting in Mainz (9–11 November 2008). First, there was a consensus that the feasibility of the study in terms of patient numbers needed to randomise should be given high priority. Second, the majority of group members favoured designs with a greater emphasis on potential improvements of the treatment outcomes over those focusing on the validation of the PET methodology in the clinical setting. Discussants emphasised that they deemed the negative predictive value of the PET test sufficiently validated by the previous studies. They also

expressed concerns that a study focusing too much on validation aspects of the PET methodology would not be attractive enough for patients and investigators and would be at high risk of recruiting poorly. Of the four study designs outlined above, the phase II design shown in Fig. 5 was deemed to be most attractive and clinically relevant. Applied to oesophageal adenocarcinoma, the study is expected to be designed like that shown in Fig. 6.

14. Working group B: colorectal cancer (Chairs: Theo Ruers, Amsterdam, Netherlands; Manfred P. Lutz, Saarbrücken, Germany; Patrick Flamen, Brussels, Belgium)

The most interesting situations for PET-based response evaluation are those of potentially resectable liver metastases and of locally advanced rectal cancer. In both situations informations from PET may alter the treatment strategy in terms of the duration of neoadjuvant treatment, the selection of drugs, the dose of radiotherapy (rectal cancer), the choice of the surgical procedure and the indication for adjuvant treatment.

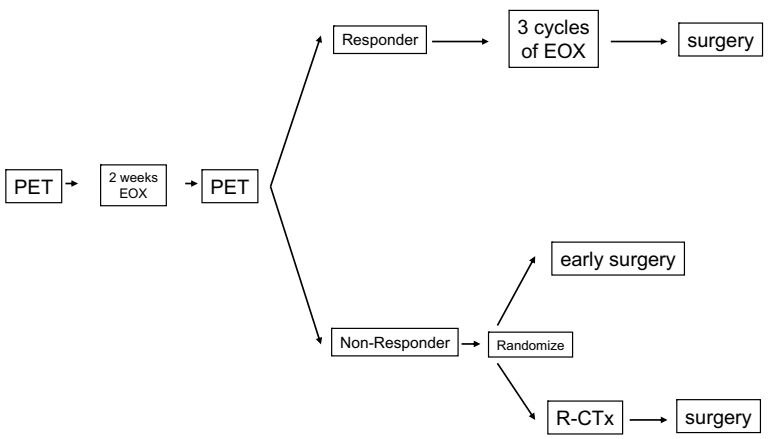
Of note, the optimal PET protocol still needs to be defined, including the definition of the appropriate regions of interest (ROIs)/volumes of interest (VOIs) for defining the SUV, and thresholds for significant decreases of the SUV during and after neoadjuvant treatment. It is very likely that these thresholds are drug-specific and may therefore vary between different treatment regimens. The major problem is that quantitative PET-CT response evaluation yields a continuous variable (ranging from 0% to 100% reduction of the FDG uptake), which reflects a continuous metabolic response process. The challenge is to transform this information to a categorical yes-no response variable without loosing the relation to treatment outcome and prognosis, which are also continuous end points. The most straightforward and reproducible way of answering the clinical need for dichotomous classification would be the use of PET-CT exclusively for (early) identification of non-responders, thus identifying the patients in whom PET-CT during treatment shows a change of the tumour FDG activity within the normal physiological and technical variability (about 25%). All other patients could be classified as partial or complete metabolic responders in whom the prognostic benefit of the treatment would probably be related to the PET response amplitude (in analogy to what has been documented in lymphoma).

14.1. *Colorectal liver metastases*

Building on the results of the recently published EORTC Intergroup study 40983, the EORTC 40051 trial (the Biologics-Oxaliplatin-Surgery (BOS) study) (Fig. 7) investigates the role of biologically targeted drugs in the pre-operative treatment of liver metastases from colorectal cancer.[5] This study is an ideal platform for integrating sequential 18F-FDG-PET investigations. Appropriate time points of PET assessments could be:

- Baseline PET with the definition of target lesions and definition of baseline SUVs.
- Early response PET soon after the start of bio-chemotherapy at a time point when all drugs have been given in full doses (e.g. 2 weeks after the first infusion). Calculation of the decreases of the SUVs and correlation with later clinical response (RECIST) and pathological response parameters. The object at this early time point would be to identify patients who do not benefit from neoadjuvant treatment and who should switch to early surgery or to alternative bio-chemotherapy (see Fig. 7).
- Late response PET before surgery. Measurement of the residual FDG uptake to further explore a correlation between residual FDG uptake and pathological response.

Of note, the best PET protocol including the definition of the appropriate regions of interest (ROIs)/volumes of interest (VOIs) for defining the SUV, and thresholds for significant decreases of the SUV during and after neoadjuvant treatment still needs to be defined. It may also be that thresholds are drug-specific and would thus vary between different treatment regimens.



EOX: epirubicin, oxaliplatin, capcitabine; **R-CTx:** radiochemotherapy consisting of radiation therapy 45 Gray(Gy, 1.8 Gy/day plus a platinum-taxane combination and possibly a biologic response modifier

Fig. 6 – Study design of the European oesophageal carcinoma neoadjuvant trial (IMAGE).

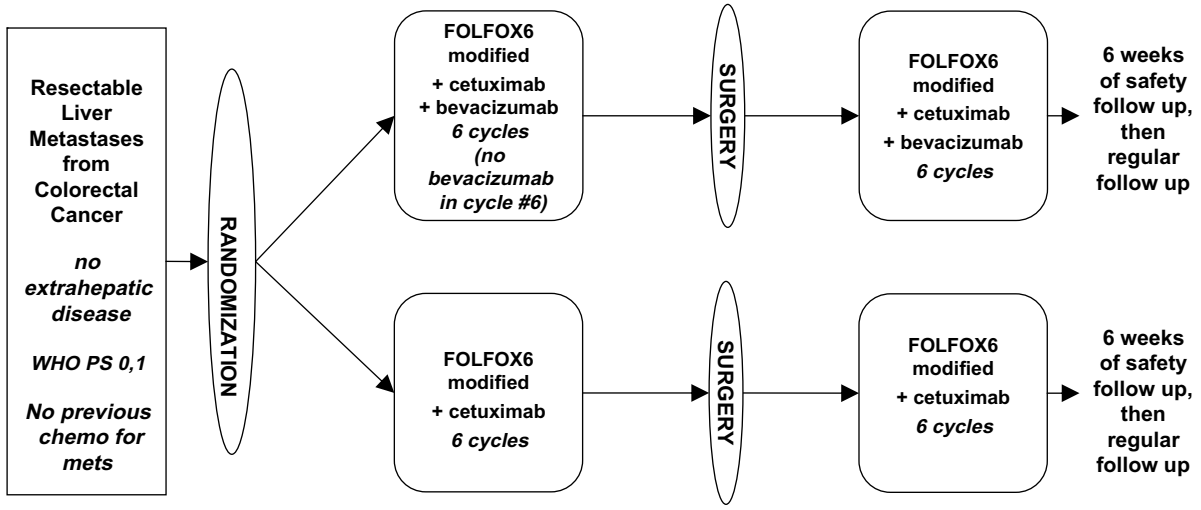


Fig. 7 – Design of the EORTC study 40051 (Biologics-Oxaliplatin-Surgery = BOS study). This study may serve as a platform for sequential PET investigations.

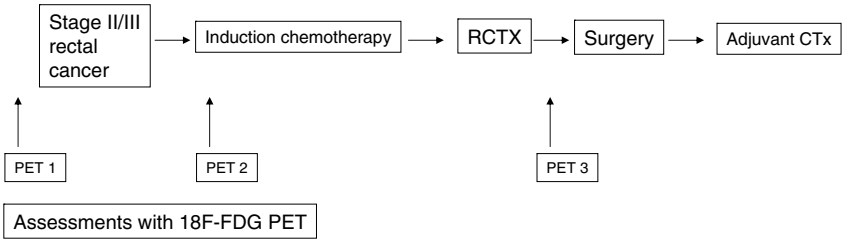


Fig. 8 – Potential design of a phase II study investigating PET-response to neoadjuvant treatment of rectal cancer.

14.2. *Rectal cancer*

Similar to the treatment of liver metastases, also in rectal cancer several methodological aspects of PET-based response assessment are worth exploring. Metabolic response to neoadjuvant radiation, which has now been accepted as a standard of care in locally advanced tumours has been poorly investigated thus far. Radiation-induced inflammation processes may blur the answer we get from sequential FDG-PET, and sequential investigations with 18F-fluorthymidine (FLT) have yielded poor correlations with pathological response.[48]

However, PET may be an intriguing tool in studying neoadjuvant treatment of rectal cancer. The following time points for an assessment of response may be particularly interesting:

- The early phase of induction chemotherapy: This approach may define patient with chemo-resistant tumours that do not benefit from neoadjuvant chemo-radiation and/or from adjuvant chemotherapy. The later question is of utmost interest: A recently published subgroup analysis of the EORTC 22921 study showed that the benefit of adjuvant chemotherapy may be limited to specific subgroups of patients.[49]
- The post-radiation/pre-operative time point: to further explore whether residual FDG uptake correlates with the extent of pathologic response. Whether such approach will be accurate enough to ultimately lead to alterations of the surgical approach remains questionable, e.g. to perform a sphincter saving operation instead of an abdominal perineal resection for low rectal tumours according to the FDG-PET result.

A potential study design for better defining the role of PET in locally advanced rectal cancer is depicted in Fig. 8.

15. Further steps

Based on these discussions trials including metabolic imaging with PET/CT will be proposed for locally advanced oesophageal cancer, for locally advanced rectal cancer and for potentially respectable liver metastases from colorectal cancer. These will be discussed during the further meetings of the EORTC GI group later this year.

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