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FDG-PET/CT based response-adapted treatment

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Abstract

It has been shown that [¹⁸F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) provides robust and reproducible data for early metabolic response assessment in various malignancies. This led to the initiation of several prospective multicenter trials in malignant lymphoma and adenocarcinoma of the esophagogastric junction, in order to investigate whether the use of PET-guided treatment individualization results in a survival benefit. In Hodgkin lymphoma and aggressive non-Hodgkin lymphoma, several trials are ongoing. Some studies aim to investigate the use of PET in early identification of metabolic non-responders in order to intensify treatment to improve survival. Other studies aim at reducing toxicity without adversely affecting cure rates by safely de-escalating therapy in metabolic responders. In solid tumors the first PET response-adjusted treatment trials have been realized in adenocarcinoma of the esophagogastric junction. These trials showed that patients with an early metabolic response to neoadjuvant chemotherapy benefit from this treatment, whereas metabolic non-responders should switch early to surgery, thus reducing the risk of tumor progression during chemotherapy and the risk of toxic death. The trials provide a model for designing response-guided treatment algorithms in other malignancies. PET-guided treatment algorithms are the promise of the near future; the choice of therapy, its intensity, and its duration will become better adjusted to the biology of the individual patient. Today's major challenge is to investigate the impact on patient outcome of personalized response-adapted treatment concepts.

Keywords: [¹⁸F]Fluorodeoxyglucose; positron emission tomography; metabolic response-adjusted therapy; risk-adapted treatment; PET-guided treatment; randomized controlled trials; malignant lymphoma; gastroesophageal cancer; breast cancer.

Introduction

For several years, fluorodeoxyglucose (FDG)-positron emission tomography (PET) has become part of the standard of care in staging and restaging of a variety of malignant diseases, focusing on the detection of malignant lesions at early stages and early detection of recurrence and metastatic spread. FDG-PET has been shown to be successful in distinguishing fibrosis and scar tissue from viable tumor in residual masses after therapy, in localization of recurrence in patients with an unexplained increase in serum tumor markers and as a tool for selecting patients eligible for surgical treatment of metastatic disease. FDG-PET has had a positive impact on overall staging and patient management in various malignancies. Furthermore, in the past

decade a large number of studies have provided considerable evidence that assessment of tumor glucose utilization by FDG-PET provides an early readout for the effectiveness of therapy, that it correlates with the degree of histologic tumor regression and allows prediction of patient survival. These studies have been performed with several tumor types and during different treatment modalities, such as chemotherapy, chemoradiation, hormone and targeted therapy. This success qualifies FDG-PET for its most exciting application in randomized trials; comparing PET-controlled strategies with standard patient management^[1]. This review discusses clinical trials and the work that has been performed in early metabolic response-adapted treatment of malignant lymphoma, gastroesophageal cancer and breast cancer.

Table 1 Main risk-adapted trials using interim FDG-PET in limited disease Hodgkin lymphoma

Reference	Study	Group	PET timing	Treatment
[35]	RAPID, NCT00943423	UK NCRI	Post ABVD 3×	PET(−)→randomize between RT or no further therapy; PET(+) →complete ABVD 1× + RT
[36]	HD16, NCT00736320	GHSG	Post ABVD 2×	Standard arm, RT regardless of PET Experimental arm, PET(−)→no further therapy; PET(+) →RT
[37]	H10, NCT00433433	EORTC, GELA, IIL	Post ABVD 2×	Standard arm, complete ABVD + RT regardless of PET Experimental arm, PET(−)→complete ABVD; PET(+) →BEACOPPesc then RT
[39]	50604, NCT01132807	CALBG	Post ABVD 2×	PET(−)→complete ABVD 2×; PET(+) →BEACOPPesc 6×
[38]	50801, NCT01118026	CALBG	Post ABVD 2×	PET(−)→complete ABVD 4×; PET(+) →BEACOPPesc 4× + RT

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CALBG, Cancer and Leukemia Group B; EORTC, European Organisation for Research and Treatment of Cancer; esc, escalated; GELA, Groupe d'Étude des Lymphomes de l'Adulte; GHSG, German Hodgkin Study Group; IIL, Intergruppo Italiano Linfomi; RT, radiotherapy; UK NCRI, United Kingdom National Cancer Research Institute.

FDG-PET-based risk-adapted studies on malignant lymphoma

It has been recognized that interim FDG-PET provides strong prognostic information in Hodgkin lymphoma and aggressive B-cell non-Hodgkin lymphoma. The widely cited study by Gallamini et al.^[2] showed that the 2-year progression-free survival was 95% in patients with a negative PET after 2 cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), but only 13% in patients with a positive interim PET (i.e. residual lesions with FDG uptake clearly above normal mediastinal uptake). In multivariate analysis, interim PET overshadowed the prognostic value of the International Prognostic Scoring (IPS) and emerged as the single most important tool for planning of risk-adapted treatment in advanced Hodgkin lymphoma^[2]. This is not surprising, since the IPS comprises population-based, rather static, pre-treatment parameters in comparison with the dynamic metabolic information of FDG-PET, which provides individualized information about prognosis and quality of response to a certain therapy. The definition of a negative or positive interim PET was published in 2009 in a consensus report known as the Deauville criteria^[3]. These criteria are specifically designed for interim PET, in contrast to the International Harmonization Project (IHP) end-of treatment response evaluation criteria^[4]. The advantages of these former criteria include simplicity, high reproducibility and preservation of the data on the degree of response. This scoring system permits adaptation of the thresholds of the binary scale (positive or negative) according to the research question, i.e. a high positive predictive value is desired when escalation of therapy is intended, and a high negative predictive value is important in case of de-escalation of treatment^[5]. Attempts have been made to improve the results by semi-quantitative analysis of FDG uptake. However, current data suggest that this does not have additional value in Hodgkin lymphoma^[6–8], but might be beneficial in the assessment

of response of non-Hodgkin lymphoma^[9,10]. The successful application of FDG-PET for early response assessment in malignant lymphoma has opened up a unique opportunity to use interim FDG-PET for stratification of patients in risk-adapted treatment regimens. Survival outcomes did not simply depend on PET response but also on the promptness with which that occurred^[11]. The highly significant results of all these studies^[2,6–8,12–25] provided a reliable basis for several (ongoing) clinical trials in patients with Hodgkin lymphoma and aggressive non-Hodgkin lymphoma, which investigate the value of treatment adaptation based on early response monitoring using interim FDG-PET (Tables 1–3). Indolent non-Hodgkin lymphomas are less suitable for this kind of trial because, in general, they are less FDG avid at baseline. In addition, they generally show a long natural history and a high incidence of recurrence, which decreases the clinical impact of a potential risk-adapted or response-adapted approach. The following sections discuss the (ongoing) clinical trials on Hodgkin and non-Hodgkin lymphoma, investigating the performance of metabolic response-adjusted treatment.

Limited-stage Hodgkin lymphoma

Patients with limited-stage Hodgkin lymphoma are traditionally treated with combined chemo- and radiotherapy, which now results in a 10-year overall survival of 84–97%^[26,27]. In early-stage Hodgkin lymphoma, in consequence, treatment-related illnesses, such as acute leukemia, second malignancies and cardiovascular diseases, account for more deaths than Hodgkin lymphoma itself^[28]. Since Hodgkin lymphoma is typically a disease of younger individuals, late treatment toxicities are a major concern. Therefore, studies are now aiming at putting the central slogan “reduce if possible, intensify if needed” into practice^[29]. Clinical trials have focused on decreasing toxicities of overly intensive treatment

Table 2 Main risk-adapted trials using interim FDG-PET in advanced-stage Hodgkin lymphoma

Reference	Study	Group	PET timing	Treatment
[29]	NCT00305149	ISRA	Post BEACOPP(esc) 2×	$^{67}\text{Ga}/\text{PET}(-)\rightarrow\text{BEACOPP } 4\times$ $^{67}\text{Ga}/\text{PET}(+)\rightarrow\text{BEACOPPesc } 4\times$
[45]	HD15, ISRCTN32443041	GHSg	Post BEACOPPesc/14 6–8× + RD ≥ 2.5 cm	PET(-) \rightarrow follow-up, PET(+) \rightarrow RT
[50]	HD18, NCT00515554	GHSg	Post BEACOPPesc 2×	PET(-) \rightarrow randomize between 2 and 6 more cycles BEACOPPesc; PET(+) \rightarrow randomize between BEACOPPesc + or – rituximab Post-chemotherapy PET(+) RD ≥ 2.5 cm \rightarrow RT
[46]	HD0607, NCT00795613	GITIL	Post ABVD 2×	PET(-) \rightarrow complete ABVD; if still PET(-) randomize between + or – RT PET(+) \rightarrow randomize between BEACOPPesc + or – rituximab Post BEACOPPesc 4× \pm rituximab PET(-) \rightarrow BEACOPP \pm rituximab
[47]	RATHL, NCT00678327	UK NCRI	Post ABVD 2×	PET1(-) \rightarrow randomize between ABVD 4× or AVD 4× PET1(+) \rightarrow BEACOPP-14 4× or BEACOPPesc 3× \rightarrow PET2; PET2(+) \rightarrow RT or salvage PET2(-) \rightarrow PET(+) \rightarrow BEACOPP-14 2× or BEACOPPesc 1×
[51]	HD0801, NCT00784537	IIL	Post ABVD 2×	PET(-) \rightarrow complete ABVD; if still PET(-) randomize between + or – RT PET(+) \rightarrow high dose therapy with autologous BMT
[48]	S0816, NCT00822120	SWOG intergroup	Post ABVD 2×	PET(-) \rightarrow further ABVD 2× PET(+) \rightarrow BEACOPPesc; standard BEACOPP if human immunodeficiency virus positive
[77]	CIA-HL-1, NCT01304849	Cancer Institute (WIA), India	Post ABVD 2×	PET(-) \rightarrow further ABVD 2× PET(+) \rightarrow BEACOPPesc
[55]	NCT00255723	Memorial Sloan- Kettering Cancer Center, New York	Post (ICE/ICEa) 2×	PET(-) \rightarrow HDT/ASCT PET(+) \rightarrow GVD \rightarrow no PD \rightarrow HDT/ASCT

(a)ICE, (augmented) ifosfamide, carboplatin, etoposide; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; esc, escalated; BMT, blood or marrow transplantation; GHSg, German Hodgkin Study Group; GITIL, Gruppo Italiano Terapie Innovative Nei Linfomi; GVD, gemcitabine, vinorelbine, and liposomal doxorubicin; HDT/ASCT, high-dose chemoradiation followed by autologous stem cell transplantation; IIL, Intergruppo Italiano Linfomi; ISRA, Israel Rambam Health Care Campus; PD, progressive disease; RATHL, response-adapted therapy in Hodgkin lymphoma; RD, residual disease; RT, radiotherapy; SWOG, Southwest Oncology Group; UK NCRI, United Kingdom National Cancer Research Institute.

(without compromising disease control) in good-risk patients, and on identifying poor-risk patients who could benefit from treatment intensification (Table 1). These efforts include the reduction of radiotherapy dose and in the application of involved-field^[30] and involved-node^[31] instead of extended-field radiotherapy. In patients with non-bulky disease, chemotherapy alone has emerged as a viable alternative to combined modality treatment^[32,33], although the risk of relapse is probably higher compared with combined modality treatment^[32]. Therefore, it is important to identify upfront those patients who will be affected by the omission of radiotherapy. It has been shown that the subset of patients with a rapid response to chemotherapy, already after 2 cycles of ABVD, have a significantly better 5-year progression-free survival than those without an early response (95% versus 81%, $P=0.007$)^[32]. Since PET has been shown to be helpful in identifying this subset of patients^[2,6,7,20,21,23–25,34], the impact of PET-based approaches is now being evaluated. Four clinical trials are investigating the performance of an interim

FDG-PET-based approach, omitting radiotherapy in case of a negative PET after 2–3 cycles ABVD^[35–38]. If radiotherapy is omitted, however, there is a risk of undertreatment if an adequate number of chemotherapy cycles is not delivered, because a negative PET scan does not reflect the complete absence of any viable malignant cells^[11]. To pursue a favorable outcome, additional or unabbreviated chemotherapy is given to this PET-negative population in several trials in which radiotherapy is withheld^[37–39]. In the HD16 trial^[36] and the RAPID trial^[35], however, further treatment is stopped in the experimental arm after a negative interim PET, given that these trials are restricted to patients with early favorable disease. It must be emphasized that the PET-positive population often faces the problem of the coexistence of chemo- and radiotherapy resistance. It has been shown that tumors with a suboptimal response to chemotherapy, commonly show progression or relapse within the radiation field^[40]. In addition, radiotherapy should not necessarily be considered the appropriate next step in the case of a positive interim PET, because it may increase the

Table 3 Main risk-adapted trials using interim FDG-PET in non-Hodgkin lymphoma

Reference	Study	Group	PET timing	Treatment
[62]	NCT01285765	GELA	Post R-CHOP21 2× and 4×	Standard arm, R-CHOP21 6× Experimental arm, PET2×(-/+) \rightarrow R-CHOP21 4×; PET4×(+) + biopsy(+) \rightarrow intensive chemotherapy
	PET CHOP LNH2007–3B	Alberta Cancer Board GELA	Post R-CHOP 2× Post R-CHOP 2×	PET(+) \rightarrow salvage with high-dose chemotherapy + ASCT PET(+) \rightarrow salvage with high-dose chemotherapy + ASCT
[78]	NCT00324467	British Columbia Cancer Agency	Post R-CHOP 4×	PET(-) \rightarrow R-CHOP 2× PET(+) \rightarrow R-ICE 4×
[59]	-	Johns Hopkins	Post (R)-CHOP 2–3×	PET(+) \rightarrow salvage with high-dose chemotherapy + ASCT
[79]	PETAL, NCT00554164	University Hospital, Essen	Post (R)-CHOP 2×	PET(-) \rightarrow R-CHOP 4× PET(+) \rightarrow (R)-CHOP 6× or Burkitt regimen (B-ALL protocol)
[63]	NCT00712582	Memorial Sloan-Kettering Cancer Center	Post RR-CHOP-14 3×, CHOP 1×	PET(-)/PET(+)+biopsy(-)+Ki67<80% \rightarrow ICE 3× PET(-)/PET(+)+biopsy(-) + Ki67 \geq 80% \rightarrow augmented R-ICE 2× Biopsy(+) \rightarrow opt for allogenic SCT
[64]		Memorial Sloan-Kettering Cancer Center	Post R-CHOP 4×	PET(-) \rightarrow ICE 3× PET(+)/biopsy(-) \rightarrow ICE 3× PET(+)/biopsy(+) \rightarrow ICE+ASCT

ASCT, autologous stem cell transplantation; GELA, Groupe d'Étude des Lymphomes de l'Adulte; PETAL, Positron Emission Tomography guided therapy of Aggressive non-Hodgkin Lymphomas; R-CHOP, cyclophosphamide, hydroxydaunorubicin, oncovin (vincristine), prednisone + rituximab; R-CHOP21, cyclophosphamide, hydroxydaunorubicin, oncovin (vincristine), prednisone + rituximab, G-CSF; R-ICE, ifosfamide, carboplatin, etoposide + rituximab.

risk of toxicity from subsequent therapies, such as bone marrow transplantation. So, although apparent progress is being made, questions for optimal patient management still remain and should be the focus of further research.

Advanced-stage Hodgkin lymphoma

In advanced Hodgkin lymphoma, the same questions as in limited-stage Hodgkin lymphoma may arise: "Does outcome improve in interim PET-positive patients after treatment intensification, and can toxicity be minimized in PET-negative patients while retaining the high efficacy?" One standard of care, outside the setting of a clinical trial, in patients with advanced Hodgkin lymphoma is 6 cycles of ABVD. Eight cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) is superior to standard BEACOPP, COPP-ABVD (cyclophosphamide, vincristine, procarbazine, prednisone and ABVD) or ABVD in terms of disease control^[41–43], progression-free and overall survival^[42,44]. It is, however, more toxic and results in an increased risk of acute hematologic toxicity, secondary myelodysplasia, acute leukemia and infertility. This hindered its widespread acceptance as standard therapy. Recent results from the HD15 trial show superiority of both safety and efficacy of 6 cycles of BEACOPPesc over 8 cycles of BEACOPPesc. In this trial, 2182 patients were randomly assigned to receive either 8 × BEACOPPesc, 6 × BEACOPPesc, or 8 × BEACOPP14 (BEACOPP in baseline doses at 14-day intervals). After a median follow-up of 48 months, there were 53 deaths (7.5%) in the 8 BEACOPPesc group, 33 (4.6%) in the 6 BEACOPPesc group and 37 (5.2%) in the 8 BEACOPP14 group. The higher number

of deaths in the 8 BEACOPPesc group mainly resulted from acute toxicity of chemotherapy (15 vs 6 vs 6) and second neoplasms (13 vs 5 vs 8). There were 72 second cancers including 29 secondary acute myeloid leukemias and myelodysplastic syndromes, 19 (2.7%) after 8 BEACOPPesc, 2 (0.3%) after 6 BEACOPPesc and 8 (1.1%) after 8 BEACOPPesc14. Freedom from treatment failure at 5 years was 84.4% in the 8 BEACOPPesc group, 89.3% in the 6 BEACOPPesc group, and 85.4% in the 8 BEACOPPesc14 group, respectively. Overall survival at 5 years was 91.9%, 95.3%, and 94.5%, and was also significantly better with 6 BEACOPPesc compared with 8 BEACOPPesc^[45]. However, this more effective but more toxic treatment should be reserved for the high-risk patient category. In several trials^[46–49], it is being investigated whether patients with a positive interim PET benefit from an approach including escalated BEACOPP (Table 2). The first PET-driven clinical trial in malignant lymphoma, published by Dann et al.^[29], showed that FDG-PET is a useful tool for adjustment of chemotherapy on an individual basis (Fig. 1). By using an FDG-PET-based risk-adapted BEACOPP regimen they showed that the cumulative dose of chemotherapy can be reduced for standard and high-risk Hodgkin lymphoma with no detrimental effects on outcome. One hundred and eight patients with newly diagnosed Hodgkin lymphoma and adverse prognostic factors were assigned to therapy according to defined risk stratification based on the IPS. Patients with IPS \geq 3 received 2 cycles of escalated BEACOPP. All others received 2 cycles of standard BEACOPP. Subsequent therapy was based on the results of early interim ⁶⁷Ga-scintigraphy or FDG-PET/computed tomography (CT). In the case of a positive interim scan, 4

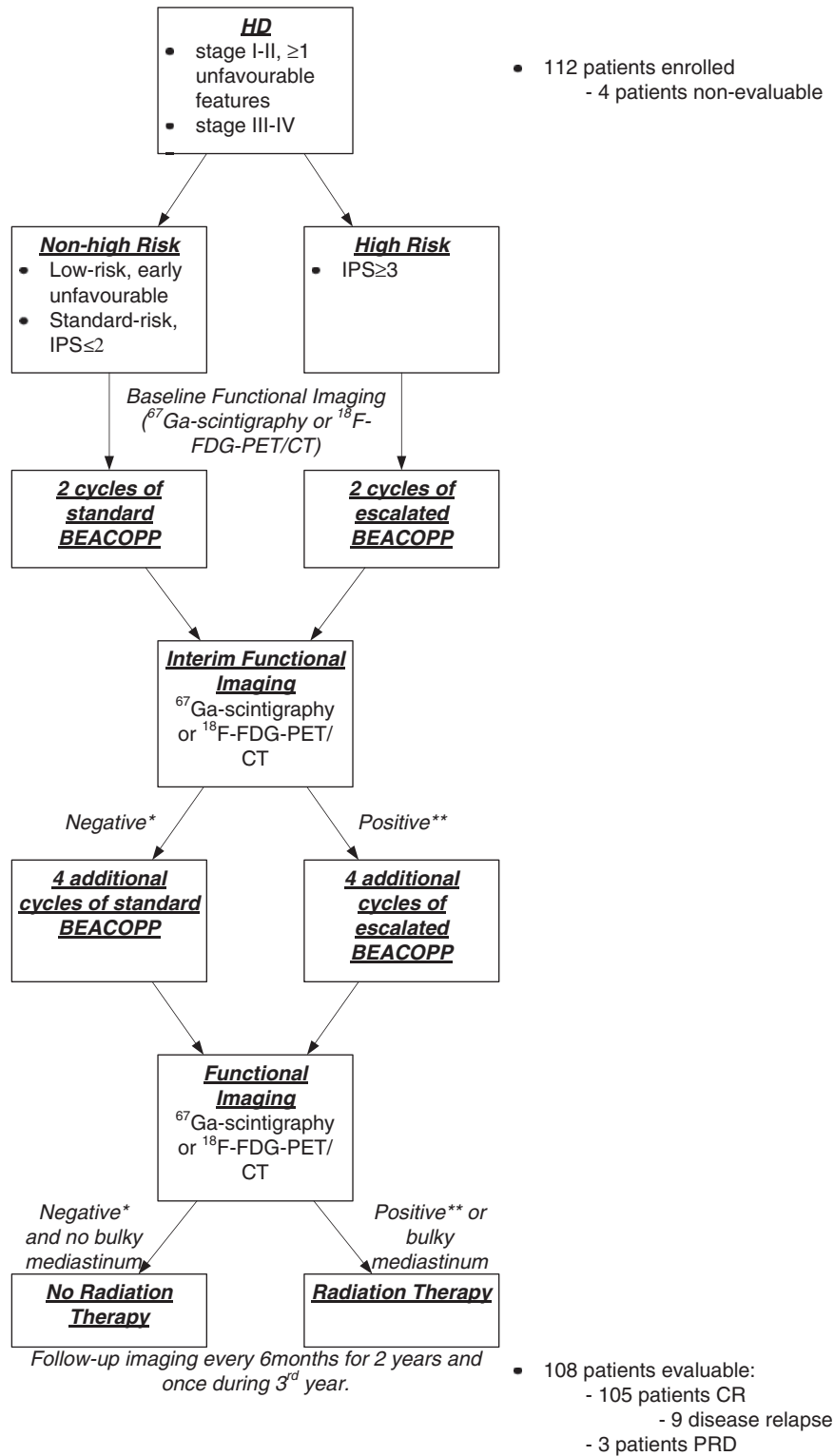


Figure 1 Study scheme as used by Dann et al.^[29]. BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CR, complete remission; HD, Hodgkin disease; IPS, Hasenclever international prognostic score; PRD, primary resistant disease (persistence of disease or occurrence of new lesions); unfavorable features, B symptoms, bulky disease, 4 or more sites of disease, age ≥ 50 years, erythrocyte sedimentation rate ≥ 50 mm in first hour, lymphocyte-depleted histology or E site. *Negative, no foci of increased uptake unrelated to physiologic or benign tracer uptake; **positive, any focus of increased uptake unrelated to physiologic or benign tracer uptake.

cycles of escalated BEACOPP were administered, whereas 4 cycles of standard BEACOPP were given to patients with a negative scan. The complete remission rate, the 5-year event-free survival and 5-year overall survival rates were 97%, 85% and 90%, respectively. Relapse or progression occurred in 27% of patients with interim positive PET/CT versus 2.3% of negative scans ($P < 0.02$). Although this approach has not been studied in a randomized fashion, the results demonstrate that only a minority of patients require upfront intensified therapy. The HD18 trial^[50] and the HD0607 trial^[46] also investigate the effectiveness of the addition of rituximab, a drug that is effective on Reed Sternberg cells despite the absence of CD20, to escalated BEACOPP. In the interim PET-negative populations (Table 2) the main questions are whether the number of chemotherapy cycles can be reduced^[50] and the pulmonary toxic agent bleomycin^[47] or consolidative radiotherapy^[46,51] can be omitted. Because of its cumulative late toxicities and questionable impact on overall survival, up to now the role of radiotherapy remains undefined in advanced-stage Hodgkin lymphoma as well as in non-Hodgkin lymphoma^[52]. Therefore, the HD15 trial^[45] and the HD18 trial^[50] omit radiotherapy in all patients with a negative PET scan after BEACOPP. The HD15 trial^[45] showed a negative PET in 74% and a positive PET in 25% of patients after 6–8 cycles of BEACOPP chemotherapy. PET was performed in 728 patients with residual disease > 2.5 cm, of whom 701 had at least 12 months of follow-up. In the PET-negative group, 22 patients relapsed and 8 patients had radiotherapy, resulting in a negative prognostic value of 94% (95% confidence interval (CI) 92–96). Overall, only 12% of patients had additional radiotherapy compared with 70% after escalated BEACOPP in the previous HD9 trial^[42]. Furthermore, there was no difference in progression-free or overall survival compared with earlier trials in advanced Hodgkin lymphoma. The high negative predictive value of PET suggests that additional radiotherapy can be omitted in 74% of patients.

Despite the high cure rate, approximately 25% of patients with Hodgkin lymphoma have relapsed or developed refractory disease^[53]. For relapsed or refractory Hodgkin lymphoma, the standard treatment is high-dose chemoradiation followed by autologous stem cell transplantation. It is common, however, for chemoresistance and radioresistance to coexist in these patients. For patients with persistent FDG-avid disease after a full course of chemotherapy, radiotherapy is less beneficial. These patients are at high risk for relapse and poor prognosis and should be considered for alternative treatments. Therefore, efforts have been made to better guide patient selection in this regard. Moskowitz et al.^[54] showed by multivariate Cox proportional regression analysis that treatment response determined by functional imaging is the only independent prognostic factor for treatment outcome when performed before high-dose

chemoradiation followed by autologous stem cell transplantation. Subsequently, the same group^[55] designed a phase II study, using both pre-salvage chemotherapy prognostic factors (remission duration < 1 year, extranodal disease, and B symptoms) and post-salvage chemotherapy FDG-PET response in a risk-adapted approach. This was performed to improve progression-free survival after high-dose chemoradiation and autologous stem cell transplantation, as well as to show that a preceding salvage chemotherapy program, documenting that the disease is still chemosensitive, is mandatory. They started with 2 cycles of ifosfamide, carboplatin, etoposide (ICE) in a standard or augmented dose (aICE), followed by FDG-PET. Patients with a negative PET immediately proceeded to high-dose chemoradiation followed by autologous stem cell transplantation. In the case of a positive scan, patients continued with gemcitabine, vinorelbine, and liposomal doxorubicin. Patients without progressive disease proceeded to high-dose chemoradiation followed by autologous stem cell transplantation. One might criticize that it could have been possible that the 2 months needed for patients to receive this non-cross-resistant chemotherapy resulted in transplant-ineligibility secondary to progression of disease or chemotherapy-induced side effects. The results, however, show that the outcome for patients with a negative PET after gemcitabine, vinorelbine, and liposomal doxorubicin was comparable with the outcome for patients with a negative PET after ICE-based therapy. This prospective study provides evidence that the goal of salvage chemotherapy in patients with Hodgkin lymphoma should be a negative FDG-PET scan before high-dose chemoradiation followed by autologous stem cell transplant.

Non-Hodgkin lymphoma

In both early and advanced stages of aggressive non-Hodgkin lymphoma, the 1-year progression-free survival for patients with a positive interim PET ranges from 10 to 50%, compared with 79 to 100% in interim PET-negative patients^[56–58]. As summarized in Table 3, several (ongoing) trials are investigating whether patients with a positive interim PET will benefit from an early switch to a more intensified approach or even high-dose therapy with autologous stem cell transplantation. Controlled reduction of treatment, on the other hand, is only justified in the favorable young subpopulation, without bulky disease or International Prognostic Index (IPI) risk factors. Also for aggressive non-Hodgkin lymphoma, the metabolic response determined on interim PET is a stronger prognostic factor than the IPI^[15].

The results of a phase II risk-adapted trial^[59] showed that early FDG-PET was able to identify those patients who benefit most from preemptive blood or marrow transplantation. Patients with a positive PET after 2–3 cycles of first-line chemotherapy received rituximab, etoposide, methylprednisolone, cytarabine and cisplatin (R-

Table 4 Main FDG-PET early response-adjusted trials on solid tumors

Reference	Study	Group	PET timing	Treatment
[65]	Gastroesophageal cancer, MUNICON-I	Munich, Heidelberg, Germany	2 weeks into chemotherapy (platinum-FU based)	PET responder, complete chemotherapy 12 weeks + surgery PET non-responder, surgery
[72]	Gastroesophageal cancer, MUNICON-II	Munich, Heidelberg, Germany	2 weeks into chemotherapy (platinum-FU based)	PET responder, complete chemotherapy 12 weeks + surgery PET-non-responder, chemoradiation + surgery
[75]	HICON, NCT01271322	Heidelberg, Germany	2 weeks into EOX	PET-responder, complete EOX 3× + surgery PET-non-responder, DC 1× + DC/RT + surgery
[76]	Breast cancer, CCAM-11-01, NCT01330212	UK NCRI	Post TEC 4×, post TEC 4×, post TEC 1×	Her2+, CR/PR→docetaxel+trastuzumab 4× + surgery; PD/SD→NTX 4× + surgery + RT ER-, CR→TEC 4× + surgery; PR/SD→NAX 4× + surgery ER+, responders→TEC 3×; non-responders/ER+,HER2.→change treatment (depending on Oncotype)

CR, metabolic complete response; DC, docetaxel, cisplatin; EOX, epirubicin, oxaliplatin, capecitabine; ER, estrogen receptor; FU, fluorouracil; HER2, human epidermal growth factor receptor 2; HICON, Heidelberg Imaging program in Cancer of the esophago-gastric junction during Neoadjuvant treatment; MUNICON, Metabolic response evaluation for Individualisation of neoadjuvant Chemotherapy in esophageal and esophagogastric adenocarcinoma; NAX, vinorelbine, bevacizumab, capecitabine; NTX, vinorelbine, trastuzumab, capecitabine; PD, metabolic progressive disease; PR, metabolic partial response; RT, radiotherapy; SD, metabolic stable disease; TEC, docetaxel, epirubicin, cyclophosphamide; UK NCRI, United Kingdom National Cancer Research Institute.

ESHAP) or rituximab, ifosfamide, carboplatin and etoposide (R-ICE), followed by high-dose therapy and autologous stem cell transplantation; patients with a negative midtreatment PET completed full-course, standard rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). Of 59 evaluable patients (98% with large B-cell lymphoma), 33 (56%) had a positive interim PET, of whom 28 received autologous stem cell transplantation regardless of stage or IPI. The 2-year event-free survival of these 28 patients was 75% (95% CI 60–93%). On intention-to-treat analysis, the 2-year event-free survival was 67% (53–86%) in all PET-positive patients and 89% (77–100%) in PET-negative patients. No association was found between the IPI category and the interim PET results.

Thus, the predictive value of FDG-PET/CT for Hodgkin lymphoma is superior overall to the predictive value for non-Hodgkin lymphoma. The lower negative predictive value is probably caused by the intrinsically worse prognosis of non-Hodgkin lymphoma and the lower positive predictive value is likely to be related to the higher risk of infections among typically older patients who are treated with higher dose density and intensity regimens. Furthermore, the addition of rituximab induces an inflammatory response by activation of antibody dependent cellular cytotoxicity and complement dependent cytotoxicity, resulting in a high rate of false-positive results^[60,61]. Therefore, some trials included a biopsy^[62–64] to verify the results of interim PET. Nevertheless, it must be kept in mind that biopsies are invasive and can be false-negative due to sampling errors. Another option is to perform short-term follow-up (clinical, CT and/or PET/CT) to assess for objective evidence of disease progression.

FDG-PET-guided treatment trials in solid tumors

Adenocarcinoma of the esophagogastric junction

Compared with malignant lymphoma, less data are available in the field of PET-controlled trials in solid tumors (Table 4). The stage in this field has been set by Lordick et al.^[65] with their frequently cited MUNICON-I trial (Metabolic response evaluation for Individualisation of neoadjuvant Chemotherapy in esophageal and esophagogastric adenocarcinoma), which reports the results of a PET-guided treatment algorithm in adenocarcinoma of the esophagogastric junction. Neoadjuvant chemotherapy is an accepted choice for the treatment of the locally advanced stage of this tumor type^[66,67]. For non-responders, however, the prognosis is inferior to that of patients primarily treated with surgery^[68,69]. This may be due to the fact that ineffective neoadjuvant treatment allows tumor progression during chemotherapy, but also to the risk of toxic deaths as observed in the MUNICON phase II trial^[65]. This highlighted the necessity to identify those patients who might potentially benefit from neoadjuvant chemotherapy. This concept has been realized in the MUNICON-I trial^[65], which prospectively confirmed that responders to induction chemotherapy can be identified by metabolic imaging as early as 2 weeks on treatment (Fig. 2). In this trial, a PET scan was performed in 119 patients before the start and after 2 weeks of platinum and fluorouracil-based induction chemotherapy. Patients with a predefined decrease in standardized uptake value (SUV) of $\geq 35\%$ were defined as metabolic responders, which was based on previous studies by the

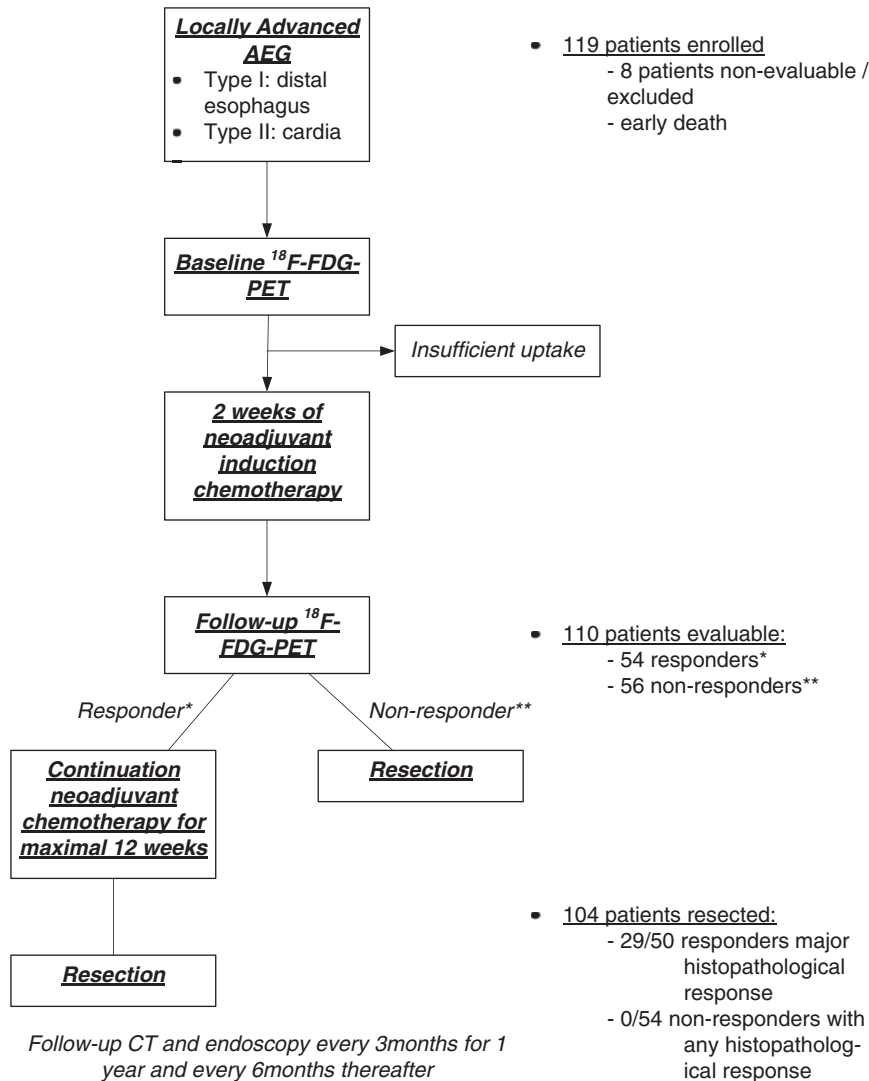


Figure 2 Study scheme as used by Lordick et al.^[65]. AEG, adenocarcinoma of the esophagogastric junction; *responder (metabolic responder), reduction in SUV $\geq 35\%$ compared with baseline FDG-PET/CT; **non-responder (metabolic non-responder), increase or reduction in SUV $< 35\%$ compared with baseline FDG-PET/CT.

same group that assessed and validated the optimum cut-off level^[69,70]. Responders continued to receive neoadjuvant chemotherapy for 12 weeks and then proceeded to surgery. Metabolic non-responders discontinued chemotherapy and immediately proceeded to surgery. The rate of major histopathologically confirmed remissions was 58%. Continuation of neoadjuvant chemotherapy in the responders resulted in a favorable outcome. Median overall survival was not reached in metabolic responders compared with a median overall survival of 25.8 months in metabolic non-responders. Compared with cohorts from previous studies, one can conclude that the outcome of metabolic non-responders was not at all compromised by the early discontinuation of chemotherapy. It must be emphasized, however, that all data are derived from single-centre studies and that a randomized multicentre trial for confirmation would be desirable. The European

Organisation of Research and Treatment of Cancer (EORTC) is currently planning an international validation trial of the MUNICON findings, using a central imaging platform and central quality assurance of PET and histopathologic response^[71].

What we can learn from the approach is that step-by-step implementation of cut-off values is very important when metabolic thresholds for response monitoring are implemented in clinical practice. A higher metabolic cut-off value of 45% or more would result in higher specificity for histological response (86% vs 75%)^[70], but in a lower negative predictive value, which would translate into a bigger proportion of patients from whom chemotherapy would be withheld, despite having chemosensitive tumors.

On the basis of the results of the MUNICON-I trial, the MUNICON-II trial was initiated^[72]. In this trial,

56 patients with locally advanced adenocarcinomas of the esophagogastric junction were included. In contrast to MUNICON-I, where metabolic non-responders proceeded to surgery, metabolic non-responders in the MUNICON-II trial were switched to salvage neoadjuvant chemoradiation before surgical resection in order to improve histopathologic response, the R0 resection rate and the prognosis of these patients. The results of this trial showed an increased histopathologic response after salvage chemoradiation (26% vs 0% in the MUNICON-I trial), however, the primary end point of the study to increase the R0 resection rate from 74% to 94% was not met. No benefit in prognosis was observed in the subgroup of PET non-responders. Almost 50% of the metabolic non-responders showed distant metastases shortly after chemoradiation, indicating the unfavorable tumor biology that could not be reversed by radiation (total dose of 32 Gy) plus concurrent chemotherapy (cisplatin or 5-fluorouracil). The moderate-intensity schedule was chosen to prevent high toxicity rates, which could lead to a higher pre-operative drop-out rate and post-operative morbidity and mortality. Median overall survival of metabolic non-responders in the MUNICON-II trial was 18.3 versus 25.8 months in MUNICON-I, whereas time to progression was 15.4 months for MUNICON-II versus 14.1 months for MUNICON-I. When radiotherapy is part of the regimen, overestimation of FDG uptake due to the radiation-mediated inflammatory component can occur, which may persist from weeks to months and could potentially have confounded metabolic response assessment. Currently, an international multicentre PET-guided randomized controlled trial, comparing salvage chemoradiation and other treatment strategies, is on its way to find out which strategy affects patient outcome^[73,74]. New ongoing trials on the same subject are the EUROCON trial^[74] and the HICON trial^[75]. The EUROCON trial randomizes metabolic non-responders with localized esophagogastric adenocarcinoma after 2 weeks of chemotherapy to immediate resection or chemoradiation followed by surgery. The HICON trial^[75] is a prospective, non-randomized, explorative imaging study to evaluate the value of PET as a predictor of histopathologic response to salvage neoadjuvant chemoradiation in metabolic non-responders. Metabolic non-responders 2 weeks after the start of neoadjuvant chemotherapy (EOX (epirubicin, oxaliplatin, capecitabine) or EOF (epirubicin, oxaliplatin, 5-fluorouracil)) are taken to intensified taxane-based chemoradiation (docetaxel/cisplatin + 45 Gy) before surgery. FDG-PET scans are performed before and after 14 days of standard neoadjuvant therapy as well as after the first cycle of salvage docetaxel/cisplatin chemotherapy and at the end of chemoradiation (Table 4).

Other solid tumors

In solid tumors other than adenocarcinoma of the esophagogastric junction, a first step has been taken in

breast cancer. The ongoing CCAM-11-01 phase II trial^[76] is investigating the feasibility of FDG-PET-guided chemotherapy and hormone therapy in patients with newly diagnosed invasive breast cancer (Table 4). In this trial, patients are divided according to receptor status into three groups. Group 1 consists of HER2+ patients (positive for the human epidermal growth factor receptor 2), which includes ER+ (estrogen receptor positive), ER-, and PR+ (progesterone receptor negative). Group 2 consists of ER- patients (including triple negative and ER/PR/Her2- patients) and group 3 of ER+ patients (including ER+/PR+/Her2- and ER+/PR-/Her2- patients). All groups receive docetaxel, epirubicin and cyclophosphamide (TEC regimen). For ER+/Her2- patients, subsequent therapy after TEC course 1 depends on the Oncotype score. For other patients, treatment with TEC is repeated every 21 days for up to 4 courses in the absence of disease progression or unacceptable toxicity. Patients in group 1 are being evaluated after 4 courses of TEC. Patients who achieve complete or partial remission receive 4 courses of docetaxel and trastuzumab followed by surgery. Patients with progressive or stable disease receive vinorelbine, trastuzumab and oral capecitabine (NTX regimen) for 4 courses followed by surgery. After surgery, patients receive radiotherapy (when indicated) and maintenance trastuzumab for 1 year. ER-positive or PR-positive patients also receive hormonal therapy for 5 years. The second group of patients (ER-) are also evaluated after 4 courses of TEC. Patients who achieve complete remission receive 4 more courses of TEC and undergo surgery. Patients who achieve partial remission or stable disease receive 4 courses of vinorelbine, bevacizumab and capecitabine (NAX regimen) followed by surgery. Group 3, ER+ patients undergo a PET scan 2 weeks after finishing 1 course of TEC. Patients receive 3 additional courses of TEC if the SUV decreases >5%. Patients with an SUV decrease ≤5% (after 1 course of TEC therapy) receive additional therapy depending on the Oncotype results. The primary outcome measure of this trial is the pathological response rate.

Take home messages

A large number of studies have shown that FDG-PET is a robust, reliable, easy-to-adopt tool for early response monitoring in several malignancies. Based on these studies, several (ongoing) clinical trials are investigating the impact of FDG-PET-based treatment changes on patient outcome. The first PET-driven clinical trials on malignant lymphoma and solid tumors, published by Dann et al.^[29] and Lordick et al.^[65] (the MUNICON trials) prospectively showed the feasibility of a PET-guided treatment algorithm in a multidisciplinary setting leading to an overall better treatment outcome. The results of these trials are an important step forward in tailoring (multimodal) treatment in accordance with tumor biology. The trials provide a model for designing response-guided treatment

algorithms in other malignancies, such as lung, head and neck and ovarian cancer, for which induction treatment has a potential role and the algorithms need to be addressed in randomized phase III trials. The application of FDG-PET for response-adjusted treatment in clinical trials is still in its infancy. Much more work has to be done to provide definite proof of the clinical impact of metabolic response monitoring, to establish FDG-PET as an imaging biomarker to adjust and personalize cancer therapy. The preliminary findings discussed in this review call for systematic implementation of FDG-PET in randomized trials comparing PET-controlled strategies in order to be able to adequately position FDG-PET in treatment time lines and bring about a paradigm shift in the evidence-based approach of individualized patient management of malignancies.

Conflict of interest

The authors have no conflicts of interest to report.

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