Role of PET in Lymphoma

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In Hodgkin's lymphoma (HL), PET imaging should be performed in all patients, particularly in stage I or II disease where change in staging will alter management. For aggressive Non-Hodgkin's lymphoma (NHL), PET imaging is valuable to provide a baseline for response evaluation. For indolent NHL, it is concluded that PET imaging is not generally indicated. For HL, a negative FDG-PET scan is highly indicative of long-term, disease-free survival and is particularly useful in the presence of residual CT mass. For aggressive NHL, a positive FDG-PET scan is predictive of disease persistence or recurrence. There is a significant incidence of false-negative FDG-PET scans, which in most cases means minimal residual disease that cannot be detected by the current instrumentation. For both NHL and aggressive HL, early assessment of response appears to be predictive of long-term outcome. Optimal time of FDG-PET scan during therapy needs to be determined. For indolent NHL, the high rate of false-negative FDG-PET scans raises questions to its clinical role in response evaluation. FDG-PET and PET-CT improve primary staging and restaging of lymphomas. Metabolic imaging will be the standard technology for assessment of therapy with documented prognostic value. Imaging during therapy may be valuable to individualize therapeutic protocols and to define chemosensitivity of tumor tissue. Minimal residual disease cannot be detected with current imaging devices. *(Chang Gung Med J 2005;28:315-25)*

Key words: positron emission tomography (PET), lymphoma, fluoro-2-deoxy-D-glucose (FDG).

Introduction

Lymphoma is a common disease, and positron emission tomography (PET) plays an important role in its management. About 60,000 cases are diagnosed each year in the United States, and about 25,000 patients die each year from lymphoma. It is the fifth most common cancer in the US, and the third most common cause of cancer death in the US. Lymphoma consists of a group of sub-diseases. Non-Hodgkin's lymphoma (NHL) is the most common, and is about 14 times more common than Hodgkin's lymphoma (HL). Similarly, the mortality rate is higher in patients with NHL compared with HL.

Management of patients with lymphoma is a major clinical problem. Fortunately, there are a number of established therapies as well as experimental therapies that can benefit from functional imaging.

Perspectives for PET-CT

The role of functional imaging has changed and advanced in recent years. Multimodality imaging combines high spatial resolution with biological specificity and detection sensitivity of tracer techniques. These tracers are far superior to conventional computed tomography (CT) contrast agents because of their high detection sensitivity; a picomolar concentration can be detected in tissue, so the combination is ideal.

It is important to understand the fate and metabolism of these radiopharmaceuticals in tissue.

Biological targeting of tumor tissue requires in-depth understanding of cellular processes. Even though we think we understand 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), there are many alterations of FDG-PET kinetics that we may not fully comprehend. To advance our field, an interdisciplinary approach is mandatory to improve the spectrum of radiopharmaceuticals.

Biological imaging targets

The radiopharmaceuticals play the most important role in further advancement of biological imaging. As we have heard, there are tracers in development for proliferation, oxygenation, angiogenesis, apoptosis, etc. But the most important tracers express the metabolic activity of tumour tissue. For therapy as well as for diagnostic studies, the surface receptors are important because they can be targeted directly by the tracer or therapeutic agent. In some cases, then, the ligand is incorporated into the cell, and radioactivity can be used not only to diagnose the tumour but also for treatment. The combination of imaging and therapy appears to be very attractive, and it especially applies to the CD20 antigen, which is expressed on B-cell lymphomas. This is being used for therapy with cold antibodies as well as in combination with radio-immunotherapy to actually change or target the tumour with internal radiation.

PET biological tracer techniques in lymphoma

As far as imaging is concerned, glucose transport (FDG-PET) is the primary biological target. FDG-PET is well validated. As animal studies have shown, it appears to be well correlated with the extent of viable tumour cells in a given population. This applies to most tumours, and it is particularly applicable for lymphoma. There is ongoing discussion about how much the degree of FDG-PET retention corresponds to grading. In lymphoma it seems to be that high-grade NHL and low-grade NHL have a different intensity of FDG-PET uptake, which may relate to the histopathology. However, this relationship is not very strong since many other factors affect the uptake of FDG-PET. To avoid some of the pitfalls of the lack of specificity of FDG-PET for malignant cells, amino acids have been introduced, e.g., methionine and fluorotyrosine (FLT), which have proved useful. However, they have been much less evaluated, and they may fullfill only two of the four 'A' requirements (avid, accurate, affordable, available) that we need for a good tracer. Thymidine kinase activity is a very attractive target for monitoring therapy because a marker of proliferation may be more suitable for therapy monitoring than merely a marker of cell number. Finally, there is antigen expression (CD20) for combination therapy.

The FDG-PET imaging success story

It has been known for more than 40 years that upregulation of glucose transport phosphorylation in tumor tissue is an important characteristic of tumour tissue. Deoxyglucose is a specific marker of viable tumor cells; however, because FDG-PET is also taken up by macrophages or inflammatory cells, it is specific for the biologic process of inflammation as well as for malignancy. There is extensive clinical validation for staging and therapy control. An important point is that FDG-PET is now moving from being simply an interesting complementary diagnostic approach to becoming a surrogate endpoint in some trials that are evaluating new therapies in patients with lymphoma. The German Hodgkin's group, for example, is now starting a Phase III trial that includes FDG-PET imaging as one of the endpoints in the study.

How does FDG-PET uptake correlate with the histopathologic classifications? There are a large number of various ways to classify tumors. Elstrom et al retrospectively evaluated FDG-PET scans in 172 patients with lymphoma and correlated results with the pathologic diagnosis using the World Health Organization (WHO) classification system (Table 1). In total, FDG-PET detected disease in at least one site in 161 patients (94%) and failed to detect disease in 11 patients (6%). The most frequent lymphoma diagnoses were diffuse large B-cell lymphoma (LBCL; $n = 51$), HL ($n = 47$), follicular lymphoma (FL; $n = 42$), marginal zone lymphoma (MZL; $n = 12$), mantle cell lymphoma (MCL; $n = 7$), and peripheral T-cell lymphoma (PTCL; $n = 5$). FDG-PET detected disease in 100% of patients with LBCL and MCL, and in 98% of patients with HL and FL. In contrast, FDG-PET detected disease in only 67% of MZL and 40% of PTCL. Comparison with bone marrow biopsies showed that FDG-PET was not reliable for detection of bone marrow involvement in any lymphoma subtype.

These results are somewhat limited by the num-

Table 1. FDG-PET in Lymphoma Compared with the WHO Classification[1]

Histology	Positive	Negative	Total	% Positive
LBCL	51	0	51	100
FL	41	1	42	98
HL	46	1	47	98
MZL	8	4	12	67
MCL	7	0	7	100
ALCL	2	0	2	100
PTCL	2	3	5	40
CBCL	0	2	2	0
MF	1	0	1	100
BL	1	0	1	100
SLL	1	0	1	100
T/NK	1	0	1	100

Abbreviations: LBCL: large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin lymphoma; MZL: marginal cell lymphoma; MCL: mantle cell lymphoma; ALCL: anaplastic large cell lymphoma; PTCL: peripheral T-cell lymphoma; CBCL: cutaneous Bcell lymphoma; MF: mycosis fungoides; BL: Burkitt's lymphoma; SLL: small lymphocytic lymphoma; T/NK: natural killer cell lymphoma.

ber of patients studied, but they appear to be valid for most of the NHLs as well as for the HLs. It seems that B-cell lymphomas are more easily imaged by FDG-PET than the T-cell lymphomas. As for the other subtypes of lymphoma, at the present time we have to be very careful because the number of studied patients is low.

Clinical issues: the utility of FDG-PET

PET is used in the following ways in the management of lymphoma: (1) staging of disease; (2) restaging after therapy; (3) monitoring of therapy; and (4) prediction of outcome.

Restaging is very important as it relates to a given therapy, especially in lymphoma, but also as it relates to clinical outcome. In more recent studies the emphasis is on predicting the response to therapy very early, as well as relating the changes in metabolic activity in the tumour to the clinical outcome of the patient, fulfilling thereby the criterion of a surrogate endpoint used in the evaluation of therapy. Many other presentations have discussed the advantages of FDG-PET: the high biologic contrast of tumour tissue to non-tumour tissue and the possibility of viewing the entire body after one imaging procedure. For lymphoma this latter advantage is most suitable because lymphoma is a systemic disease in which staging is an important part in the therapy approach, especially staging types 1 and 2. Adding the metabolic information to CT provides specificity in localizing the disease process.

In many institutions CT is used initially in a low-dose mode in order to provide an anatomic map. More recently, many centers are moving to a combination of a diagnostic CT and PET imaging, which increases the efficiency of the diagnostic process. On the other hand, it requires close cooperation between nuclear medicine and radiology, which is easier in some countries than in others. We are lucky. We have a very close relationship with our radiologists. Our residents rotate through radiology and spend a half-year in the CT unit before they enter the PET-CT rotation.

Overall staging: PET vs CT

What are the results for overall staging using FDG-PET compared with CT (Table 2)?[2-7] The problem with the validation of these studies is that, as we know, the therapy is not surgery in lymphoma. As a result, it is very difficult to validate the imaging procedures by investigating each lymph node that is detected by PET or CT. Most of these studies are based on clinical outcomes, on concordances

Table 2. Overall Staging by FDG-PET and CT in Patients with Lymphoma[2-7]

Author	Year	N	Positive lesions	Type	Sensitivity		Sensitivity	
					CT	PET	CT	PET
Buchmann	2001	52	148 regions	Mixed	84%	99%	100%	100%
Weihrauch	2002	22	77 sites	HD	74%	88%	100%	100%
Wirth	2002	50	117 sites	Mixed	68%	92%	-	-
Sasaki	2002	46	152 sites	Mixed	65%	92%	99%	99%
Foo	2004	24	-	Mixed	71%	96%	-	-
Schäfer	2004	60	-	Mixed	88%	94%*	86%	100%*

between PET and CT, and on clinical impressions about disease progression.

With these limitations in mind, however, it becomes relatively clear that the sensitivity of FDG-PET imaging is about 10-15% higher than conventional CT imaging (Table 2). The specificity is about comparable with CT. Thus, more lesions can be detected with PET than with CT. This applies not only to HL, but also to NHL.

Change of staging by FDG-PET in patients with lymphoma

Table 3 summarizes data on change of staging by FDG-PET, indicating about a 15-18% change in staging. Most patients, as would be expected, are upstaged, but a few patients are downstaged. By applying PET, about 20% of patients are upstaged. The critical question is - how does improved staging affect outcome? There are relatively few data yet to demonstrate that a change in staging affects outcome in patients. In only a relatively few cases does it change the particular therapy. It is very difficult to compare studies in this respect, because the therapeutic regimen varies from institution to institution. More prospective studies are needed to define the impact of improved staging in patients with lymphoma.

Nodal and extranodal staging with PET and CT

In the most recent data comparing the role of CT and PET in nodal and extranodal staging, the diagnostic gain was higher in the extranodal than in the nodal staging procedure. The data by Schaefer, published this year, used PET-CT in combination and had very high diagnostic accuracy for both nodal and extranodal staging. Although PET imaging is now recognized as a useful tool for staging intermediate and high-grade NHL, few data are available about its accuracy in low-grade NHL. In a study by published

Najjar in 2001, 12 PET was compared with physical examination and CT in 36 patients with histologically proven low-grade NHL. Whole-body FDG-PET was performed at the time of initial diagnosis ($n = 21$) or for disease recurrence ($n = 15$) before any treatment.

Results

The sensitivity and specificity were 87% and 100% for FDG-PET, 100% and 100% for physical examination, and 90% and 100% for CT. In addition, 42 of 97 peripheral lymph node lesions observed by FDG-PET were clinically undetected, whereas the physical examination detected 23 additional nodal lesions. PET and CT both indicated 12 extranodal lymphomatous localizations. FDG-PET showed seven additional extranodal lesions, while five additional unconfirmed lesions were observed on CT.

Conclusion

The combination PET-CT/physical examination seemed to be more sensitive than the conventional approach for staging low-grade NHL.

At first glance these results are not that different from those for an aggressive high-grade NHL. There may be differences in various areas, however. PET may not perform as well in areas with low activity in the abdominal cavity because there is higher background activity. In this study, the advantage was primarily in the hilar area, whereas in low-grade tumors PET demonstrated many more lesions than CT.

Limitations of FDG-PET staging are (1) validation of the procedure is limited by the heterogeneity of histopathology; (2) only limited validation by biopsy, and there may be regional heterogeneity in the expression of glucose transport resulting in various sensitivities to detect various sites; (3) inflammation and infection can cause false-positive results; (4) muscle and brown fat induced uptake; this is espe-

Table 3. Change of Staging by FDG-PET in Patients with Lymphoma[3,8-11]

Author	Year	N	Type	Change of stage	Upstage	Downstage
Bangerter	1998	44	HD	6 (13%)	5 (11%)	1 (2%)
Buchmann	2000	52	mixed	4 (8%)	4 (8%)	-
Jerusalem	2001	33	HD	4 (12%)	3 (9%)	1 (3%)
Weihrauch	2002	22	HD	4 (18%)	4 (18%)	-
Naumann	2003	88	HD	18 (20%)	11 (12%)	7 (8%)

cially difficult in the cervical regions where it is important to be highly sensitive and specific in patients with lymphoma. Therefore, the combination of PET-CT has helped us to identify fat deposits. The muscle uptake is best relieved by sedating the patient lightly and making the patient comfortable on the scanner; and (5) nonspecific FDG-PET uptake after chemotherapy must be considered. There is a rebound phenomenon with increased FDG-PET uptake in the thymus and in bone marrow in some cases.

FDG-PET *vs* gallium-67

For many years, gallium-67 citrate was the standard procedure for therapy monitoring. However, a number of studies indicate that FDG-PET is superior to gallium in the application of imaging of lymphomas. PET has some practical advantages, such as a shorter half-life of FDG and better kinetics. With gallium the wait is 1 to 2 days; with FDG-PET the results are ready in 1 or 2 hours. PET also has an advantage because of the lower amount of radiation exposure to the patient.

A recent retrospective study of 50 patients with newly diagnosed or progressive HL or NHL by Wirth et al4 confirmed the superiority of FDG-PET over gallium scintigraphy and conventional imaging, especially for patients with HL. But in other series it has also been shown to be true for patients with NHL.

Results

PET and gallium scanning each upstaged 14% of patients ($n = 7$). Management was altered by PET in nine cases (18%) and by gallium scanning in seven (14%, $p = 0.6$). Disease was evident in 117 sites in 42 patients. The case positivity rate for conventional assessment was 90%; for PET, 95%; for gallium scanning, 88%; for conventional assessment plus PET, 100%; and for conventional assessment plus gallium scanning, 98%. Site positivity rates for conventional assessment were 68%; for PET, 82%; for gallium scanning, 69%; for conventional assessment plus PET, 96%; and for conventional assessment plus gallium scanning, 94%. PET and gallium scanning were entirely concordant in 31 patients; in the other 19 patients, PET identified 25 sites missed by gallium scanning, whereas gallium scanning identified 10 sites missed by PET.

Conclusion

PET demonstrated a higher site positivity rate than did gallium scanning, with similar case positivity rates. These data support the use of PET in place of gallium scanning for the staging of patients with HL or NHL. So FDG-PET is likely to replace gallium-67 scintigraphy.

Bone marrow involvement in lymphoma

Bone marrow involvement in lymphoma can be appreciable. With the overlay of a CT scan, lesions in the bone marrow can more easily be identified. However, it is known that CT is not as good for identifying bone marrow involvement. Biopsy is the standard for detecting bone marrow involvement. There are a number of studies comparing results of unilateral or bilateral biopsies with the FDG-PET scan. Overall, when FDG-PET deposition is compared with biopsy, there is relatively good agreement in negative and positive results. However, primarily in populations with NHL, there are PET-negative/biopsy-positive results, while in HL there seems to be very good agreement, with only a few positive ET scans that were biopsy-negative.

There are difficult issues in this correlation here. The biopsy may be very patchy and may not precisely locate the area of involvement. In the future more studies have to address the regional concordance of these findings. The issue of whether FDG-PET has less sensitivity in detecting bone marrow involvement in NHL must be addressed.

Summary

Staging FDG-PET

In HL, PET imaging should be performed in all patients, but particularly in stage I or II disease, where change in staging will alter management. For aggressive NHL, PET imaging is valuable to provide a baseline for response evaluation; in stage I disease, where fewer cycles of chemotherapy may be considered. For indolent NHL, at the current time it is concluded that PET imaging not generally indicated.

FDG-PET for restaging applications

There is no question that functional imaging adds to the morphological evaluation of residual tumor tissue after chemotherapy in NHL. We all know that a residual.

Mass on CT is not specific for malignant tissue. Our experience and that of many other centers demonstrates that by adding PET to CT, the findings are more specific. This is especially true in negative FDG-PET findings, where it can then be demonstrated that the lesion was not metabolically active; therefore, it is unlikely that it represents residual disease. For example, in Figure 1, a para-aortal residual mass was seen on the CT scan, but it did not show any glucose utilization and was, therefore, considered macroscopically not viable.

Freudenberg et al. compared data (Table 4) for restaging by FDG-PET with CT and PET-CT in a recent study. The combined mode of PET-CT had very high sensitivity and specificity associated with high positive and negative predictive values. However, retrospective fusion of PET and CT had results very close to those of combined PET-CT. Statistically it will be very difficult to demonstrate the superiority of combined PET-CT. In our opinion, the advantage of PET-CT is that it offers are more efficient diagnostic work-up of patients in terms of time spent by both the patient and physician.

The most important data, published a few years ago by Spaepen et al, demonstrated that a negative PET result after therapy is associated with a much longer progression-free survival than residual metabolic activity after therapy (Fig. 2). It is this difference, with a relatively simple signal, that makes PET such an attractive clinical tool in the evaluation of therapy. This result has been confirmed by many studies, which indicate that patients responding to therapy have a very high percentage of progression-free survival at 1 and 2 years after end of therapy (Table 5). The same applies for non-responders, which show a very poor or very short progression-free survival. The exception was one study in which there was about a 40% progression-free survival after 1 year. There is also a learning curve implied behind these data because if a number of false-positive results are included, the progression-free survival rate will improve. As technology improves, as attenuation-corrected images replace non-attenuation-corrected images, and as the combination of PET-CT becomes more widespread, results on the separation of these groups will improve, and there will be better prediction of outcome.

Limitations of morphologic criteria to monitor cytotoxic therapy

The limitations of morphologic criteria to monitor cytotoxic therapy are well known. It is a historic
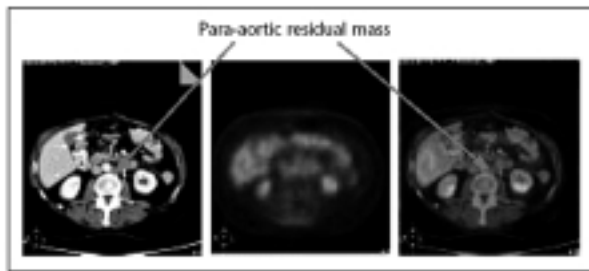

Fig. 1 PET-CT scan (with IV contrast) of a 57-year-old patient with a follicular NHL after CTx. Para-aortic residual mass.
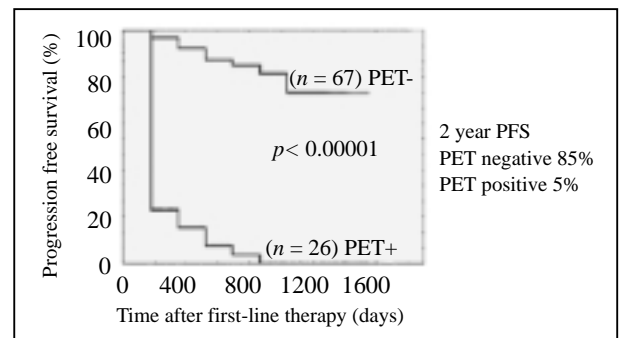

Fig. 2 FDG-PET in NHL after first-line chemotherapy. 15 Figure reproduced with permission from the source.

Table 4. Re-Staging by FDG-PET, CT and PET-CT in Patients with Lymphoma[14]

Imaging modality	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
CT	61	89	54	92	84
PET	78	98	90	96	95
PET and CT	91	99	96	98	98
Combined PET-CT	96	99	96	99	99

Table 5. Assessment of Tumour Response by FDG-PET at the End of Therapy and Patient Outcome[15-22]

Author	Year	N	Type	FU (month)	Progression free survival		p
					Responder	Nonresponder	
Jerusalem	1999	54	Mixed	21	1 yr: 86%	0%	< 0.001
Zinzani	1999	44	Mixed	20	2 yr: 95%	0%	< 0.001
Mikhaeel	2000	45	NHL	30	1 yr: 83%	0%	< 0.001
Spaepen	2001	93	NHL	22	2 yr: 85%	4%	< 0.001
Juweid	2002	38	NHL	15.5	1 yr: 88%	8%	< 0.001
Weihrauch	2001	28	HD	28	1 yr: 95%	40%	0.032
Spaepen	2001	60	HD	31	2 yr: 85%	4%	< 0.001
Mikhaeel	2002	65	HD	36	1 yr: 93%	0%	< 0.001
Zinzani	2004	75	Mixed	-	100%	9%	< 0.001

and arbitrary definition. It takes considerable time after therapy - weeks and months - to get final morphologic results. Therefore, patients can be mislabeled. Non-responding patients may undergo prolonged treatment without benefit, while responding patients are erroneously classified as nonresponding.

Our hypotheses are that (1) tumor glucose utilization can be assessed by FDG-PET with high reproducibility; (2) the decrease of glucose utilization during therapy correlates with the reduction of viable tumor cells; and (3) in responding tumors, a reduction of glucose utilization occurs early after initiation of therapy. In our study published in the late 1990s, we used FDG-PET imaging in patients with lymphoma undergoing therapy. We studied them before therapy, at day 7, and at day 42 (Fig. 3). Within 7 days there was a marked decrease in metabolic activity, with a further decline at day 42. Therefore, performing an early evaluation after therapy may help to predict outcome at a time when medications can be changed. A number of studies in the literature now confirm that in one or up to four cycles the chemosensitivity of the tumor tissue can be predicted (Table 6). This applies especially to patients undergoing high-dose therapy in combination with stem cell transplantation, a very costly procedure associated with many side effects. PET may be a valuable tool before this very involved procedure to stratify patients and to identify possible responders as compared with nonresponders (Table 7).

We have used FDG-PET to evaluate radioimmunotherapy labeled with ^{131}I (Fig. 4). Studies were done up to 6 weeks after immunotherapy. The
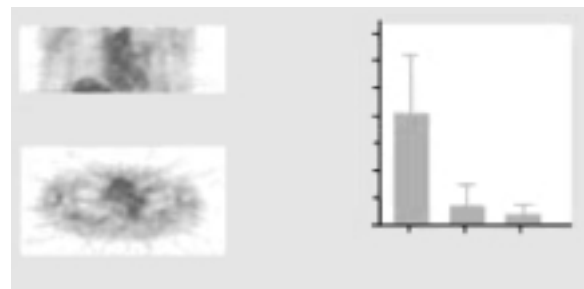

Fig. 3 Time course of therapy-induced changes during CHOP therapy.[23] Figure reproduced with permission from the source.

Table 6. Assessment of Tumor Response by FDG-PET during Therapy and Patient Outcome[18,21,24-26]

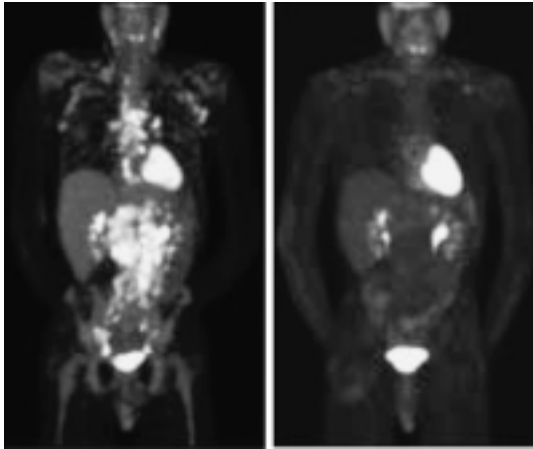| Author	Year	N	Type	FU (month)	Follow-up	Progression free survival	
						Responder	Nonresponder
Jerusalem	2000	28	NHL	28	After 2-3 cycles	2 yr: 62%	0%
Mikhaeel	2000	23	NHL	30	After 2-4 cycles	100%	12%
Spaepen	2002	70	NHL	36	After 3-4 cycles	2 yr: 85%	4%
Mikhaeel	2002	32	HD	36	After 2-4 cycles	1 yr: 92%	0%
Kostakoglu	2002	23	Mixed	19	After 1 cycle	1 yr: 87%	13%

Fig. 4 Response to radio-immunotherapy (RIT).

Fig. 5 Response to radio-immunotherapy FDG-PET SUV baseline to 6.

decrease in metabolic activity was most pronounced in patients with complete remission. In terms of the changes of SUV measured for individual patients, it is evident that FDG-PET uptake in fact decreased in all patients after 14 days of therapy (Fig. 5). However, the decrease in FDG-PET uptake was much faster for responders (triangles) than for nonresponders (circles). Therefore, inflammatory reactions after radiochemotherapy appear less relevant for FDG-PET uptake than therapy-induced reduction of tumor volume.

Summary

Response evaluation with FDG-PET32

For HL, a negative FDG-PET scan is highly indicative of long-term, disease-free survival. It is particularly useful in the presence of residual CT mass. For aggressive NHL, a positive FDG-PET scan is predictive of disease persistence or recurrence. There is a significant incidence of false-negative FDG-PET scans, which in most cases means
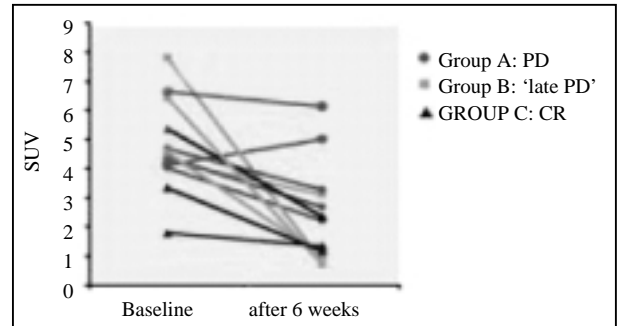
minimal residual disease that cannot be detected by the current instrumentation. For both NHL and aggressive HL, early assessment of response appears to be predictive of long-term outcome. Optimal time of FDG-PET scan during therapy needs to be determined. For indolent NHL: the high rate of false-negative FDG-PET scans question the clinical role in response evaluation.

Amino acid uptake of cancer cells

Amino acid uptake can be studied with natural amino acids labeled with C-11 or with amino analogs. Natural amino acids include C-11-methionine, C-11-leucine, and C-11/F-18-tyrosine. Amino acid analogs include I-123-α-methyltyrosine (IMT), F-18-α-methyltyrosine (FMT), and F-18-ethyltyrosine (FET).

Tyrosine analogs are very useful for evaluation for brain tumors. However, in lymphoma, as shown in this study using F18-tyrosine (Fig. 6), FDG-PET imaging seems to be much more reliable than amino acid uptake. However, at the current time, there are not enough data to document the utility of this tracer.

Assessment of proliferation

There are a number of studies with C-11-thymi-

Table 7. Assessment of Tumor Response by FDG-PET before Stem Cell Transplantation and Patient Outcome[27-30]

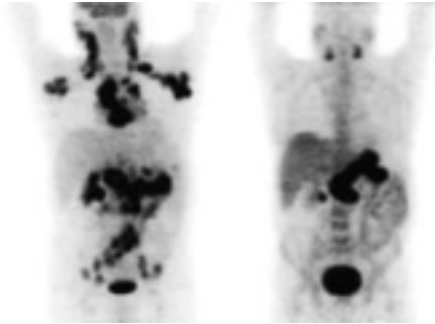| Author	Year	N	Type	FU (month)	Progression free survival	
					Responder	Nonresponder
Filmot	2002	21	Mixed	13.3	1 yr: 94%	25%
Cremerius	2002	22	NHL	25	1 yr: 72%	28%
Becherer	2002	16	Mixed	17	1 yr 100%	18%
Spaepen	2003	60	Mixed	50	2 yr: 96%	23%

Fig. 6 Whole-body tumor imaging using 2-[^{18}F]Tyr.^{18}F-FDG-PET (A) and ^{18}F-TYR (B). Patient with highgrade NHL. Extensive nodal involvement seen on ^{18}FFDG-PET.[33] Figure reproduced with permission from the source.

dine, especially by the Seattle group. However, more recently, fluoro-labeled compounds and FLT have been introduced. The advantage of this tracer is that it is not metabolized; it accumulates as a function of its phosphorylation by the thymidine kinase. It resembles FDG-PET in its kinetics, which means that the increase actually reflects the activity of the thymidine kinase, which is proportional to the incorporation of thymidine into the DNA.

We are currently evaluating FDG-PET and FLT in patients with lymphoma. Figure 7 shows a comparison of FDG-PET and FLT for axilla lymph node involvement. In both cases the SUV was similar, indicating that the biologic contrast was about the same with both tracers. Interestingly, there was a good correlation between the SUVs of both tracers.
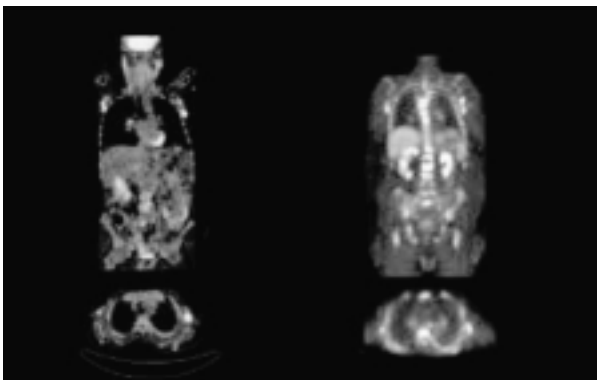

Fig. 7 Comparison of FDG-PET and FLT-PET. A 55-year-old patient with high-grade NHL treated with CHOP.

With the measurement of proliferation by in vitro testing, this quantification may make sense in order to probe the proliferation rate of the tumour.

Our first results during therapy monitoring after 7 days of chemotherapy (Fig. 8) showed a very rapid decrease of the proliferation rate, as measured by SUV values from 8.5 to 0.5. It is still too early to make a judgment yet about the role of this serial imaging tracer in therapy evaluation. However, we are looking forward to presenting these results in the near future.
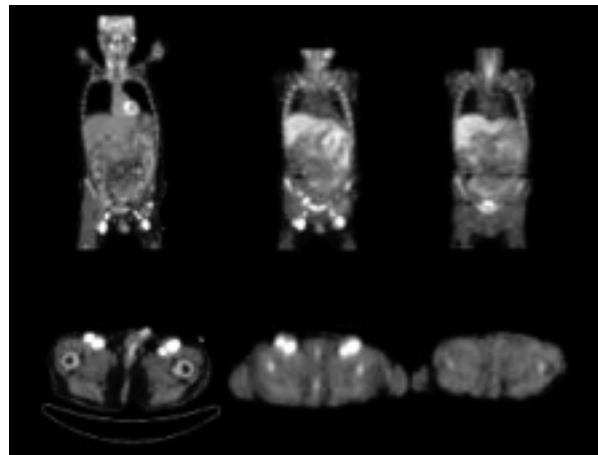

Fig. 8 Monitoring of high-dose chemotherapy in lymphoma by FLT-PET. A 55-year-old patient with high-grade NHL treated with CHOP.

Recommendations for implementation of FDG-PET in the management of lymphoma

FDG-PET should be used in diagnosis. If it is negative, there should be no follow-up. A PET-positive scan helps to stratify the patient, especially in the follow-up after therapy. Information is now accumulating that patients with residual activity should be considered for more aggressive therapy, leading to the concept of more individualized therapy in patients with lymphoma. In my opinion PET may play a very important role by guiding these changes in therapy.

Conclusion

FDG-PET and PET-CT improve primary staging and restaging of lymphomas. Metabolic imaging will be standard technology for assessment of therapy

with documented prognostic value. Imaging during therapy may be valuable to individualize therapeutic protocols and to define chemosensitivity of tumor tissue. Minimal residual disease cannot be detected with current imaging devices.

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