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Limited clinical benefit for surveillance PET-CT scanning in patients with histologically transformed lymphoma in complete metabolic remission following primary therapy

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Abstract

Background

The optimum follow up of patients with transformed indolent lymphoma (TrIL) is not well defined. We sought to determine the utility of surveillance PET-CT in patients with TrIL achieving complete metabolic remission (CMR) after primary therapy.

Methods

We performed a retrospective analysis of patients with TrIL treated at Peter MacCallum Cancer Centre between 2002 and 2012 who achieved CMR after primary therapy who had ≥1 subsequent surveillance PET-CT.

Results

Of 55 patients with TrIL, 37 (67%) received autologous stem cell transplantation as consolidation following chemoimmunotherapy. After median follow-up of 34 (range 3 – 101) months, the actuarial 3-year progression free (PFS) and overall survival (OS) were 77% (95% CI 62–86%) and 88% (75–94%) respectively. Of 180 surveillance PET-CT scans, there were 153 true negatives, four false positives, one false negative, seven indeterminate and 15 true positives. Considering indeterminate scans as false positives, the specificity of PET-CT for detecting relapse was 94%, sensitivity 83%, positive predictive value 63% and negative predictive value was 98%. All seven subclinical (PET detected) relapses were of low-grade histology; in contrast all nine relapses with DLBCL were symptomatic.

Conclusion

In our cohort of patients with TrIL achieving CMR, PET-CT detected subclinical low-grade relapses but all DLBCL relapses were accompanied by clinical symptoms. Thus, surveillance imaging of patients with TrIL achieving CMR is of limited clinical benefit. PET-CT should be reserved for evaluation of clinically suspected relapse.

Introduction

Histologic transformation from indolent to high-grade lymphoma is an important cause of treatment failure[1]. Patients with transformed indolent lymphoma (TrIL) were previously thought to have an adverse prognosis[2-5] although more recent data suggests that in the rituximab era outcomes may be improving, particularly in patients attaining complete response to therapy.[6,7] A series from MD Anderson Cancer Centre found 9/21 (43%) of patients with TrIL relapsed beyond two years.[8] Similarly, a study from Lyon reported that in a cohort of patients with DLBCL, 13/54 (24%) of late relapses (defined as more than five years after completion of therapy) occurred in patients who had TrIL demonstrated at diagnosis. These relapses occurred at a median of 7.5 (range 5-20.5) years after initial treatment.[9] In chemotherapy naïve patients, anthracycline containing chemotherapy regimens with rituximab (typically rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP)) are considered standard of care.[10] Current treatment guidelines do not offer explicit guidance on recommended follow up of patients with TrIL.[11,12] In particular, no studies to our knowledge have examined the role of surveillance imaging for patients with TrIL in complete metabolic remission (CMR) after therapy. We have previously showed that in *de novo* DLBCL, surveillance ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scanning did not result in clinical benefit in patients with low- or intermediate-risk disease by International Prognostic Index (IPI) at any time, nor in patients with high-risk IPI beyond 18 months from completion of therapy.[13] In this paper we examine the utility of surveillance PET-CT scans following immunochemotherapy for patients with TrIL achieving CMR.

Methods

We reviewed the clinical, pathology and PET databases for patients with TrIL treated at Peter MacCallum Cancer Centre between 2002 and 2012. The definition of TrIL was a documented diagnosis of indolent lymphoma (including non-follicular histology) and a synchronous or subsequent diagnosis of DLBCL. For some exploratory analyses, patients were divided into two groups. Those in whom the diagnosis of histologic transformation was made concurrently with diagnosis of indolent lymphoma (either due to composite histology on a single biopsy, or two biopsies from different anatomic sites within one month with one showing indolent lymphoma and the other DLBCL) were termed “Group 1”. Those patients in whom diagnosis of histologic transformation was made greater than one month after diagnosis of indolent lymphoma were termed “Group 2”. Patients suspected to have transformed disease on clinical grounds (any one or more of the following features; rapid disproportionate growth of a single nodal area, rapidly rising serum lactate dehydrogenase (LDH), new extranodal sites of disease, constitutional symptoms or hypercalcemia) were included, as their prognosis has been shown to be similar to biopsy-proven TrIL.[2,5] Of these, only patients who achieved CMR after primary therapy who had ≥1 subsequent surveillance PET-CT were included in the final analysis. During the period analysed, if there was intention to intervene on detection of subclinical relapse departmental protocol recommended six-monthly scans for patients in CMR for the first 2 years, then once annually until 5 years had elapsed after completion of therapy.

Data collection

For each patient, we collected baseline characteristics including sex, performance status, age, serum LDH, primary therapy, date and details of follow up PET-CT scans, and follow-up data including the date and site of relapse, type (subclinical or suspected), biopsy results, cause and date of death. The primary endpoint was

determination of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PET-CT for the detection of relapse. The study was conducted in accordance with the declaration of Helsinki and data collection was compliant with institutional ethics requirements.

FDG PET-CTs were obtained on a dedicated PET/CT scanner (Discovery LS, GE Medical Systems, Milwaukee, USA; Discovery STE, GE Medical Systems, Milwaukee, USA or Biograph 64, Siemens Medical Solutions, Knoxville, USA) from the skull-base to upper-thigh level, unless there was suspicion or known disease outside this field-of-view. Patients were fasted for six hours before administration of 5 MBq/kg ^{18}F-FDG, to a maximum of 400 MBq adapted for weight and imaged after a ≥60-minute uptake phase.

Scan interpretation

PET-CT reports were reviewed and classified as “positive”, “negative” or “indeterminate” for relapsed lymphoma by one (clinician) investigator blinded to patient outcome (as described in [13]). In generating the original PET report, the imaging specialist had access to prior investigation results, including the baseline and post-treatment FDG PET-CT studies. A positive scan was defined by a new area of FDG avidity usually of intensity greater than liver in a nodal or extranodal structure for which relapsed lymphoma was considered the most likely explanation. True positive results requiring either biopsy confirmation or unequivocal disease progression at that site within three months. A scan was considered to be *false* positive if refuted by biopsy and clinical follow up, or in the absence of biopsy, progression did not occur. A negative scan was defined by either absence of areas with new FDG avidity, or new FDG avidity attributed to aetiology other than relapsed lymphoma such as FDG-avid cervical nodes in a patient with upper respiratory tract infection or symmetric hilar/mediastinal nodal activity in a distribution typical of

reactive/granulomatous aetiology. True negatives had no clinical relapse and false negatives manifest relapse within three months from the date of the scan. Indeterminate scans were defined by an abnormal increase in FDG avidity in which the reporting nuclear medicine physician was not able to confidently differentiate between a benign cause such as infection and relapsed lymphoma. For the purposes of calculating test performance, indeterminate scans were scored as false positives or negatives, depending on subsequent clinical outcome. It should be noted that the time period covered by the study was mostly prior to the publication of both the International Harmonisation Project[14] and the Deauville criteria[15]. A “suspected relapse” was defined as relapse preceded by signs, symptoms or other clinical features such as rising serum LDH. A “subclinical relapse” was defined as relapse detected without any of the above features, on the basis of imaging findings.

Statistical analysis

Continuous variables were expressed as median and range and compared using the Mann-Whitney U-test. Categorical variables are reported as percentages, and compared using Chi squared test. Progression-free survival (PFS), overall survival (OS) were calculated from the time of transformation using the method of Kaplan and Meier, and compared using log-rank analysis. *P*-values were two-sided, and values <0.05 were considered significant. Statistical analyses were performed using STATA version 12.1 (StataCorp, College Station, TX).

Results

Ninety-eight patients with TrIL were identified of whom 43 were ineligible for the following reasons: no surveillance PET-CT scan (*n*=35), did not achieve CMR (*n*=7), insufficient follow up data available (*n*=1) leaving 55 available for analysis. Of these, 30 patients were in Group 1 (concurrent diagnosis of histologic transformation and indolent lymphoma) and 25 patients were in Group 2 (delayed diagnosis of

transformation). The characteristics of these patients are summarised in Table 1; characteristics were similar between groups apart from more patients in group 1 receiving rituximab as part of their primary chemotherapy (93% v 64%, *P*=0.007). Fifty-three (96%) patients had biopsy proven DLBCL at time of transformation. After a median follow-up of 34 (range 3 – 191) months, the actuarial 3-year PFS for Groups 1 and 2 were 82% (95%CI 68 – 96%) and 70% (95%CI 52 – 88%) respectively. The actuarial 3-year OS were 89% (95%CI 78 – 99%) and 88% (75 – 99%) respectively. There was no significant difference in PFS (P=0.54, Figure 1) or OS (P=0.60) between the two groups. Other potential prognostic factors including IPI score at time of transformation, advanced stage, serum LDH at transformation and type of indolent histology were not shown to be predictive of PFS by univariate analysis. (data not shown)

In total 180 surveillance PET-CT scans were performed during the period analysed, 103 and 77 in groups 1 and 2 respectively. This equated to a median of 3 (range 1-10) scans per patient. The results of these scans as a function of time are displayed in Tables 2 (Group 1) and 3 (Group 2) respectively. In total, there were 153 true negatives, four false positives, one false negative, seven indeterminate and 15 true positives. Considering the five indeterminate scans which were not followed by relapse as false positives, and two indeterminate scans which were followed by relapse as false negatives, the overall specificity of PET-CT for detecting relapse was 94%, sensitivity 83%, positive predictive value 63% and negative predictive value 98%. Considering groups 1 and 2 separately resulted in similar test performance. (Supplementary Table 1). Sixteen patients experienced relapsed lymphoma; seven were subclinical (three in group 1, four in group 2), and nine symptomatic (three in group 1, six in group 2). The symptomatic relapses were invariably with DLBCL and occurred at a median of 17 (range 2.8 – 41.8) months post therapy. The presenting symptoms were patient-detected lymphadenopathy (*n*=6), hypercalcemia (*n*=1),

cranial nerve palsies in a patient with isolated CNS relapse (*n*=1), and shortness of breath in a patient who developed malignant pleural effusion (*n*=1). All patients were confirmed histologically by excisional biopsy (*n*=6), lumbar puncture (*n*=1) or analysis of pleural fluid (*n*=1). Eight of the nine were true positive scans; the patient presenting with shortness of breath due to malignant effusion had a false negative PET-CT scan at the time of relapse (although the pleural effusion was demonstrated by the CT component, the FDG avidity was considered physiological and the scan was reported as ongoing complete metabolic response of the lymphoma).

The seven subclinical relapses occurred a median of 9.8 (range 2.9 – 20.6) months following completion of therapy. In six cases, biopsy of the lesion with the highest FDG avidity showed follicular lymphoma. In one case, CT guided core biopsies of a right retrocrural node was non-diagnostic but the lymph node continued to enlarge on interval imaging and the patient was treated for presumed relapsed lymphoma with salvage chemotherapy, involved field radiotherapy, achieved CMR and remains in remission seven years later. Although the histology of relapsed lymphoma was not proven to be follicular, given the durability of response this seems more likely. The patients with subclinical/low grade relapse had a trend towards better OS post relapse compared to those with symptomatic/high grade relapse (3-year OS 100% vs 56%, *P*=0.07).

The four false positive results occurred at 3, 8, 17 and 37 months post therapy, respectively. In all cases the abnormal ^{18}F-FDG uptake was confined to the mediastinum and/or Waldeyer's ring; two of these cases had symptoms of upper respiratory tract infection, one patient had recent *Varicella zoster* infection, and one patient had no symptoms to suggest infection. All received follow up scans around three months later, which showed resolution of prior abnormalities. The seven indeterminate scans showed increased FDG uptake in the cervical (*n*=2), tonsillar (*n*=2), axillary (*n*=1), para-aortic (n=1) and inguinal (*n*=1) regions. In five cases there

was clinical suspicion of infective process to explain the FDG uptake; in one case (uptake isolated to an inguinal node) progressed in intensity and extent on a follow up scan six months later and was associated with increased multifocal nodal abnormalities in keeping with unequivocally relapsed disease (interpreted as a true positive scan). An excisional biopsy showed follicular lymphoma. In the other case low volume axillary lymphadenopathy was reported as potentially reactive, but on repeat scanning just over three months later there was persistent abnormal uptake. Excisional biopsy again revealed follicular lymphoma.

Discussion

In our cohort of patients with TrIL, who were managed mostly with upfront transplantation and rituximab containing chemotherapy and achieved CMR, we were unable demonstrate clinical benefit from a PET-CT surveillance strategy weighted towards more frequent scanning at the time of greatest likelihood of lymphoma relapse. Patterns of relapse were somewhat surprising: all relapses with low grade histology (follicular lymphoma in this study) were subclinical, and occurred within two years from completion of therapy. In contrast, large cell relapses occurred up to 3.5 years after completion of therapy and all nine were accompanied by signs or symptoms of relapse - prompting unscheduled early review and PET-CT scanning. The finding of subclinical relapse of low grade histology is of limited clinical benefit, as such patients rarely merit further therapy based on imaging findings alone. In contrast, patients with relapsed large cell lymphoma, who may have theoretically benefited from early detection of relapse[16] were not detected by the surveillance strategy. Separate analysis of Groups 1 and 2 showed similar patterns of relapse and test performance.

One finding from this study is the value of end of treatment PET-CMR to identify a subset of patients with excellent outcomes. This prognostic information can be of great reassurance to patients. Although further negative surveillance PET-CT scans

had high negative predictive value for relapsed lymphoma and can give reassurance to patients of ongoing remission, this must be weighed against the anxiety arising from indeterminate or false positive scans, cost and inconvenience of a small number of unneeded biopsies and radiation exposure. Notwithstanding, the false positive rate of PET-CT in this series was very low.

We analysed a number of prognostic factors in an attempt to define a high-risk population of patients who may benefit from a surveillance strategy. Age at transformation >60 was the only significant predictor of inferior PFS on univariate analysis; the presence of B symptoms displayed a non-significant trend (*P*=0.06). The most consistently identified prognostic factors for patients with TrIL in previous studies is raised serum LDH at time of transformation,[3,1,17,18] although numerous other factors have been proposed (Table 4). Although we identified age >60 as a prognostic factor, the pattern of relapses were such that confining a surveillance strategy to such patients would not have resulted in clinical benefit. It is important to point out that although there is limited benefit from surveillance PET-CT, there is even less of a role for CT, which has higher false positive rates, poor sensitivity for extranodal disease[13] and is only able to detect 11-17% of relapses prior to clinical evidence of relapses.[19-21]

The actuarial 3-year PFS of 77% observed in this cohort is promising, but must be interpreted in the context of 1) the exclusion of patients with refractory disease 2) most patients (69%) undergoing ASCT and 3) most patients (80%) receiving rituximab. The outcomes are superior to the reported median PFS of 13-26 months in published series of patients with TrIL undergoing autologous stem cell transplantation (ASCT) prior to the incorporation of rituximab.[22-25,18] Published series of patients with TrIL receiving rituximab containing chemotherapy as part of initial therapy are limited, but outcomes appear to be improving, with 5-year OS from recent series 48-

75%.[26,27,17,28-31] Selected recent studies of patients with TrIL receiving ASCT are displayed in Table 3.

There are several limitations to this study. The patient population studied was selected (young, good performance status and primary refractory patients excluded) and was managed aggressively with ASCT performed in over two-thirds of cases. However, patients falling outside these criteria (either unfit for stem cell transplantation or chemo-refractory) have limited options for treatment and therefore a surveillance strategy to detect early relapse is rarely of clinical benefit. The number of relapses was relatively small, in part due to the favourable outcomes seen from our treatment strategy. Although a departmental scanning protocol was in place, adherence was dependent on the individual treating physician and thus adherence was variable, as evidenced by the number of patients otherwise eligible who did not receive surveillance PET-CT scans. This, a consequence of the retrospective design introduces the possibility of bias. The study spans a period of almost a decade during which time interpretation of PET findings has improved. In particular, symmetric tonsillar and associated cervical nodal activity which constituted several of the false positive results is now recognised a feature of lymphoid repopulation or hyperplasia post chemotherapy. Finally, our findings with regard to the performance characteristics of surveillance PET-CT scans are specific to our setting, an academic tertiary referral centre with high imaging volume and physician expertise.

Conclusion

In our cohort of patients with TrIL achieving CMR, PET-CT detected subclinical relapses of low-grade histology with high sensitivity but with a low false-positive rate. This is of limited clinical benefit as the initiation of further therapy in these circumstances is rarely based on imaging findings alone. In contrast, all DLBCL

relapses in our cohort were accompanied by clinical symptoms. Thus, surveillance imaging of patients with TrIL achieving CMR is not indicated. PET-CT should be reserved for evaluation of suspected relapse.

Disclosures

The authors declare that they have no conflict of interest.

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Tables and Figures

Patient characteristics	**entire group**	**Group 1** Evidence of transformed histology at time of initial diagnosis of lymphoma	**Group 2** Initial diagnosis of indolent lymphoma with time interval to transformation	**P-value**
Number	55	30	25	
Median age (range), years	59 (35 – 83)	57 (37 – 72)	61 (35 – 83)	0.56
Female (%)	22 (40%)	15 (50%)	7 (28%)	0.10
Chemotherapy prior to transformation		N/A	17/25 (68%)	
Indolent histology (data available n=55) FL MALT CLL/SLL other	 46 (65%) 5 (9%) 3 (5%) 1 (2%)	 28 (93%) 2 (7%)	 18 (72%) 3 (12%) 3 (12%) 1 (4%)	0.17
IPI at transformation (n=52) low (0 – 1) intermediate (2 – 3) high (4 – 5)	 15 (27%) 31 (61%) 6 (12%)	 9 (30%) 16 (56%) 4 (14%)	 6 (26%) 15 (65%) 2 (9%)	0.24
Median serum LDH:ULN (range) (n=51)	1.03 (0.6 – 4.7)	1.0 (0.6 – 4.7)	1.1 (0.7 – 2.2)	0.22
Extranodal sites (n=53) 0-1 ≥2	 33 (62%) 20 (38%)	 19 (66%) 10 (33%)	 14 (58%) 10 (42%)	0.35
ECOG performance status (n=54) 0-1 ≥2	 51 (95%) 3 (5%)	 29 (97%) 1 (3%)	 22 (92%) 2 (8%)	0.14
Stage (*n*=55) I-II III-IV	 11 (20%) 44 (80%)	 7 (23%) 23 (77%)	 4 (13%) 21 (87%)	0.42
B symptoms (*n*=52)	12 (23%)	7 (24%)	5 (22%)	0.52
Stem cell transplantation after histologic transformation (*n*=55)	38 (69%)	21 (70%)	17 (68%)	0.87
Rituximab as part of initial therapy (*n*=55)	44 (80%)	28 (93%)	16 (64%)	**0.007**
Maintenance rituximab after histologic transformation (*n*=55)	12 (21%)	5 (17%)	7 (23%)	0.31

Table 1. Patient characteristics. Abbreviations - IPI: International Prognostic Index, FL: follicular lymphoma, SLL: small lymphocytic lymphoma, CLL: chronic lymphocytic leukaemia, MALT: mucosa associated lymphoid tissue lymphoma, MZL: marginal zone lymphoma; ALCL: anaplastic large cell lymphoma, HT: histologic transformation, LDH: lactate dehydrogenase, ULN: upper limit of normal, ECOG: Eastern Cooperative Oncology Group.

	0-6 mo	6-12 mo	12-18 mo	18-24 mo	24-36 mo	36-48 mo	48+ mo	total
True positives (subclinical)	0	2	0	1	0	0	0	**3**
True positives (suspected)	0	1	0	0	1	1	0	**3**
False positives	0	0	1	0	0	0	0	**1**
False negatives	0	0	0	0	0	0	0	**0**
Indeterminate	0	0	5	0	0	0	0	**5**
True negatives	18	23	15	14	11	5	5	**91**
Total	18	26	21	15	12	6	5	**103**
% PET scans detecting subclinical relapse	0%	4%	0%	7%	0%	0%	0%	

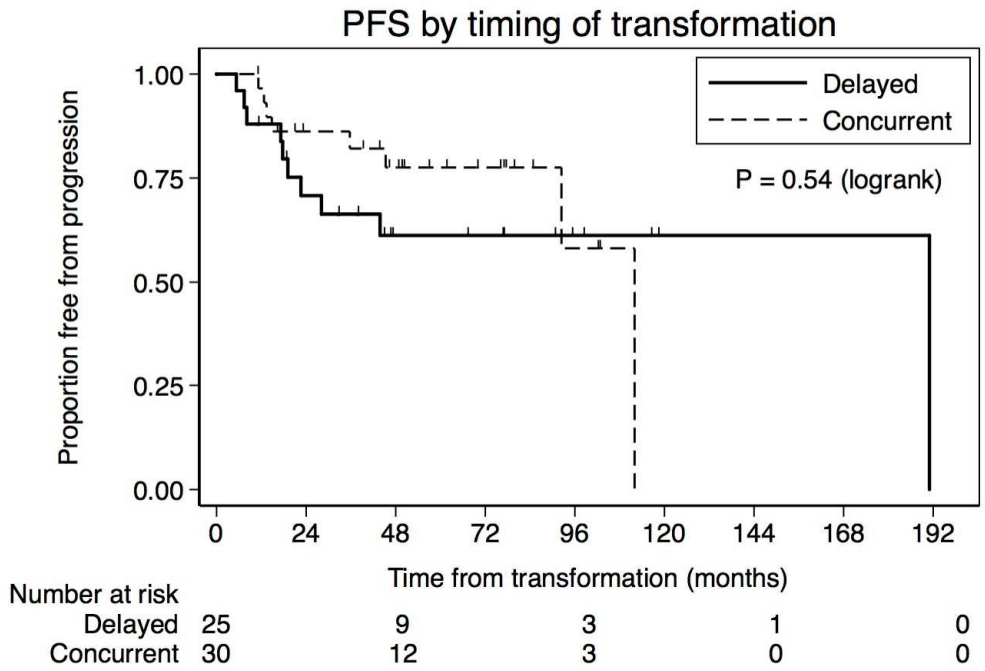
Table 2. Results of surveillance PET-CT scans, by time elapsed since completion of therapy for group 1 (patients with histologic transformation present at time of initial diagnosis of indolent lymphoma).

	0-6 mo	6-12 mo	12-18 mo	18-24 mo	24-36 mo	36-48 mo	48+ mo	total
True positives (subclinical)	1	2	1	0	0	0	0	**4**
True positives (suspected)	1	0	2	0	1	1	0	**5**
False positives	1	1	0	0	0	1	0	**3**
False negatives	0	0	0	0	0	1	0	**1**
Indeterminate	0	0	1	1	0	0	0	**2**
True negatives	16	15	10	7	9	5	0	**62**
Total	**19**	**18**	**14**	**8**	**10**	**8**	**0**	**77**
% PET scans detecting subclinical relapse	5%	0%	7%	0%	0%	0%	0%	

Table 2. Results of surveillance PET-CT scans, by time elapsed since completion of therapy for group 2 (patients with time delay between initial diagnosis of indolent lymphoma and histologic transformation).

author, year	n (trans-formed)	rituximab with induction (%)	ASCT (%)	PFS	OS	adverse prognostic factors
Villa[17], 2013	172	100%	97 (56%)*	5-yr 48%	5-yr 61%	raised LDH (at transformation)
Ban-Hoefen[29], 2011	18	100%	18 (100%)	2-yr 59%	2-yr 82%	-
Conconi[30], 2012	37	33%	NR	NR	5-yr 75%	age>60, ECOG PS >1
Armand[28], 2013	38	97%	100%	4-yr 40%	4-yr 51%	primary refractory disease, remission duration < 6 months,
Link[31], 2013	60	yes, variable	18 (30%)	NR	5-yr 48%	time to transformation <18 months after FL diagnosis, R-CHOP prior at HT
Bastion[3], 1997	53	no	7(13%)	NR	3-yr 20%	not achieving CR, prior chemo, raised LDH, marrow involvement, advanced stage, B symptoms, treatments other than CHOP-like
Eide[32] 2011	52	no	30 (59%)	5-yr 32%	5-yr 54%	number of prior treatments, male
Montoto[5], 2007	88	no	8 (9%)	NR	median 1.2y	raised LDH, poor ECOG PS
Williams[18], 2001	50	no	50 (100%)	5-yr 30%	5-yr 51%	raised LDH, chemo-resistant at time of ASCT

Table 4. Outcomes of selected recent studies in transformed indolent lymphoma. Abbreviations: n – number of patients, ASCT –autologous stem cell transplantation, PFS – progression free survival, OS – overall survival, NR – not reported, FL – follicular lymphoma *this study included 22 patients (13%) who underwent allogeneic stem cell transplantation


PFS by timing of transformation
Proportion free from progression
1.00
0.75
0.50
0.25
0.00
Delayed
Concurrent
P = 0.54 (logrank)
0
24
48
72
96
120
144
168
192
Time from transformation (months)
Number at risk
Delayed 25 9 3 1 0
Concurrent 30 12 3 0 0