The Utility of Bayes' theorem in positron emission tomography positive suspected cases of relapsed non-Hodgkin's lymphoma

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Citation

Abstract

The role of Positron Emission Tomography (PET) in suspected non Hodgkin's lymphoma (NHL) relapse is not well established. An illustrative case report of a patient with a positive PET scan and suspected recurrence is presented and analyzed using Bayes' theorem. We find that the positive predictive value (PPV) of the PET scan significantly depends on the patient's initial prognosis and time from diagnosis. The greater the elapsed time and the better the initial prognosis, the lower the PPV of a positive PET scan. We have developed a reference table to estimate the PPV of a positive PET scan for treated NHL patients with suspected relapse. From this analysis we strongly recommend repeating a biopsy in the vast majority of suspected relapsed NHL patients with a positive PET scan to confirm the diagnosis.

INTRODUCTION

In Non-Hodgkin's lymphoma, PET scans are being utilized to help differentiate residual fibrosis from viable tumor after treatment, [1,2] indolent from more aggressive lymphomas[2], and as an early predictor of chemotherapy response to guide treatment [4-6]. PET sensitivity and specificity in treated NHL have been reported to range between 60-100% and 71-100%, respectively [2, 7-12]. Although consensus recommendations have been made for PET imaging in assessing treatment response of lymphoma [13] there is insufficient evidence for its routine use in post treatment surveillance [14] or in the evaluation of recurrence.

The International Prognostic Index (IPI) has been considered the best predictor of disease free and overall survival in treated NHL patients in the pre rituximab era. Recently, Sehn et al [15] developed a Revised International Prognostic Index (R-IPI) score to account for improved patient outcomes observed since the addition of rituximab to standard CHOP chemotherapy for aggressive NHL. In the R-IPI system, the same 5 variables used for IPI, namely age, performance status, stage, LDH and extra nodal sites are summated to determine a score. However, only 3 groups instead of the 4 used in IPI are defined; the very good risk cohort (no poor prognostic factors), the good risk cohort (1-2 poor prognostic factors), and the poor risk cohort (3 to 5 poor prognostic factors).

Interpretation of PET imaging is dependant on both imaging related factors and individual patient specific factors. Bayes' theorem can be used to calculate the post test probability of a positive PET considering both of these factors. In this paper, the importance of the pre test probability of recurrence in evaluating a positive PET scan in follow up is explored using Bayes' theorem. This pre test probability is dependent upon variables that include the patient's initial (R-IPI) and the time from diagnosis. We present the following case as an example of the interaction between these two variables and the positive predictive value (PPV) of a PET scan.
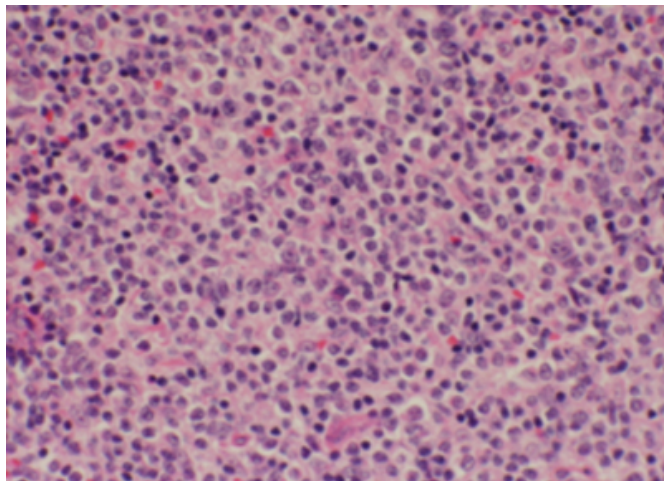
PATIENT AND METHODS

Case History: A 59-year-old woman originally presented with a left inguinal lymph node which had been enlarging over the previous 6-months with no other symptoms. Her prior medical history included cervical dysplasia and migraine headaches. The physical examination was normal aside from the 7.0 cm inguinal lymph node. Her presenting ECOG performance status was one. Laboratory values included normal complete blood counts, serum chemistries, liver function tests and lactate dehyrogenase levels. An incisional biopsy of the mass revealed a grade III / III follicular lymphoma (Figure 1A). The malignant cells stained positive for CD10 and CD20 by flow cytometry, and

negative for BCL-2 by immunohistochemistry. KI-67 was estimated at 30%. A staging CT scan of the chest/abdomen and pelvis was significant only for the left inguinal lymph node. A bone marrow biopsy and aspirate were negative. The patient was staged at stage I with an International Prognostic Index (IPI) score=0. The patient was subsequently treated with a total of 4 cycles of rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP) followed by 4500cGy of external beam radiation to the left pelvic and groin regions. The mass was not palpable after the first cycle of R-CHOP and post treatment imaging revealed no residual mass.

Three years after her initial diagnosis, the patient developed an enlarged right axillary lymph node, again with no other symptoms. A PET-CT scan revealed two highly FDG-avid axillary lymph nodes (Figure 1B).
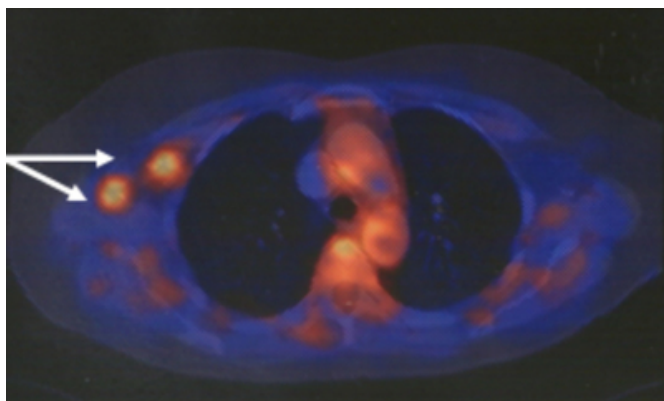
Figure 1

Figure 1A

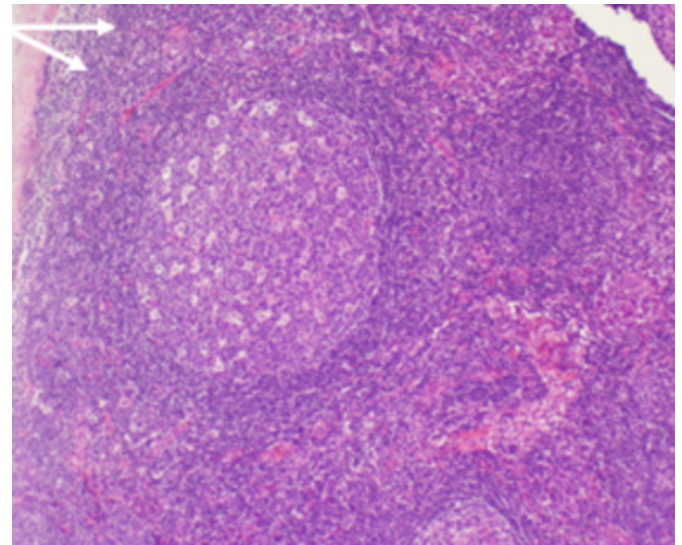## Figure 2

Figure 1B

Figure 3

Figure 1C

Figure 1. Diagnostic images of biopsied lymph nodes and PET scan. (A) Histopathology of the grade III follicular lymphoma of the left anterior thigh. Hematoxylin and eosin stain, original magnification 400x. (B) PET scan showing two enlarged right axillary lymph nodes with increased FDG avidity, suspicious for recurrent lymphoma (arrows). (C) Histopathology of the enlarged PET-avid right axillary lymph node, showing follicular hyperplasia but no evidence of lymphoma. Hematoxylin and eosin stain, original magnification 100x. Photomicrographs were taken with an Olympus DP11 camera on an Olympus Venox-T microscope. No further digital image processing was performed.

Using Bayes' theorem, we explored how clinical factors influence the positive predictive value (PPV) of a positive PET scan in the post treatment setting. Bayes' theorem can be represented as follows;

Figure 4

$$PPV= \frac{p(preRR) \times p(sen)}{p(preRR) \times p(sen) + p(1-preRR) \times p(fp)} \qquad (1)$$

PPV is the probability of NHL given that a patient has a positive PET scan, i.e. p(NHL/positive PET scan) where p(preRR) is the pre-PET scan risk of relapse, p(sen) is the sensitivity of PET scan, p(1-preRR) is the complement of p(preRR) and p(fp) is the false positive rate of PET scans.

All PET scan related factors can be obtained by literature searches but pre test probability of relapse is patient specific

and depends on factors such as time from diagnosis and R-IPI score. We used the progression free survival (PFS) curves derived from Sehn et al [15] to calculate the risk of relapse. We assume that patients are at a negligible risk of relapse if they are relapse free at 5 years. Thus the risk of relapse is first computed as the difference between the PFS at the time of analysis and the ultimate PFS (the value of PFS at 5 years). This value is then divided by the number of patients at risk (PFS at the time point in question). We thus utilized the R-IPI progression free survival curve (figure 2) to determine the patient's p(preRR) using the following formula:

Figure 5

$$p(preRR)= \frac{PFS\ at\ time\ of\ PET\ -\ PFS\ at\ 5yrs}{PFS\ at\ time\ of\ PET} \quad (2)$$

Figure 6

Figure 2

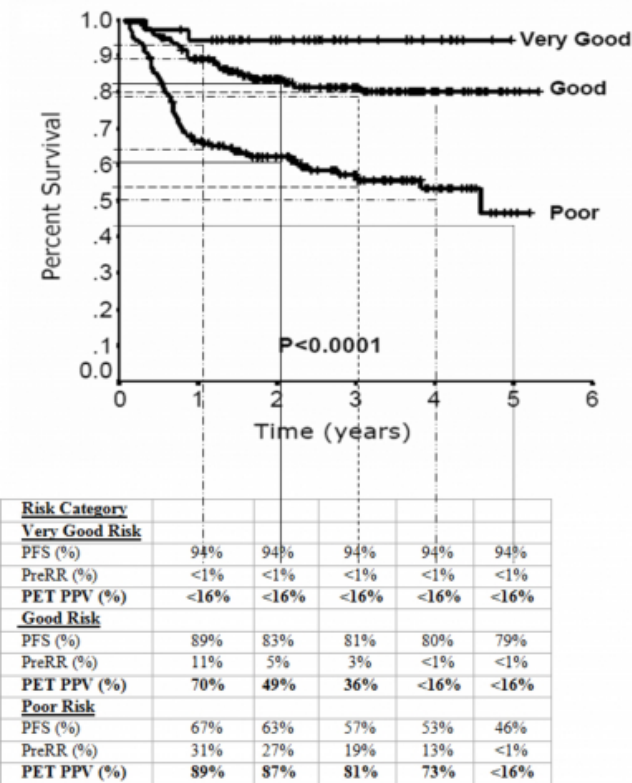| Risk Category					
Very Good Risk					
PFS (%)	94%	94%	94%	94%	94%
PreRR (%)	<1%	<1%	<1%	<1%	<1%
PET PPV (%)	<16%	<16%	<16%	<16%	<16%
Good Risk					
PFS (%)	89%	83%	81%	80%	79%
PreRR (%)	11%	5%	3%	<1%	<1%
PET PPV (%)	70%	49%	36%	<16%	<16%
Poor Risk					
PFS (%)	67%	63%	57%	53%	46%
PreRR (%)	31%	27%	19%	13%	<1%
PET PPV (%)	89%	87%	81%	73%	<16%

Figure 2. Progression free survival curve with corresponding yearly risk of relapse and PET positive predictive value. This figure has been adapted with permission from figure 4a by Sehn et al[15] and shows corresponding yearly pre-PET scan risk of relapse (p(preRR)) and positive predictive value (PPV) by R-IPI category. PPV has been calculated by

Bayes' theorem using a PET sensitivity of 95% and a false positive rate of 5%. p(preRR) is calculated deriving the progression free survival (PFS) at each yearly time interval on the three curves and then inserting them into formula 2 in the main text.

RESULTS

Our patient had a very good risk R-IPI. Using a PFS of 94% at 3 and 5yrs, a risk of relapse or p(preRR) of less than 1% was calculated using formula 2. We previously reported a PET sensitivity of 92% and a false positive rate of 5% in patients with NHL [16]. Using Bayes' theorem these values were used to calculate the PPV.

Figure 7

$$PPV= \frac{(0.01)\ x\ (0.92)}{(0.01)\ x\ (0.92) + (1.0-0.01)\ x\ (0.05)} = 15.7\%.$$

The patient thus had a 15.7% possibility of having recurrent NHL after the positive PET scan. This computed risk is in stark contrast to the clinical impression of the treating physician at that time. An incisional biopsy was performed on one of the axillary lymph nodes, revealing follicular hyperplasia (Figure 1C). The patient has subsequently been followed for over two years with no evidence disease recurrence.

DISCUSSION

This patient's case demonstrates the importance of performing a biopsy in a suspected case of relapsed NHL as a consequence of a suspicious PET scan. Although this patient's pathologic diagnosis is not specifically diffuse large B-cell lymphoma, it is assumed that given the similar aggressive clinical course and treatment of follicular grade III NHL, this case provides an appropriate case study.

Despite high sensitivity and specificity rates, false positive PET scans present a significant problem in the evaluation of NHL recurrence. Understanding the significance of a positive PET scan depends on understanding its PPV. The PPV is dependent on factors related to both the PET scan (sensitivity and false positive rates) and to each individual patient's pre-test probability of relapse. In general, the more time that elapses from the original diagnosis of NHL and the lower the R-IPI score, the lower the PPV of a positive PET scan.

We felt it was appropriate to define the PFS curves of treated

patients with NHL by the Sehn data set as most patients are now treated with a rituximab based chemotherapy regimen. Based on the PFS curves by Sehn et al [15], we have developed a reference table (figure 2) that can be used to estimate the PPV of a positive PET scan for patients with a suspected relapse of aggressive NHL treated with R-CHOP.

CONCLUSION

PET scans are increasingly being utilized in post therapy surveillance of treated patients with NHL. Without histologic confirmation, patients may then be subjected to further therapies based on this study alone. Furthermore, a systematic analysis of the use and usefulness of PET scans in this setting is currently lacking. It is hoped that this report will firstly encourage physicians to cautiously reflect on the results of a positive PET scan in this setting, and secondly that researchers in the field consider careful studies of this issue.

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