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ORIGINAL ARTICLE

Outcome of patients with early-stage follicular lymphoma staged with ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) and treated with radiotherapy alone

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Abstract

Purpose/objective(s) To evaluate the impact of positron emission tomography (PET) staging on overall survival (OS) and progression-free survival (PFS) in patients with early-stage (stages I and II) follicular lymphoma (ESFL) treated with radiation therapy alone.

Materials/methods Eighty-five patients with ESFL treated with curative-intent radiation therapy (RT) between December 2000 and May 2011 were identified. Of those, 13 who had no PET staging and 25 who received additional systemic therapy were excluded from the analysis. Thus, we analyzed 47 patients with PET-staged ESFL treated with definitive radiation therapy alone (dose > 23Gy). Tumour features, pre-treatment computed tomography (CT) and PET stage, dose fractionation, and radiation therapy field extent were recorded. The Kaplan–Meier method was used to estimate the OS and PFS. Patterns of failure were assessed as cumulative incidences assuming competing risks.

Results Median age was 57 years (range 24–83); 43% were females. Most were PET stage 1 (76.6%). Median maximum nodal diameter was 3 cm. Median pre-treatment lactate dehydrogenase (LDH) was 327.5 (range 123–607, upper normal limit = 220). Twenty-six patients (55.3%) had infra-diaphragmatic disease. All received 30–36Gy in 15–24 fractions, with 59.6% treated with involved-field radiation therapy (IFRT) techniques. There was no significant difference in PFS between CT stage I and stage II (HR 1.30 95% CI [0.25–6.72], $p = 0.75$) with a 5-year PFS of 77% and 78% respectively. However, stage I on PET staging had a significantly better PFS than stage II (HR 4.66 95% CI [1.15–18.8], $p = 0.038$), with 5-year PFS of 84% and 60% respectively. Ten patients had recurrent disease, with distant disease being the first site of failure in seven patients. Seven-year OS was 91% (95% CI 79–100) for the whole cohort.

Conclusion FDG-PET should be considered an essential element in the evaluation of patients with ESFL being considered for RT.

Keywords lymphoma · Positron emission tomography · Prognosis · Radiotherapy · FDG

Preliminary data was presented as a poster presentation at the American Society for Radiation Oncology (ASTRO) 57th Annual Meeting in San Antonio, USA and as an oral presentation at the Royal Australian and New Zealand College of Radiologists (RANZCR) 66th Annual Scientific Meeting in Adelaide, Australia in 2015.

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Introduction

Follicular lymphoma (FL) is the second most common form of non-Hodgkin lymphoma, comprising up to 20% of cases in western countries [1]. Although the majority of patients present with advanced disease (stage III–IV), approximately 20–26% present with localized disease (stage I–II) [2, 3], which is potentially curable with radiation therapy [4, 5]. Careful assessment of an adequate marrow biopsy sample is critical for optimal detection of bone marrow involvement [6]. Anatomical staging accuracy is also of paramount importance in selecting patients for radiation therapy delivered with curative intent, both in terms of excluding patients with stage III–IV disease, and in ensuring tumour coverage of all disease sites in patients with stage I–II. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been shown to be of value in initial staging of patients with lymphoma [7–11]. Our previous data have demonstrated that approximately one in three patients with apparent stage I–II disease on conventional imaging and marrow biopsy was found to have more extensive disease by FDG-PET, and 14% of patients had their radiotherapy treatment volumes altered due to PET findings [8]. It is thus likely that stage migration will be observed in this cohort, due to PET correctly identifying small-volume stage III disease, which would have otherwise have been classified as stage I–II. The aim of this study was to report the long-term outcomes of patients with early-stage (stages I and II) FL (ESFL) staged with PET who remained suitable for, and were treated with, radical radiotherapy alone.

Methods

Patient selection

This was a single institution, ethically-approved (Research Number: 12/122), retrospective study of patients identified from the hospital electronic medical record and radiotherapy treatment record. This list was cross-referenced with the data from the Victorian Cancer Registry, which covers the population served by the institution. Patients over the age of 18 with a diagnosis of previously untreated FL treated with curative-intent radiotherapy alone at the Peter MacCallum Cancer Centre (PMCC) between 2000 and May 2011 were included in the study. Patients who received chemotherapy pre- or post-radiotherapy (as in the TROG 99.03 trial) as part of their initial therapy were excluded. All patients were staged with a pre-treatment FDG-PET or PET/CT scan within 2 months prior to the initiation of treatment, in addition to standard work-up with CT scan and adequate bone marrow aspirate and trephine [6]. It was not possible to compare the relative sensitivity and specificity of PET/CT and CT for staging and treatment selection in this cohort because the denominator represents patients actually treated with curative-intent based on FDG-PET stage. Patients with CT stages I and II and who were upstaged to III or IV by PET are not included in this cohort. However, within this cohort, the outcomes for patients could be compared based on their CT stage and their FDG-PET stage.

Data collected for analysis

Demographic data, tumour characteristics, disease stage and distribution on CT and PET imaging, treatment details, and pre-treatment haemoglobin and lactate dehydrogenase (LDH) were recorded when available from the clinical record. The number and distribution of Ann Arbor sites on each imaging test was recorded. Dates and sites of relapse (in-field or distant) were recorded.

Survival data were provided from Victorian Cancer Registry (VCR) with accurate data until 31 December 2013 (closeout date). It was possible to link the data for all but a few patients. If those patients had follow-up data from PMCC after closeout date, they were censored for survival at the closeout date. If last follow-up data from PMCC was before the closeout date, then the patient was considered lost to follow-up and censored for survival at their last follow-up date.

Statistical analysis

All statistical analyses were performed in R (version 3.0.3; R Development Core Team 2009). Baseline characteristics were summarised using descriptive statistics including counts and frequencies for categorical variables and mean, standard deviation (SD), median and range for continuous variables. The Kaplan–Meier method was used to estimate the overall survival (OS) and progression-free survival (PFS) curves. OS and PFS estimates with associated 95% confidence intervals were reported. All time-to-event endpoints were measured from the date of commencement of RT.

Univariable analysis of possible prognostic variables for freedom from progression (FFP) was performed using the log-rank test for categorical variables (or exact log-rank test for small group numbers) and likelihood ratio test for quantitative variables with hazard ratios obtained from the Cox proportional hazards models. PET stage I vs II, largest transverse nodal diameter, number of Ann Arbor sites, and year of treatment were evaluated for association with FFP. Patterns of failure were assessed as cumulative incidences assuming competing risks.

Table 1 Patient characteristics

Variable	Statistic	*N* (%)
Age	Mean (SD)	56 (14)
	Median [range]	57 [24–83]
	Interquartile range	47–65
Gender	Female	20 (42.6%)
	Male	27 (57.4%)
ECOG	0	38 (80.9%)
	1	8 (17.0%)
	2	1 (2.1%)
Overall stage	I	37 (78.7%)
	II	10 (21.3%)
Tumour site count (number of nodal regions involved)	1	37 (78.7%)
	2	9 (19.1%)
	3	1 (2.1%)
Transverse node size (missing $n = 11$)	Mean (SD)	3.23 (1.27)
	Median [range]	3 [1–6.2]
	Interquartile range	2.45–4
Tumour grade (missing $n = 4$)	I	29 (67.4%)
	II	13 (30.2%)
	IIIA	1 (2.3%)
Pre-treatment LDH (missing $n = 23$)	Mean (SD)	324.75 (137.55)
	Median [range]	327.5 [123–607]
	Interquartile range	210.25–423.25
Pre-treatment haemoglobin (missing $n = 10$)	Mean (SD)	143.41 (13.31)
	Median [range]	145 [116–165]
	Interquartile range	134–153
FLIPI score (missing $n = 23$)	Low risk	16 (66.7%)
	Intermediate risk	8 (33.3%)
CT stage (missing $n = 8$)	I	28 (71.8%)
	II	10 (25.6%)
	III	1 (2.6%)
PET stage	I	36 (76.6%)
	II	11 (23.4%)
Dose total	30	31 (66.0%)
	30.5	1 (2.1%)
	30.6	5 (10.6%)
	34	1 (2.1%)
	36	9 (19.1%)
Number of fractions	15	17 (36.2%)
	17	7 (14.9%)
	18	5 (10.6%)
	20	17 (36.2%)
	24	1 (2.1%)
RT extent	Involved-field	28 (59.6%)
	Other	10 (21.3%)
	Whole abdomen	9 (19.1%)

Table 2 Comparison between CT and PET staging

CT stage	PET stage		
	I	II	III
I	26	2	0
II	3	7	0
III	0	1	0

Results

Eighty-five patients with ESFL were reviewed, of whom 13 who had no PET staging and 25 who received systemic therapy were excluded from the analysis, leaving 47 patients with ESFL confirmed by PET and treated with radical radiotherapy alone (dose > 23Gy) for the analysis. The median follow-up was 4.8 (range: 0.8–13) years. All patients received 30–36Gy in 15–24 fractions. Median age was 57 years (range: 24–83), and 43% were females. The majority had PET stage 1 (76.6%). Baseline characteristics are described in Table 1.

Of the 47 patients, six were unable to be linked to the VCR for survival data. Of those six patients, three had clinical follow-up after the closeout date (31/12/2013) and were censored at the closeout date for overall survival. The other three patients without link to VCR data who had follow-up assessment before the closeout date were considered lost to follow-up and censored at their last follow-up time for OS.

Of the 39 patients staged with CT and PET, six patients had their disease staging altered as a result of PET findings (Table 2). PET upstaged two patients from stage I to stage II, and downstaged four patients — three from stage II to stage I, and one from stage III to stage II. After treatment, disease progression occurred in nine patients. In seven cases, distant progression occurred (outside RT fields). In-field (within the irradiated volume), and marginal (within 5 cm of the irradiated volume) progressions occurred in one case each. One patient died without progression.

The PFS at 3 and 5 years were 86% (95% CI 76–97) and 78% (95% CI 65–94) respectively. The OS at 3 and 5 years were 100% and 97% (95% CI 91–100). The FFP at 3 and 5 years were 86% (95% CI 76–97) and 78% (95% CI 65–94). On univariable analysis of FFP, only PET stage II predicted for treatment failure (HR 4.66; 95%CI 1.15–18.80, $p = 0.018$). Largest transverse nodal diameter by centimetre (cm), number of sites and year of treatment were not statistically significant (Table 3). On multivariable analysis, the PET-stage retained statistical significance in the model.

PFS according to CT and PET staging is shown in Fig. 1. As only one patient was classified as CT stage III, he was omitted from the plot. On PET imaging, he was downstaged to stage II and therefore was considered to have ESFL suitable for IFRT. He was alive without progression at the closeout date with 5.5 years of follow-up. No separate curves were provided for OS given the small number of events. Only two deaths were recorded. There was no evidence that the CT stage II PFS curve is different than the stage I PFS curve (HR 1.30 95% CI [0.25–6.72], $p = 0.751$) but PET stage II PFS curve is statistically inferior to the PET stage I PFS curve (HR 4.66 95% CI [1.15–18.8], $p = 0.038$).

Discussion

There is already strong evidence that FDG-PET-based staging is more accurate than CT alone in FL, but long-term outcomes for PET-staged patients treated with RT alone are lacking in the literature. ESFL is apparently cured with radiation therapy of 24–30 Gy in approximately 35–50% of cases [4, 12–15] (see Table 4), and relapses are uncommon within the irradiated field [17]. Disease recurrence in conventionally-staged patients is usually manifest early, with 40% of patients relapsing within 4 years [4]. In the series from Stanford University, with a median follow up of 7 years, only five of 47 patients who were progression-free at 10 years subsequently manifested disease recurrence [4]. Historically, failure rates of over 50% after RT have been largely due to distant (out of initial radiation field) relapse [5, 18, 19]. This presumably reflects the presence of initially unrecognised sub-clinical disease beyond the radiation volume when patients are staged only with CT. Our previous study highlighted the importance of PET staging compared to CT alone, as PET frequently upstaged patients and changed radiotherapy planning for those who remained candidates for curative RT. Accurate radiotherapy planning, particularly in the era of involved site or involved nodal RT where RT fields are smaller, to encompass all disease is particularly important, as it has been established that in-field recurrence is relatively rare in FL.

Table 3 Univariable analysis of freedom from progression

Variable	Level	*N*	Events	HR (95% CI)	*P*-value
PET Stage	I	36	5	1	0.018
	II	11	4	4.66 (1.15–18.80)	
Transverse node size	Per cm	36	9	0.66 (0.36–1.23)	0.160
Tumour site count	Per unit increase	47	9	2.90 (1.03–8.14)	0.074

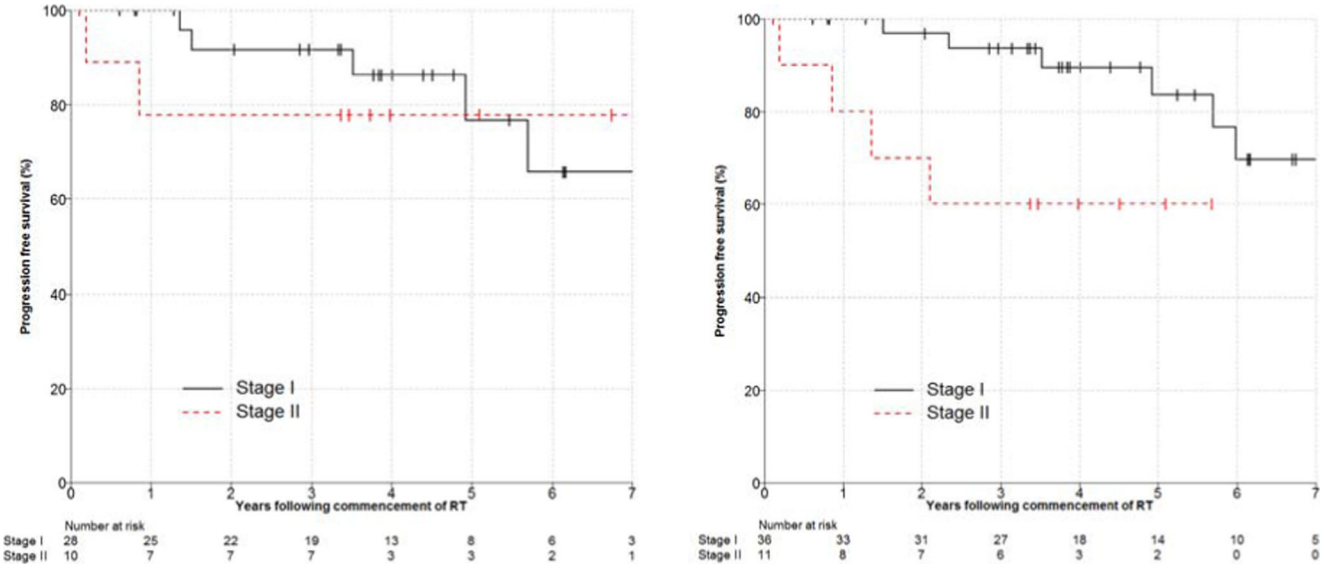

Fig. 1 Progression-free survival according to CT (*left*) and PET (*right*) stage*. * 1 patient had stage III disease, and CT-stage could not be ascertained in eight patients imaged externally, but all were referred for "early-stage" follicular lymphoma

FDG PET has been shown to be of value in initial staging of patients with non-Hodgkin lymphoma by other groups [20]. In an early study, Stumpe et al. [21] reported an overall diagnostic accuracy of PET in lymphomas as 93%, compared to 73% for patients evaluated using conventional imaging. There were initial concerns that PET imaging may be less accurate in histologically lower grades or indolent lymphomas such as follicular lymphoma. However, Wohrer et al. [22] demonstrated that PET imaging has an overall high sensitivity (98%), specificity (94%), and positive and negative predictive values (95% and 98% respectively) for follicular lymphomas, with no significant difference between grade 1–2 and grade 3 follicular lymphoma. PET/CT can detect more extensive disease than CT alone, with Metser et al. [23] demonstrating that 24% of patients with CT-staged I and II disease were upstaged to stage III or IV after PET imaging, resulting in change in overall management of these patients. Similarly, Wirth et al. [8] demonstrated that approximately 30% of patients with stage I–II disease on conventional imaging have more extensive disease detected by PET, leading to upstaging or an alteration of radiation treatment volume, indicating the additional benefit of minimising geographic miss when defining treatment volumes.

The greater sensitivity of PET staging is critically important in settings in which loco-regional radiotherapy is used as the sole therapy, since unrecognised disease outside the treatment field is highly likely to progress, and it is plausible that the outcome for PET-staged stage I–II FL will be superior to that in CT-staged patients. In our study, the cohort had an improved 5-year PFS of 78% compared to historical data where patients were CT staged. The Stanford and Royal Marsden Hospital series previously reported similar 5-year PFS of 55% [4] and 59% [15] respectively. Our cohort's outcomes are similar to those reported by Guadagnolo et al. [5] and Friedberg et al. [24], but their cohorts included patients who had received chemotherapy. The difference in PFS between PET-staged I and II appears to have diminished over time. This may be due to the relatively small number of patients at risk after 4 years, or perhaps reflects the presence of subclinical disease below the threshold for PET detection in patients with PET stage I disease. Furthermore, higher-risk stage II patients may have been excluded from the study (as they were treated with RT and chemotherapy).

One of the potential limitations of this study, in addition to the caveats of a single-institution retrospective study, is that it

Table 4 Results of representative studies of radiation therapy alone for localised low-grade lymphoma

Centre	Year	No of patients	Stage	FFR	Survival
Princess Margaret Hospital [14]	1984	190	I & II	53% @ 12 years	58% @ 12 years
BNLI [12, 16]	1995	208	I	49% @ 10 years	64% @ 10 years
Stanford [4]	1996	177	I & II	44% @ 10 years	64% @ 10 years
Royal Marsden Hospital [15]	1995	58	I & II	43% @ 10 years	79% @ 10 years
M.D. Anderson Cancer Center [13]	2001	80	I & II	41% @ 15 years	43% @15 years

BNLI British National Lymphoma Investigation

covers a period of marked evolution in PET technology from stand-alone PET scanners through progressively more sophisticated PET/CT devices, including time-of-flight and improved reconstruction algorithms. These improvements have progressively enhanced the sensitivity of PET [25, 26]. Potentially, the use of PET/CT will lead to even better detection of occult stage III/IV disease and better GTV delineation than were reflected in the results of the present study. Although the current study includes a few patients who had stand-alone PET, the majority had PET/CT studies, which was installed in our facility in 2001. We believe that the long duration of follow-up justifies inclusion of patients imaged with older technology.

The potential role of chemotherapy in ESFL was not addressed in this study. Given that the majority of relapses were beyond the radiation field, it would be reasonable to consider systemic therapy with the goal of controlling occult distant disease, particularly in the subgroup of patients with stage II disease on PET. There is non-randomised evidence from population-based datasets that systemic therapy improved PFS but not OS in patients with ESFL [24]. In the last decade, rituximab, a chimeric anti-CD20 monoclonal antibody, has been shown to be well tolerated and to improve progression-free survival when added to chemotherapy for advanced stage follicular lymphoma [27, 28]. The role of rituximab in ESFL is less defined than in advanced disease and potentially adds to the cost and morbidity of treatment. However, a retrospective study by Janikova et al. [29] suggested that rituximab in combination with radiotherapy provided better PFS than radiotherapy alone. Recently, TROG99.03, a randomised trial evaluating the addition of immune/chemotherapy to RT, has reported improved 10-year PFS of 59% for patients who had systemic therapy compared to 41% for those who received radiotherapy alone (HR 0.26, $p = 0.045$) [30]. In addition, this study also showed that lower PET stage was associated with superior PFS [30].

Conclusion

In this study, we have shown that a series of patients selected by PET has excellent 5-year PFS (78%), far superior to historical non-PET series. Within our cohort, we have shown that PET stage has a more powerful correlation with PFS than CT stage. FDG-PET should be considered an essential element in the evaluation of patients with ESFL being considered for RT both to exclude patients with more distant disease but also to more accurately define radiation treatment volumes.

Compliance with ethical standards

Conflict of interest Authors Sweet Ping Ng, Richard Khor, Mathias Bressel, Michael MacManus, John F Seymour, Rodney J. Hicks, and Andrew Wirth declare that they have no conflict of interest. Sweet Ping Ng is funded by the Australian Postgraduate Award, Radiological Society of North America (RSNA) Fellow Grant, and Royal Australian and New Zealand College of Radiologists (RANZCR) Research Grant. Professor Hicks is supported by an Australian National Health and Medical Research Council Practitioner Fellowship.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Muller AM, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. Ann Hematol. 2005;84:1–12.
2. Tsang RW, Gospodarowicz MK. Radiation therapy for localized low-grade non-Hodgkin's lymphomas. Hematol Oncol. 2005;23:10–7.
3. Pugh TJ, Ballonoff A, Newman F, Rabinovitch R. Improved survival in patients with early stage low-grade follicular lymphoma treated with radiation: a surveillance, epidemiology, and end results database analysis. Cancer. 2010;116:3843–51.
4. Mac Manus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol. 1996;14:1282–90.
5. Guadagnolo BA, Li S, Neuberg D, Ng A, Hua L, Silver B, et al. Long-term outcome and mortality trends in early-stage, grade 1–2 follicular lymphoma treated with radiation therapy. Int J Radiat Oncol Biol Phys. 2006;64:928–34.
6. Campbell JK, Matthews JP, Seymour JF, Wolf MM, Juneja SK. Australasian Leukaemia lymphoma G. Optimum trephine length in the assessment of bone marrow involvement in patients with diffuse large cell lymphoma. Ann Oncol. 2003;14:273–6.
7. Jerusalem G, Beguin Y, Najjar F, Hustinx R, Fassotte MF, Rigo P, et al. Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) for the staging of low-grade non-Hodgkin's lymphoma (NHL). Ann Oncol. 2001;12:825–30.
8. Wirth A, Foo M, Seymour JF, Macmanus MP, Hicks RJ. Impact of [18f] fluorodeoxyglucose positron emission tomography on staging and management of early-stage follicular non-hodgkin lymphoma. Int J Radiat Oncol Biol Phys. 2008;71:213–9.
9. Specht L. 2-[18F]fluoro-2-deoxyglucose positron-emission tomography in staging, response evaluation, and treatment planning of lymphomas. Semin Radiat Oncol. 2007;17:190–7.
10. Sasaki M, Kuwabara Y, Koga H, Nakagawa M, Chen T, Kaneko K, et al. Clinical impact of whole body FDG-PET on the staging and therapeutic decision making for malignant lymphoma. Ann Nucl Med. 2002;16:337–45.
11. Schoder H, Meta J, Yap C, Ariannejad M, Rao J, Phelps ME, et al. Effect of whole-body (18)F-FDG PET imaging on clinical staging and management of patients with malignant lymphoma. J Nucl Med. 2001;42:1139–43.
12. Denham J, Denham E, Dear K, Hudson G. The follicular non-Hodgkin's lymphomas—I. The possibility of cure. Eur J Cancer. 1996;32:470–9.
13. Wilder RB, Jones D, Tucker SL, Fuller LM, Ha CS, McLaughlin P, et al. Long-term results with radiotherapy for stage I–II follicular lymphomas. Int J Radiat Oncol Biol Phys. 2001;51:1219–27.

14. Gospodarowicz MK, Bush RS, Brown TC, Chua T. Prognostic factors in nodular lymphomas: a multivariate analysis based on the Princess Margaret Hospital experience. Int J Radiat Oncol Biol Phys. 1984;10:489–97.
15. Pendlebury S, el Awadi M, Ashley S, Brada M, Horwich A. Radiotherapy results in early stage low grade nodal non-Hodgkin's lymphoma. Radiother Oncol. 1995;36:167–71.
16. Denham J, Denham E, Dear K, Hudson G. The follicular non-Hodgkin's lymphomas—II. Prognostic factors: what do they mean? Eur J Cancer. 1996;32:480–90.
17. Mac Manus MP, Bowie CAR, Hoppe RT. What is the prognosis for patients who relapse after primary radiation therapy for early-stage low-grade follicular lymphoma? Int J Radiat Oncol Biol Phys. 1998;42:365–71.
18. Bentur OS, Gurion R, Gafter-Gvili A, Gatt M, Shvidel L, Horowitz NA, et al. Treatment and prognosis of stage I follicular lymphoma in the modern era — does PET matter? Leuk Lymphoma. 2017;59(5):1163–71.
19. Ahmed N, Owen TE, Rubinger M, Williams G, Nugent Z, Ahmed S, et al. Early stage W.H.O. Grade I and II follicular lymphoma treated with radiation therapy alone. PLoS One. 2013;8:e65156.
20. Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Mueller SP, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on malignant lymphomas imaging working group. J Clin Oncol. 2014;32:3048–58.
21. Stumpe K, Urbinelli M, Steinert H, Glanzmann C, Buck A, Von Schulthess G. Whole-body positron emission tomography using fluorodeoxyglucose for staging of lymphoma: effectiveness and comparison with computed tomography. Eur J Nucl Med Mol Imaging. 1998;25:721–8.
22. Wöhrer S, Jaeger U, Kletter K, Becherer A, Hauswirth A, Turetschek K, et al. 18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG-PET) visualizes follicular lymphoma irrespective of grading. Ann Oncol. 2006;17:780–4.
23. Metser U, Dudebout J, Baetz T, Hodgson DC, Langer DL, MacCrostie P, et al. [18 F]-FDG PET/CT in the staging and management of indolent lymphoma: a prospective multicenter PET registry study. Cancer. 2017;123:2860–6.
24. Friedberg JW, Byrtek M, Link BK, Flowers C, Taylor M, Hainsworth J, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. J Clin Oncol. 2012;30(27):3368-75.
25. Hany TF, Steinert HC, Goerres GW, Buck A, von Schulthess GK. PET diagnostic accuracy: improvement with in-line PET-CT system: initial results. Radiology. 2002;225:575–81.
26. Martinez MJ, Bercier Y, Schwaiger M, Ziegler SI. PET/CT biograph sensation 16. Performance improvement using faster electronics. Nuklearmedizin. 2006;45:126–33.
27. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood. 2005;105:1417–23.
28. Fisher RI, LeBlanc M, Press OW, Maloney DG, Unger JM, Miller TP. New treatment options have changed the survival of patients with follicular lymphoma. J Clin Oncol: Off J Am Soc Clin Oncol. 2005;23:8447–52.
29. Janikova A, Bortlicek Z, Campr V, Kopalova N, Benesova K, Belada D, et al. Radiotherapy with rituximab may be better than radiotherapy alone in first-line treatment of early-stage follicular lymphoma: is it time to change the standard strategy? Leukemia Lymphoma. 2015;56:2350–6.
30. MacManus MPFR, Roos D, O'Brien P, Macann AMJ, Christie D, Tsang RW, et al. Treatment with 6 cycles of CVP or R-CVP after involved field radiation therapy (IFRT) significantly improves progression-free survival compared to IFRT alone in stage I-II low grade follicular lymphoma: results of an international randomized trial. Int J Radiat Oncol Biol Phys. 2016;96:938.