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**Primary central nervous system lymphoma in the elderly:
a multicentre retrospective analysis**

M. Schuurmans,⁽¹⁾ J.E.C. Bromberg,⁽¹⁾ J. Doorduijn,⁽²⁾ Ph. Poortmans,⁽³⁾ M.J.B. Taphoorn,⁽⁴⁾
T. Seute,⁽⁵⁾ R. Enting⁽⁶⁾ G. van Imhoff⁽⁷⁾ Y. van Norden,⁽⁸⁾ M.J. van den Bent.⁽¹⁾

ErasmusMC, Daniël den Hoed Cancer Center, Rotterdam, departments of Neuro-Oncology⁽¹⁾,
hematology⁽²⁾, and trials and statistics; ⁽⁸⁾ Bernard Verbeeten Institute for radiotherapy⁽³⁾; MC
Haaglanden, department of Neurology⁽⁴⁾; Utrecht University Medical Center department of
Neurology⁽⁵⁾; Groningen University Medical Center, departments of neurology⁽⁶⁾ and Hematology⁽⁷⁾

Running title: PCNSL in the elderly

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Corresponding author:

Jacoline E.C. Bromberg MD

Dept Neuro-Oncology

Daniel den Hoed Cancer Center / Erasmus University Medical Center

PO Box 5201

3008 AE Rotterdam

The Netherlands

Tel +31 10 7041415

Fax: +31 10 7041031

email: j.bromberg@erasmusmc.nl

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Summary

Elderly patients with primary CNS lymphoma (PCNSL) do not tolerate treatment with combined radio-chemotherapy well because of leuko-encephalopathy and are usually treated initially with chemotherapy or radiotherapy alone. Little is known about efficacy and toxicity of these treatments outside clinical studies.

Methods: retrospective analysis of all patients aged 60 or over admitted with PCNSL to one of 5 Dutch centers between 1998 and 2007.

Results: 74 patients were identified. 29 were treated with radiotherapy only (group A), in 36 intended treatment was chemotherapy alone (group B), in 9 intended treatment was chemotherapy followed by radiotherapy (group C). **Median OS was 20 months;.4 months in patients with KPS < 70, 25 months in patients with KPS ≥ 70 (p<0.001). Treatment modality was not an independent prognostic factor.** Forty patients were treated with MTX 3g/m²: there were 2 toxic deaths. Ten patients discontinued chemotherapy because of toxicity. Delayed encephalopathy was reported in 10 patients. *Conclusion:* Community hospitals still utilize **WBRT frequently in elderly PCNSL patients, though a majority tolerates chemotherapy well. Performance status was the most important variable determining prognosis. Short and long term toxicities must be weighed against possible clinical benefits of each treatment, making treatment decisions a highly individualized process.**

Key words: CNS lymphoma, radiotherapy, chemotherapy, age, performance status

For Peer Review

Introduction

Primary central system lymphoma (PCNSL) is a non-Hodgkin lymphoma that arises within the brain, spinal cord, cerebrospinal fluid or eyes in the absence of systemic disease. **Given the median age at diagnosis of 55-65 yrs, a large proportion of patients is over 60 and age has a profound influence on prognosis and treatment choices.**(Abrey *et al* 2006, Panageas *et al* 2007)

Radiotherapy alone has shown a disappointing median survival time of only 5-7 months in older patients, although one retrospective study describes a median survival of 12 months (Nelson *et al*, 1992, Laack *et al* 2006, Panageas *et al*, 2007, Shibamoto *et al* 2005).

Chemotherapeutic regimens with high-dose methotrexate (HD-MTX) based chemotherapy followed by whole brain radiotherapy (WBRT), have resulted in long term remissions and improved survival rates (De Angelis *et al*, 2002, Batchelor *et al*, 2006). **However, combined treatment results in delayed neurotoxicity in 24-83% of patients and is more common in patients aged >60 years** (Blay *et al*, 1998, Omuro *et al*, 2005, Wassenberg *et al*, 2001). The efficacy of chemotherapy used alone as initial treatment was reported to be at least comparable to that of RT alone in terms of survival benefit and compares favourably to combined treatment as well as radiotherapy alone in terms of delayed neurotoxicity (Ekenel *et al*, 2008, Hoang-Xuan *et al*, 2003). **However, inclusion biases in clinical studies have a great impact on the outcome, and these trials do not necessarily reflect the outcome of treatment in a more general, aselect population. One recently published population-based study showed that a majority of patients is still treated with radiotherapy alone and supports the notion that outcome in an aselect population may not be the same as**

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that in prospective clinical studies (Panageas *et al* 2007, Abrey *et al* 2006, Pels *et al* 2003).

Little is known about the **use or the relative efficacy and toxicity** of chemotherapy, radiotherapy and combined treatment in the elderly population outside of clinical trials.

Furthermore, the strategy of leaving out consolidation radiotherapy after brief, intensive chemotherapy in responsive patients has not been evaluated. We therefore studied the outcome of an unselected patient population with PCNSL over the age of 60.

Methods

In 5 large Dutch hospitals, 3 academic and 2 non-academic teaching hospitals, all patients aged 60 or above who were **HIV negative and** diagnosed with histologically proven non-EBV associated PCNSL from 1998-2007 were identified from the neuropathology, neuro-oncology and radiotherapy databases. Patient files for all these patients were reviewed; data on age, extent of disease, performance status, treatment modality, toxicity and survival were collected. As primary endpoint for efficacy overall survival was used. Late neurotoxicity or encephalopathy was diagnosed when both cognitive decline was reported and diffuse white matter lesions were shown on MRI. Survival data were calculated from the date of diagnosis to the date of documented progression **or additional treatment (event-free survival, EFS)** or death (overall survival, OS). A multivariate cox regression analysis was used to evaluate the prognostic value of age, performance status and type of treatment.

Results

Patient characteristics;

One hundred and eleven patients were identified who were diagnosed with PCNSL. **All patients were HIV-negative.** Thirty-seven patients were excluded from further analysis for the following reasons. Twenty-four patients were not treated because their condition had been considered to be too poor. Three patients had EBV positive lymphoma. In 5 patients the lymphoma was confined to the eyes. Since isolated ocular lymphoma may have a different prognosis from PCNSL in general we excluded these patients from the analysis. Five patients had been lost to follow up.

Seventy-four patients with confirmed PCNSL who received treatment remained for further analysis. In this group the median age was 65 (range 60-82) and the KPS 70 % (range 30-100). There were 34 women and 40 men. **Pathology was DLBCL in all patients.**

Treatment and outcome;

Patients were categorized into three groups according to the intended treatment: group A, radiotherapy only (n=29), group B, chemotherapy only (n=36) and group C, combined treatment (n=9). Of the 36 patients who had received chemotherapy only as the primary treatment, five had been treated with low-dose MTX (500 mg/m²). As this dose is to be considered inadequate because of insufficient CNS penetration, these patients were excluded from all further analyses so that 31 patients remained in group B. A flowchart of all patients is shown in figure 1. Clinical characteristics for the 3 treatment groups are shown in table 1. Response and survival data for the treatment groups are summarized in table 2. Overall survival (OS) as determined by age and performance status is shown in figure 3. The median

OS for treated patients was 21 months. Survival for the 24 patients who were not treated was 1 month, **their median age was 71 and their median KPS 50.** (data not shown).

The 29 patients in group A, treated with whole brain radiotherapy only, received a median dose of 32 Gy (range 18-50 Gy). Median OS in this group was 7 months. **For a large proportion of patients in group A no date of progression was available so that EFS could not be reliably calculated.** The the 1-year OS was 41 %.

All nine patients in group C, intended to be treated by chemotherapy followed by radiotherapy had been treated with the combined MBVP scheme (MTX 3 g/m², dexamethasone, BCNU and teniposide) followed by 40 Gy WBRT. (Poortmans *et al*, 2003) **Seven of them were also treated intrathecally according to protocol.** In this group PFS and OS at 1 year were 100%.

Of the 31 patients in group B, who had been intended to be treated with chemotherapy only, 24 had also been treated with the combined MBVP scheme. The 7 other patients had received HD-MTX monotherapy: six of them received 3 g/m², one received 1.5 g/m². **All except seven patients in group B were also treated intrathecally.** Sixteen of the 31 patients in group B were additionally treated with radiotherapy after completion or abortion of chemotherapy because of toxicity (n=7), insufficient response (n=5), or recurrence (n=3). In the other 15 patients MTX-based chemotherapy was the only treatment given. In some cases this was because no progression was observed, in others because no further treatment was regarded feasible by the treating physician. In group B as a whole the **EFS** was 3 months and the OS 23 months. The 1-year survival rate was 56 %. OS of the 15 patients treated with chemotherapy who were never irradiated ranged from 1-66 months with a median of 13 months.

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6 On multivariate analysis there was no difference in **overall survival** between the treatment
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8 groups A, B and C: relative Hazard Ratio (HR) 0.9, 95% confidence interval (CI) 0.58-1.4.

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10 Performance status and age did correlate with survival: for performance status the relative HR
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12 was 0.33, 95% CI 0.17-0.64, $p = 0.001$, (figure 2). For age the relative HR was 2.33, 95% CI
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14 1.18 – 4.59, $p = 0.01$.

15 16 17 18 19 20 *Toxicity:*

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22 Of the 40 patients receiving HD-MTX, 12 suffered complications. Two fatal toxicities
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24 occurred in the chemotherapy treated patients: one patient died from neutropenic sepsis, the
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26 other developed fatal toxic epidermolysis. In 10 other patients (25%) chemotherapy was
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28 discontinued because of toxicity (nephrotoxicity, pulmonary toxicity or haematological
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30 toxicity), in all these cases only one cycle was given. Two of these patients received no
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32 further treatment, the other 8 received radiotherapy; this was pre-planned in one of them.

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39 Late neurotoxicity was documented in 10 patients (13.5%) after a median of 17.5 months
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41 (range 6 -50). Four of these patients **were in group A three in group B (two salvaged with**
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43 **radiotherapy) and three in group C. Median follow-up in all surviving patients was 20.4**
44
45 **months; in group A 13.5, group B 19.8 and group C 37.3 months.** The incidence of
46
47 encephalopathy increased with survival time: two years after diagnosis 30 % of surviving
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49 patients had documented encephalopathy and after 3 years encephalopathy was found in 70%.

50 51 52 53 54 55 *Cause of death*

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57 **Fifty-two patients (75%) died, 24/29 in group A, 24/31 in group B and 4/9 in group C.**

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59 **Cause of death was disease progression in 35 (67%); (18 in group A, 15 in B of which two**
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3 had systemic recurrence, and two in C), infections in seven (13%; (two in A, three in B
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5 and two in C), and other causes in 10 (19%; (four in A, six in B).
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10 11 12 Discussion

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17 Older patients, aged > 60, account for approximately half the cases of PCNSL. Age has long
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19 been recognized as an important prognostic factor in PCNSL and profoundly influences
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21 treatment choices in routine clinical practice. **Recent phase II studies have emphasized the**
22
23 **role of chemotherapy, but as a rule phase II studies are biased by patient selection. In**
24
25 **our study of unselected older patients in academic and teaching hospitals we found that**
26
27 **42% of patients was treated with radiotherapy only, 45% was initially treated with**
28
29 **chemotherapy alone and 9/69 (13%) with combined treatment from the outset. This is**
30
31 **similar to results of a published population-based survey, and shows that monotherapy**
32
33 **with WBRT is still common practice outside clinical trials. (Panageas *et al* 2007)**
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38 **However, in the data of Panageas et al no correlation could be made with clinical factors**
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40 **as it was based on the SEER and Medicare registrations only. In our study median age**
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42 **was higher in patients treated with radiotherapy only (group A) than in the other two**
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44 **groups (70 vs 63 yrs) and performance status was better in the group treated with**
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46 **combination therapy (group C), with a median KPS 80 compared with median KPS 70**
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48 **in the other groups, showing that indeed age and performance status played a role in**
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50 **treatment decisions.**

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57 We found that outcome was influenced most by performance status. Median survival
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59 was 25 months in patients with a KPS \geq 70 and 4 months in patients with a KPS <70
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3 (relative HR 0.33, 95% CI 0.17-0.64, p = 0.001). Age had less influence (relative HR 2.33,
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5 95% CI 1.18 – 4.59, p = 0.01) in this population of patients aged over 60. Although
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7 treatment modality was not an independent risk factor, as stated, prognostic factors were not
8
9 balanced between the groups. Age and performance status are the two variables that have
10
11 been consistently identified as independent prognostic factors in several studies (Abrey *et al*,
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13 2006, Ferreri *et al*, 2003, Pels *et al* 2003). **In daily practice these factors are used to**
14
15 **determine treatment choices. Their prognostic value seems to hold true across the**
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17 **various treatments although the worse prognosis we found in patients with poor**
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19 **performance status may in part have been determined by treatment choices. Whether**
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21 **patients, in whom poor performance status was determined by the neurological effects**
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23 **of the disease rather than by comorbidity, would do better had they been treated more**
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25 **intensively is still an unanswered question.**
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34 Response to treatment (table 2) was similar in both single modality treatment groups, but EFS
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36 was disappointingly short in group B, intended to be treated with chemotherapy only. In
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38 7/31 patients in group B WBRT was given after abortion of chemotherapy due to
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40 toxicity. Although this does not necessarily mean the chemotherapy was ineffective it
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42 does denote failure of the chemotherapy-only strategy and was therefore included as
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44 failure in the EFS analysis. Contrary to some centres in other countries, in the
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46 Netherlands salvage chemotherapy for primary CNS lymphoma is rarely given so that
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48 16/31 patients in group B were ultimately irradiated. Nevertheless, even among patients
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50 who never received radiotherapy median OS was 23 months with survival ranging up to
51
52 66 months. Despite the short EFS, the median OS of 23 months is comparable to
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54 published results of prospective studies of chemotherapy-only regimens in older patients
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56 in whom median survival has ranged between 14 and 34 months.(Hoang-Xuan *et al*
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3 **2003, Illerhaus *et al* 2009, Omuro *et al* 2007, Pels *et al* 2003) However, in these studies**
4 **salvage WBRT was either utilized less frequently than in our patients or not reported.**

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7 **Although the short EFS in our group B** is indicative of limited long-term efficacy of
8 MBVP chemotherapy alone in the group as a whole, a minority of patients is able to attain
9 long survival with MBVP chemotherapy only. This suggests that a subset of elderly patients
10 has an extremely chemotherapy-sensitive PCNSL; a phenomenon that was also found by
11 others (Pels *et al*, 2003, Omuro *et al*, 2007) Nonetheless, for only a small number of patients
12 in our population chemotherapy alone sufficed: most patients relapsed or progressed and
13 clearly more effective chemotherapy **or effective maintenance chemotherapy** is needed.
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27 In group A (radiotherapy only) median OS was 7 months. This is comparable to **results in**
28 **most (Nelson *et al*, 1992, Laack *et al* 2006, Panageas *et al*, 2007) but not all published**
29 **studies. (Shibamoto *et al* 2005) The first three are prospective phase II or population-**
30 **based studies, the last was a multicentre retrospective study without details on treated**
31 **patients not included in the study. Thus inclusion and recall biases may have played a**
32 **role in the differing survival data.**
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43 Patients in group C (predetermined combined treatment) did especially well in our study. It
44 must be born in mind, however, that both age and performance status were more favourable in
45 group C than in the other groups, **suggestive of patient selection.** Although the small number
46 of patients in this group and the retrospective nature of the study preclude definitive
47 conclusions, OS in group B, in which many patients were treated with radiotherapy after
48 failure of chemotherapy, also appeared superior to that in group A. This suggests that
49 combined treatment, even when there is a time interval between chemotherapy and
50 radiotherapy, may be more efficacious than either single modality alone. In prior studies
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3 salvage radiotherapy after failure of primary treatment with chemotherapy alone was also
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5 found to be effective.(Nguyen *et al*, 2005, Hottinger *et al*, 2007)
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10 The acute chemotherapy toxicity was generally acceptable. Most patients (75%) received HD-
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12 MTX treatment without major problems. In 10 patients the toxicity was reason for
13
14 discontinuation of chemotherapy. Myelosuppression was the most frequent side effect of the
15
16 treatment and occurred mainly during the first cycle. Other acute side effects of MTX-based
17
18 chemotherapy that were reported in our patient group consisted of renal dysfunction and
19
20 pulmonary toxicity. The toxicity data are, however, slightly higher than those reported in the
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22 younger population in which severe toxicity is reported in about 5-10% (Jahnke *et al*, 2005).
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25 Despite the common perception that high-dose MTX is too toxic for the elderly, our data
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27 confirm the observations of others (Jahnke *et al*, 2005, Illerhaus *et al*, 2009, Ng *et al*, 2000)
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29 that the majority of older patients can tolerate high-dose MTX, provided their renal function
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31 is adequate.
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39 In our population neurocognitive testing was not routinely performed. Nevertheless clinically
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41 relevant encephalopathy was reported in 10 patients. Nine of them had been treated with
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43 radiotherapy, 5 with both chemotherapy and radiotherapy; among them 3 of the 8 patients
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45 from group C who survived more than 1 year. The incidence of encephalopathy increased
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47 with survival time: two years after diagnosis 30 % of surviving patients were found to suffer
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49 from neurotoxicity, after 3 years this had increased to 70 % of surviving patients. This is
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51 compatible with previously published data (Omuro *et al*, 2005, Blay *et al*, 1998, Wassenberg
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53 *et al*, 2001) and underscores the necessity of avoiding radiotherapy in elderly patients if
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55 possible.
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3 In conclusion, **treatment of elderly patients outside clinical trials is varied and WBRT**
4 **alone is still utilized frequently. Although our chemotherapy-only results obtained in a**
5 **community hospital setting appear somewhat inferior to those obtained in published**
6 **prospective studies they do support tolerability of HD-MTX-based regimens in selected**
7 **elderly patients.** Performance status seems to be the most important prognostic factor for
8 outcome and should be used **in combination with comorbidities** to tailor treatment to the
9 individual patient. Radiotherapy should be reserved for refractory disease, considering the
10 high rate of neurotoxicity, and for patients not fit for chemotherapy. However, only a
11 minority of patients in our population was able to attain long term survival with MTX-based
12 chemotherapy without additional radiotherapy. More effective chemotherapy regimens are
13 needed to further postpone radiotherapy and to increase overall survival. **Randomized**
14 **multicentre studies are needed to define optimal treatment for this patient population.**
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3 **Legends**
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8 **Figure 1.** Description of patients with PCNSL identified
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22 **Figure 2.** Overall Survival by Performance Status
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27 Legend: A = KPS < 70%; B = KPS ≥ 70%
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Table 1. clinical and treatment characteristics

	A	B	C	Total
Total	29	31	9	69
Age median	70	63	62	65
KPS median	70	70	80	70
N age < 70	14	27	9	50
N age ≥ 70	15	4	0	19
N KPS < 70	13	11	0	24
N KPS ≥ 70	16	20	9	45

group A = radiotherapy only, group B = by intention chemotherapy only, group C = by intention chemotherapy + radiotherapy

Table 2. survival and response

	Response (CR + PR)	Median PFS* (range)	Median OS* (range)	12 months OS
Group A (n=29)	69 %	NA	7 (1-64)	41 %
Group B (n=31)	71 %	3 (2-66)	23 (2-66)	56 %
Group C (n=9)	100 %	NR (18-80)	NR (22-80)	100 %
Total (n=69)	74 %	7 (1-80)	21 (1-80)	56 %

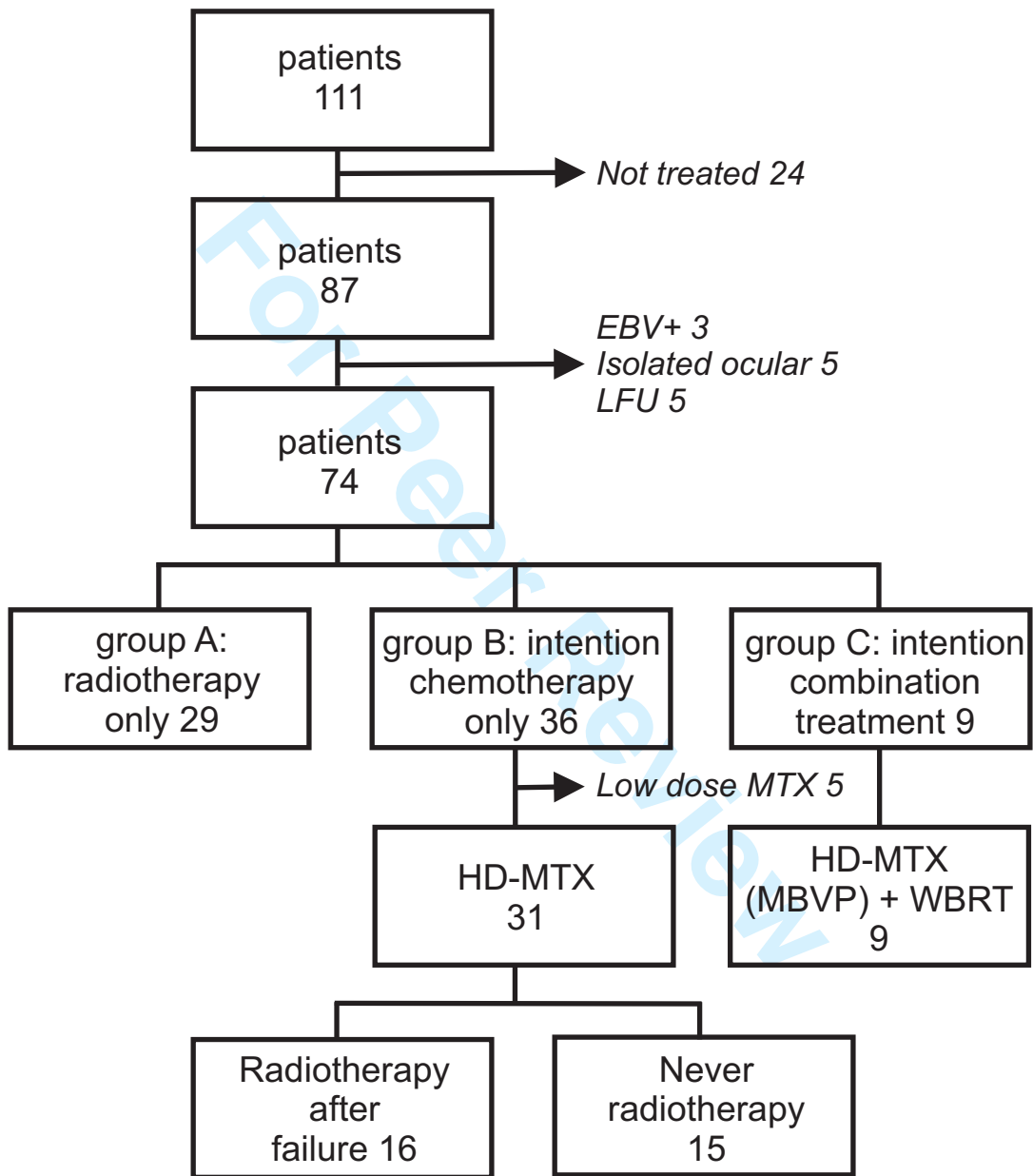
group A = radiotherapy only, group B = by intention chemotherapy only, group C = by intention chemotherapy + radiotherapy

*** OS and PFS in months**

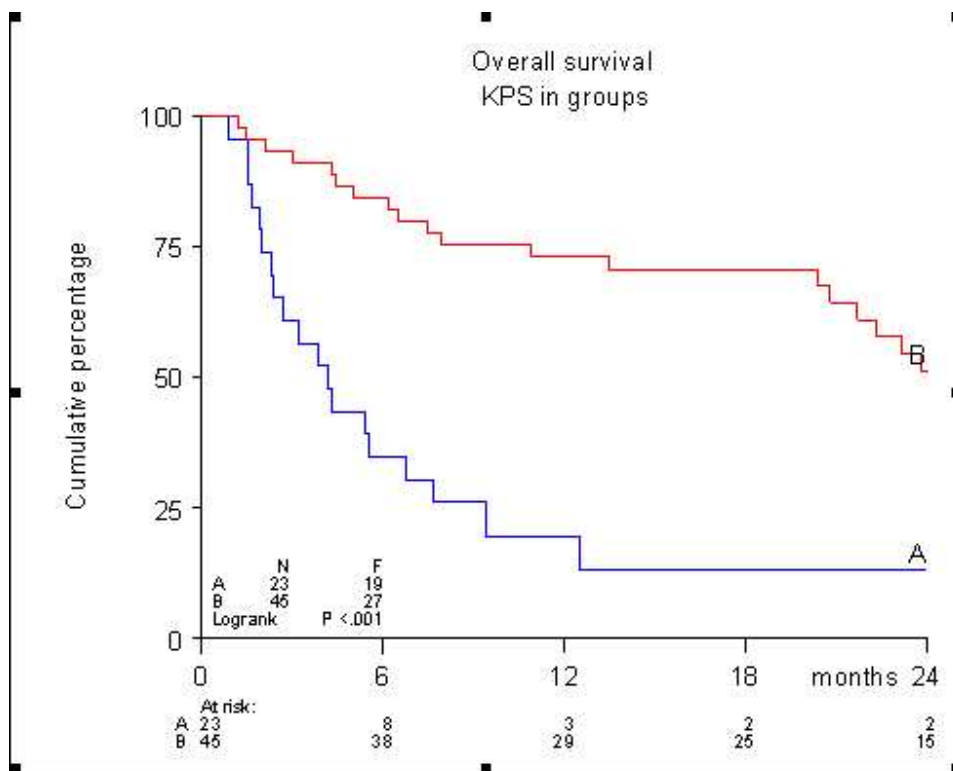
NA = not available

NR = not reached after median follow-up of 37.3 months

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