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Early Stage Primary Bone Lymphoma: a retrospective, multicenter Rare Cancer Network (RCN) study

THESE

préparée sous la direction du Professeur René-Olivier Mirimanoff

(avec la collaboration du Professeur Associé Mahamut Ozashin)

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par

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Early Stage Primary Bone Lymphoma: a retrospective, multicenter Rare Cance Network (RCN) study

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Résumé

Le lymphome Primaire Osseux de Stade Précoce: une étude retrospective multicentrique du Réseau des Cancers Rares (Rare Cancer Network, RCN)

Introduction

Le lymphome primaire de l'os (LPO) représente moins de 1% de tous les lymphomes malins. Dans cette étude, nous avons évalué le profil de la maladie, les résultats thérapeutiques, et les facteurs pronostiques d'une série consécutive de patients atteints de LPO de stade I et II.

Matériel et méthode

Dans treize institutions du Réseau des Cancers Rares (Rare Cancer Network), 116 patients ont été traités pour un LPO entre 1987 et 2008, et sont l'objet de cette étude rétrospective. Quatre-vingt-sept patients ont subi une chimioradiothérapie (CXRT) sans (78), ou avec (9) une chirurgie, 15 ont bénéficié de radiothérapie (RT) sans (13), ou avec (2) chirurgie, 14 d'une chimiothérapie (CXT) sans (9), ou avec (5) chirurgie. La dose médiane de RT était de 40 Gy (4-60). Le nombre médian de cycles de CXT était de 6 (2-8). Le suivi médian était de 41 mois (6-242).

Résultats

Le taux de réponse global à la fin du traitement était de 91% (74% de réponses complètes et 17% de réponses partielles). Une récidive locale ou une progression ont été observées chez 12 (10%) patients et une récidive systémique chez 17 (15%) patients. La survie globale, la survie spécifique, et le contrôle local à 5 ans ont été de 76%, 78% et 92%, respectivement. En analyse univariée (log-rank test), les facteurs pronostiques favorables pour la survie globale et la survie spécifique étaient: un

indice pronostique international (IPI) inférieur ou égale à 1 (P = 0.009), un grade histologique élevé (P = 0.04), une CXRT (P = 0.05), une CXT (P = 0.0004), une réponse complète (P <0.0001), et une dose de supérieure à 40 Gy (p = 0.005). Concernant le contrôle local, seules la rémission complète et stade I ont été des facteurs favorables. En analyse multivariée, le score IPI, la dose de RT, la rémission complète, et la CXT ont influencé le résultat de façon indépendante en ce qui concerne la survie globale et la survie spécifique. La rémission complète a été le seul facteur prédictif pour le contrôle local.

Conclusion

Cette étude multicentrique rétrospective confirme le bon pronostic du LPO de stade précoce traité par une combinaison de chimio-radiothérapie. Une dose de suffisant de radiothérapie et un nombre adéquat de cycles de chimiothérapie ont été suivis des résultats les plus favorables.

Early Stage Primary Bone Lymphoma: a retrospective, multicenter Rare Cancer Network (RCN) study

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ABSTRACT

Purpose

Primary bone lymphoma (PBL) represents less than 1% of all malignant lymphomas. In this study, we assessed the disease profile, outcome, and prognostic factors in patients with stage I and II PBL.

Patients and methods

Thirteen Rare Cancer Network (RCN) institutions enrolled 116 consecutive patients with PBL treated between 1987 and 2008 in this study. Eighty-seven patients underwent chemoradiotherapy (CXRT) without (78) or with (9) surgery, 15 radiotherapy (RT) without (13) or with (2) surgery, 14 chemotherapy (CXT) without (9) or with (5) surgery. Median RT dose was 40 Gy (range: 4-60). The median number of CXT cycles was 6 (range: 2-8). Median follow-up was 41 months (range: 6-242).

Results

The overall response rate at the end of treatment was 91% (CR 74%, PR 17%). Local recurrence or progression was observed in 12 (10%) patients and systemic recurrence in 17 (15%). The 5-year overall survival (OS), lymphoma-specific survival (LSS), and local control (LC) were 76%, 78% and 92%, respectively. In univariate analyses (log-rank test), favorable prognostic factors for OS and LSS were International Prognostic Index (IPI) score ≤1 (P=0.009), high grade histology (P=0.04), CXRT (P=0.05), CXT (P=0.0004), CR (P<0.0001), and RT dose > 40 Gy (P=0.005). For LC, only CR and stage I were favorable factors. In multivariate

analysis, IPI score, RT dose, CR, and CXT were independently influencing the outcome (OS and LSS). CR was the only predicting factor for LC.

Conclusion

This large multicenter retrospective study confirms the good prognosis of early stage PBL treated with combined CXRT. An adequate dose of RT and complete CXT regime were associated with better outcome.

Keywords: Primary bone lymphoma, early stage, radiotherapy, combined treatment modality

INTRODUCTION

Primary bone lymphoma (PBL), either in adults or children [1], is a rare presentation of non-Hodgkin's lymphoma, accounting for less than 1% of all malignant lymphomas, for about 5% of all primary malignant bone tumors, and for 4-5% of all extranodal non-Hodgkin's lymphomas (NHL) [2-4]. PBL was first described as a distinct clinical entity by Parker and Jackson in 1939 [5], and defined in the 2002 World Health Organization (WHO) classification of tumors of soft tissue and bone, as a single skeletal tumor with, or without regional lymph node involvement, or multiple bone lesions, without visceral or lymph node involvement [6] .

Almost 90% of PBL patients present with diffuse large B-cell lymphoma histological subtype, which may have a better prognosis than that of the less common T-cell lymphoma subtype [7-9]. The most commonly affected parts of the skeleton are within the metaphysis and diaphysis of the long bones [10]. The clinical characteristics are non-specific, making a proper diagnosis difficult at the outset. Pain, swelling and pathologic fractures are the most common presenting symptoms.

Local radiotherapy (RT) was established as the standard treatment in the 1960's with a local relapse rate of around 10-20%, but with a distant relapse rate of about 50% and a 5-year survival rate ranging between 55-65% [11-13]. The 5-year survival rate has been improved to about 70-90% with the addition of chemoradiotherapy (CXRT) in early stage disease [11, 14-17].

The role of RT was recently challenged [18, 19], as chemotherapy alone appeared to be quite effective, especially with the development of new agents such as rituximab. The purpose of our Rare Cancer Network (RCN: http//www.rarecancer.net) study was to collect substantial information from a large number of patients to more properly define the disease profile, therapeutic approach, outcome and prognostic factors of this disease.

PATIENTS AND METHODS

Patients

We collected 116 eligible patients from a total of 136 cases of PBL treated between 1987 and 2008 in 13 institutions of the RCN. Inclusion criteria included: age > 16 yrs, confirmed pathological diagnosis of bone involvement, stages I and II according to the Ann Arbor staging system [20], and a minimum of 6 months follow-up after treatment. After a review of all clinical and pathological records, 20 cases were excluded from the analysis due to disseminated disease (12 cases) and multiple bone involvement (8 cases). All the medical records were reviewed for age, gender, symptoms, physical examination, laboratory examination, imaging, pathological diagnosis, involved sites, stage, International Prognostic Index (IPI) [21], treatment modality, response, site of relapse, treatment-related complications, time to death, and date of last follow-up. In this study, all investigators obtained their own Institutional Review Board approval for patients' data collection.

All pathology reports were reviewed and "translated" into the WHO classification.

The work-up of individual patients included medical history, physical examination, complete blood count, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), complete metabolic profile, bone marrow biopsy and plain bone X-ray in all patients. Bone computed tomography (CT), magnetic resonance imaging (MRI), positron-emission tomography (PET), or whole body CT scan were performed according to each institution's policy. Stage was established with the Ann Arbor staging system. Single localized bone lesions were classified as stage IE, and in case of lymph node involvement on the same side of the diaphragm, patients were considered to have stage IIE. IPI score was established based on the medical records.

Patients were treated according to each hospital's local policy. The modality of treatment included chemotherapy, RT, surgical resection or a combination of these. Most patients had a biopsy only (100), however, 16 underwent surgery: 13 had some form of local excision or curettage, 2 had a laminectomy with partial excision, and 1 had a total hip replacement.

Response was evaluated according to lymphoma-adapted RECIST [22, 23] (Response Evaluation Criteria in Solid Tumors). Early and late treatment toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) V3.0 [24].

Statistical methods

Overall survival (OS) was calculated from the date of diagnosis to the date of last

follow-up or death from any cause. Lymphoma-specific survival (LSS) was calculated from the date of diagnosis to the date of lymphoma-related death. Local control (LC) was calculated from the date of diagnosis to the date of local recurrence. Survival curves were constructed using the Kaplan-Meier method, differences were considered significant if the P value was ≤ 0.05 (two tailed Log-rank test). Multivariate analysis (Cox model) was used to determine the independent prognostic factors. All prognostic factors identified in the univariate analyses with P value < 0.20 were included in the multivariate analyses.

RESULTS

Patient and treatment characteristics are presented in Table 1.

Median age was 51 years (range 17-93 years), and there were 69 males (59%) and 47 females (41%).

Majority of patients (75%) received combined CXRT. Treatment sequences were chemotherapy followed by radiotherapy (CT-RT) in 64%, radiotherapy followed by chemotherapy (RT-CT) in 8%, and concomitant CXRT in 3%. Eighty-eight percent received chemotherapy (CXT) in combination or alone. Of these, 68% were treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy, and 32% with rituximab plus CHOP (R-CHOP) chemotherapy.

Response to treatment was evaluated in all patients. After initial therapy, 74% patients had a complete remission (CR), 20% partial remission (PR), 1% stable

disease (SD), and 5% progressive disease (PD). One patient who experienced progressive disease, died during salvage treatment. Among patients achieving a CR, 81% were treated with combined CXRT, 10% with RT alone, and 9% with CXT alone.

The 5- and 10- year LC probability was 92% (95% CI: 86-98) and 80% (95% CI: 68-92), respectively. Local failure was observed in 10% of the patients. Of the 74% patients with CR, 6% had a local relapse, whereas of the 20% of patients who were in PR, 30% presented a further local progression (P=0.008).

Of the patients who received an RT dose of less than 40 Gy, 12% recurred locally, versus 8% of those receiving more than 40 Gy (P=0.75). In the patients with local failure, 50% occurred within the planning target volume and 50% outside .

Distant progression was observed in 15% of the patients after a median time of 7 months (range 2-72). Thirteen (13%) of the 101 patients who received chemotherapy suffered from systemic failure versus 4 (27%) of the 15 patients who did not (P=0.23). Thirteen percent of the 67 patients treated with more than 6 cycles of chemotherapy developed systemic progression, versus 16% of the 49 patients treated with fewer than 6 cycles (P=0.79).

With a median follow-up of 41 months (range 6-242 months), 63% patients were alive without evidence of disease, 12% were alive with disease, 19% patients died of lymphoma, and 6% patients died from other causes: 5 from unrelated disease, one from lung cancer, one from tonsil cancer. Overall, the 5- and 10-year OS was 76% (95% CI: 67-84) and 72% (95% CI: 61-84), respectively. The 5- and 10-year

LSS probability was 78% (95% CI: 70-86) and 78% (95%CI: 70-86), respectively.

On univariate analyses, statistically significant factors favorably influencing OS were patient age (< 50 years), IPI score 0 or 1 (Figure 1A), RT dose (> 40 Gy) (Figure 1B), high histological grade subtype, combined CXRT, CXT for more than 6 cycles (Figure 1C), and CR (Figure 1D) at the end of treatment. For LSS, the above-mentioned parameters (Figure 2A-C), except for age and number of chemotherapy cycles, were also favorable factors. RT and stage I were favorable factors with regard to LC (Figure 2D) (Table 2).

After multivariate analysis, the remaining independent prognostic factors for OS and LSS were IPI score < 2, RT dose > 40 Gy, CR, and administration of chemotherapy. For LC, CR at completion of treatment remained the only independent prognostic factor (Table 3).

Grade 1-3 leukopenia was observed in 13% patients, grade 1 lymphocytopenia in 2%, grade 1 thrombocytopenia in 2%. Grade 5 leukopenia occurred in 1% of patients after salvage chemotherapy. Late side effects were rare: grade 1 toxicity in 3% patients (edema in 3 and pain in 1), grade 2 toxicity in 2% patients (myositis in 1 and osteonecrosis in 1), grade 3 toxicity in 3% patients (joint-effusion in 1, osteonecrosis in 1 and pain in 2), grade 4 osteonecrosis in 1%. The latter patient died of a secondary lung cancer.

DISCUSSION

To our knowledge, the current study from 13 institutions of the RCN is the second largest report on early stage PBL.

It has demonstrated relatively similar patient characteristics compared to other published series. A male predominance (male to female: 1.43:1) was found, and median age was 51 years, compared to 30-60 years in other series. Pain was the most common presenting symptom, followed by a mass or swelling. The most common sites of pathological fracture were usually located in the long bones, similar to other reports [7, 25]. Like in other reports [26], most of our patients presented with Stage IE (ratio between Stage IE and IIE: 4:1).

The overall outcome of patients in this study (5-year OS of 76%, LSS of 78%) was similar to that found in the literature (5-year OS ranging between 70-90%) [11, 14-17, 27].

Univariate analysis for OS in our study revealed that younger age (< 50 years) predicted a better outcome, as reported in other series [11, 26]. Normal LDH level was considered to be a favorable prognostic factor in the report of Beal et al [11], but in our series we could not confirm this observation. Patients with IPI scores 0-1 had a markedly better outcome compared to those with an IPI score 2-4, as previously found by Ramadan et al [4], but not by Alencar et al [27]. In contrast to the study of Ostrowski et al [13] and Horsman et al [26], high grade histology was slightly beneficial compared to low grade histology for OS and LSS. Previously published papers utilizing SEER database analysis [28] have reported that patients with local disease had a better survival than those with extensive disease. However, we could not find a significant difference in 5-year OS and LSS between stage I and II (78% vs. 67%, P=0.19), which confirms the findings seen in previous series [4,

17]. This might be explained by patient selection. Soft tissue involvement was observed in 41% of the patients, and patients with extra-osseous involvement did not show a significantly worse outcome in 5-year OS, compared to those without extra-osseous involvement (62% vs. 85%, P=0.12). According to some authors, soft tissue involvement may just reflect an inflammatory process and not real tumor infiltration [29-31].

RT was established in the 1960's as the treatment of choice with a high local control rate and overall cure rates ranging from 44-63% [11, 27]. However, the role of RT alone was challenged over recent years, due to the 50% systemic progression rate [11, 30] . Barbieri et al reported that an RT dose of 40 Gy with a limited RT volume in combination with CXT seemed to be adequate for local control [17]. Our study addressed the issue of RT dose and volume. Radiation of the entire bone did not yield a superior outcome compared to partial bone radiation (62% vs. 70%, P=0.88). However, both univariate and multivariate analyse showed that RT dose > 40 Gy was associated with a significantly better 5-year OS and LSS than ≤ 40Gy (95% vs. 66%, P=0.0054, and 95% vs. 69%, respectively) and a non-significant trend towards a better local control (96% vs. 89%, P=0.32).

CXRT already demonstrated its superiority compared to single therapeutic approaches with 5-year OS between 60-90% in recent studies [11, 16, 31-33]. Interestingly, Alencar et al [27] recently reported no benefit with CXRT. Although there is no consensus regarding the optimal timing between either RT or chemotherapy, chemotherapy followed by RT was suggested to be the standard

approach [34].

With the advent of highly effective chemotherapy, the role of RT has been questioned by some authors. In advanced-stage disease, Ramadan et al found that patients who received chemotherapy and RT had a worse outcome compared to those who received chemotherapy alone [4]. In the SWOG 8736 study update which was on non-PBL lymphoma, there was no difference between CXRT and chemotherapy alone [18, 19]. Similar results were reported in some studies [11, 35, 36], and also in a report on children [37]. Rituximab is now used in association with CHOP or a CHOP-like regimen in the treatment of lymphoma, and studies have demonstrated its positive impact on survival [38]. In our series, the proportion of patients treated with R-CHOP was lower (3:7) than with CHOP alone, and we could not find any significant differences in survival between the two regimens.

Acute side effects were moderate. Leukopenia was the most common early toxicity following chemotherapy. The only reported late toxicity cases involved a limited occurrence of osteonecrosis.

In conclusion, early stage PBL has a fairly good prognosis. Local control is excellent, and systemic failure occurs infrequently. Young age (< 50) and a good IPI score (< 2) were positive prognostic factors at diagnosis. The role of chemotherapy is central in the treatment of PBL. Chemotherapy followed by RT is superior for OS and LSS to a sequence of radiotherapy followed by chemotherapy. Although chemotherapy was superior to radiotherapy alone, radiotherapy still plays a role in local control. An RT dose of more than 40 Gy, and more than 6 chemotherapy

cycles are associated with a better outcome. Although our results need to be interpreted with caution because of a relatively limited follow up (41 months) and its retrospective nature, we feel that our findings are important, especially because it is unlikely that a prospective study will be done, given how rare this cancer is.

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Figure legends

Figure 1. Univariate analyses for prognostic factors on overall survival (OS).

a) OS according to international prognostic index (IPI) score; IPI 0,1 improved survival compared with IPI ≥ 2 (P=0.009).

b) OS according to radiotherapy (RT) dose; RT dose > 40 Gy improved survival compared with RT dose ≤ 40 Gy (P=0.0054).

c) OS according to chemotherapy (CXT) cycles; CXT cycles ≥ 6 improved survival compared with CXT cycles <6 (P=0.01).

d) OS according to response rate; patients with complete response (CR) improved survival compared with those without CR (P<0.0001).

Figure 2. Univariate analyses for prognostic factors on lymphoma-specific survival (LSS) and local control (LC).

a) LSS according to radiotherapy (RT) dose; RT dose > 40 Gy improved LSS compared with RT dose ≤ 40 Gy (P=0.02).

b) LSS according to chemoradiotherapy (CXRT); patients with CXRT improved LSS compared with those without CXRT (P=0.01).

c) LSS according to response rate; patients with complete response (CR) improved LSS compared with those without CR (P<0.0001).

d) LC according to response rate; patients with complete response (CR) improved LC compared with those without CR.

Table1. Clinical and treatment characteristics of patients

Parameter	Patients (N)	%
Clinical characteristics		
Median age (50)		
≦ 50	63	54
> 50	53	46
Gender		
M	69	59
F	47	41
Histology subtype		
Diffuse large B cell	91	78
Follicular B cell	7	6
Anaplastic large cell	6	5
Other	12	11
Histological grade		
High	100	86
Intermediate	7	6
Low	9	8
Stage		
Stage IE	93	80
Stage IIE	23	20
Initial symptoms		
Pain	106	91
Mass/swelling	46	40
Neurological symptoms	28	24
Pathological fracture	20	17
B symptoms	20	17
LDH level		
Normal	70	60
High	30	26
Not done	16	14
Site involved		
Spine	33	28
Pelvis	23	20
Femur	16	14
Face bone	15	13
Humerus	12	10
Other sites	17	15
IPI score		
≤1	81	70
>2	35	30
Treatment characteristics		
Combined treatment and sequence		
CTRT	74	64
RTCT	9	8
Concomitant CXRT	4	3
CXT alone	14	12
RT alone	15	13
Chemotherapy regimens		
R-CHOP	32	28
CHOP or CHOP-like	69	60
No CXT	15	12
Treatment modality with surgery		
Yes	16	14
No	100	86

Abbreviations: LDH=lactate dehydrogenase; IPI=international prognostic index; CT-RT=chemotherapy followed by radiotherapy; RT-CT=radiotherapy followed by chemotherapy; CXRT=combined chemoradiotherapy; CXT=chemotherapy; RT=radiotherapy; CHOP=cyclophosphamide,doxorubicin, vincristine, and prednisone ; R-CHOP=rituximab with CHOP

Table 2. Univariate analyses (Log-Rank test)

Variable	N	5-y OS (%)	95% CI	P	5-y LSS (%)	95% CI	P	5-y LC(%)	95% CI	P
All patients	116	76	67-85		78	70-86		92	86-98	
Age										
<50	57	86	76-96	0.008	86	76-96	0.09	94	87-101	0.99
≧50	59	67	53-81		71	58-84		90	81-99	
Gender										
Female	47	72	58-86	0.18	74	60-88	0.10	93	85-101	0.38
Male	69	79	67-91		81	70-92		91	84-98	
IPI score										
≥2	34	59	40-78	0.009	64	46-82	0.02	93	83-103	0.62
<2	82	84	75-93		85	76-94		91	84-98	
Histological grade										
high	100	78	69-87	0.04	80	71-89	0.05	92	86-98	0.26
M/L	16	64	38-90		64	38-90		90	73-107	
Clinical symptoms										
B symptoms										
Yes	20	62	36-88	0.22	62	36-88	0.13	92	76-108	0.38
No	96	78	69-88		81	72-90		92	86-98	
Pathological fracture										

Yes	20	76	54-98	0.94	85	79-101	0.76	94	83-105	0.94
No	96	76	66-86		77	67-87		91	85-97	
LDH level										
High	30	93	83-103	0.10	93	83-103	0.17	83	68-98	0.10
Normal	70	72	60-84		75	64-86		93	86-100	
ND	16	72	48-96		72	48-96		100	100	
Extra-osseous involvement										
Yes	48	62	46-78	0.12	68	52-84	0.06	93	85-101	0.81
No	68	85	76-94		85	76-94		91	83-99	
Stage (Ann Arbor)										
IE	93	78	69-88	0.19	81	72-90	0.13	92	86-98	0.04
IIE	23	67	43-91		67	43-91		90	77-103	
Treatment modality										
CXRT	87	79	69-89	0.001	81	72-90	<0.001	93	87-99	0.13
CXT	14	92	78-106		92	78-106		77	54-100	
RT	15	49	22-76		49	22-76		100	100	
CXRT vs. RT&CXT										
CXRT	87	79	69-89	0.05	81	72-90	0.01	93	87-99	0.66
RT&CXT	29	69	51-87		69	51-87		87	73-101	
Treatment modality of CXRT&RT vs. CXT										
CXRT&RT	102	75	66-84	0.27	94	89-99	0.08	94	89-99	0.08
CXT	14	92	78-106		77	54-100		77	4-100	

Treatment modality of CXRT&CXT vs. RT										
CXRT&CXT	101	80	71-89	0.004	82	73-91	<0.0001	91	85-97	0.24
RT	15	49	22-76		49	22-76		100	100	
Subgroup for CXRT vs.CXT alone										
CXRT	87	79	69-89	0.47	81	72-90	0.63	93	87-99	0.12
CXT	14	92	78-106		92	78-106		77	54-100	
Subgroup for CXRT sequence (not including the 4 concomitant cases)										
CT-RT	74	83	72-94	0.001	86	77-95	0.0006	95	89-101	0.02
RT-CT	9	39	6-72		39	6-72		78	51-105	
R-CHOP chemoradiotherapy (RCXRT) vs. CHOP or CHOP-like chemoradiotherapy (CCXRT)										
RCXRT	23	89	74-104	0.11	89	74-104	0.04	93	80-106	0.87
CCXRT	64	77	66-88		80	69-91		93	86-100	
No CXRT	29	69	51-87		69	51-97		87	73-101	
CXT regimen comparison (R-CHOP vs. CHOP vs. No CXT)										
R-CHOP	32	81	63-99	0.002	81	63-99	<0.0001	88	75-101	0.27
CHOP	69	80	69-91		83	73-93		92	85-99	
No CXT	15	49	22-76		49	22-76		100	100	
Subgroup for RCXRT vs. CCXRT										
RCXRT	23	89	74-104	0.41	89	74-104	0.56	93	80-106	0.57
CCXRT	64	77	66-88		80	69-91		93	80-100	
Subgroup for comparison within CXT regimens (R-CHOP vs. CHOP or CHOP-like)										
R-CHOP	32	81	63-99	0.84	81	63-99	0.92	88	75-101	0.27

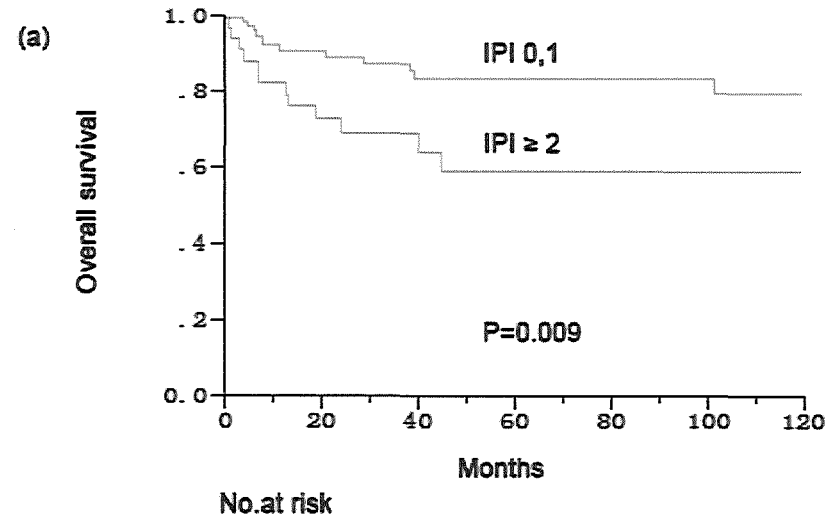
CHOP	69	80	69-91		83	64-102		92	88-99	
Cycles of CXT										
< 6	49	69	55-83	0.01	75	62-88	0.06	88	77-99	0.87
≥6	67	81	70-92		81	70-92		93	87-99	
RT dose										
>40 Gy	39	95	88-102	0.0054	95	88-102	0.02	96	89-103	0.32
≤ 40	77	66	54-78		69	57-81		89	81-97	
RT treatment volume (partial bone vs. entire bone)										
Partial	60	77	65-89	0.54	79	68-90	0.65	91	82-100	0.18
Entire	42	74	59-89		76	62-90		97	90-104	
No RT	14	92	78-106		92	78-106		77	54-100	
Response Group (CR vs. No CR)										
CR	86	84	75-93	<0.0001	87	79-95	<0.0001	96	91-101	<0.0001
No CR	30	51	28-74		51	28-74		79	62-96	

Abbreviations: OS=overall survival; LSS=lymphoma-specific survival; LC=local control; IPI=international prognostic index; M/L=Intermediate/low; LDH=lactate dehydrogenase; ND=not done; CXRT=chemoradiotherapy; RT=radiotherapy; CXT=chemotherapy; CT-RT=chemotherapy followed by radiotherapy; RT-CT=radiotherapy followed by chemotherapy; CHOP=cyclophosphamide,doxorubicin, vincristine, and prednisone; R-CHOP=rituximab plus CHOP; RCXRT=RCHOP regimen with chemoradiotherapy ; CCXRT=CHOP regimen with chemoradiotherapy; CR=complete response.

Table 3. Multivariate analyses

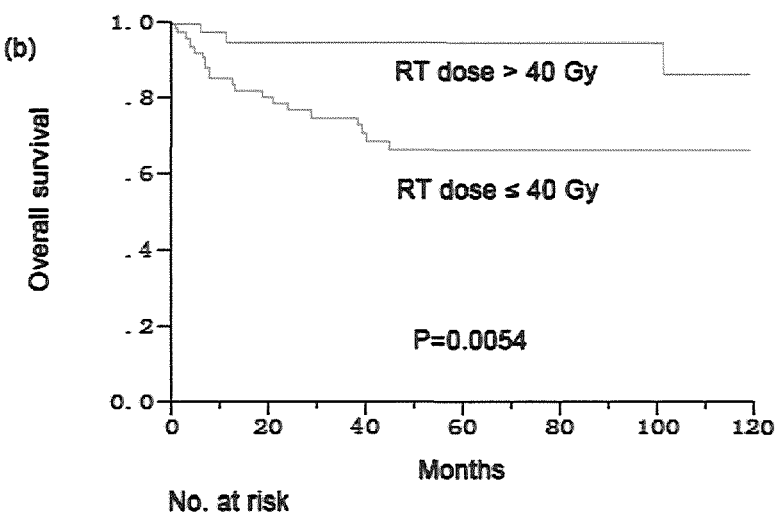
Variable	OS		LSS		LC	
	RR	P	RR	P	RR	P
IPI score (<2)	1.68	0.014	1.73	0.02	—	NS
RT dose (>40 Gy)	1.97	0.005	1.72	0.05	—	NS
Response (CR)	2.17	0.0004	2.56	<0.0001	2.96	0.00
CXT (Yes)	2.46	0.0002	2.91	<0.0001	_	NS

Abbreviations: OS=overall survival; LSS=lymphoma-specific survival; LC=local control; RR=risk ratio; IPI=international prognostic index; RT=radiotherapy; CR=complete response; CXT=chemotherapy; NS=no significant.



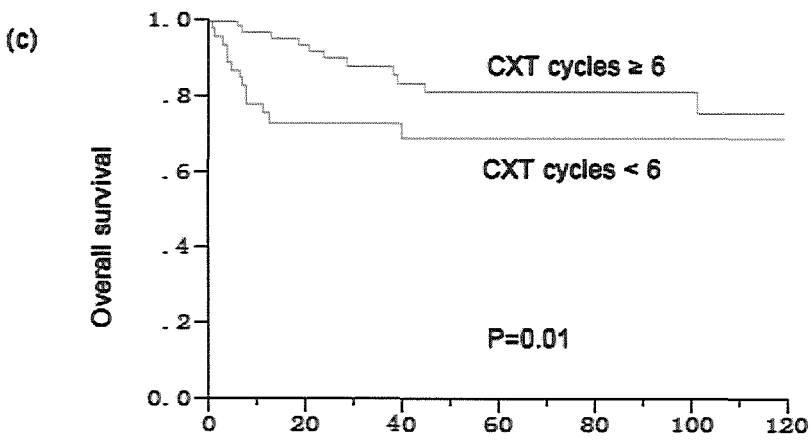
No.at risk

IPI 0,1	82	56	41	36	29	23	16
IPI ≥ 2	34	22	15	9	7	4	3



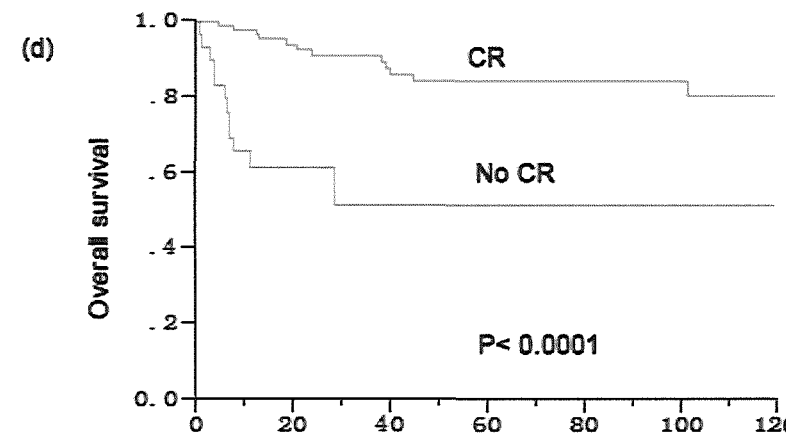
No. at risk

RT dose >40 Gy	39	30	24	19	14	12	8
Rt dose ≤40 Gy	77	48	34	28	22	15	11



No. at risk

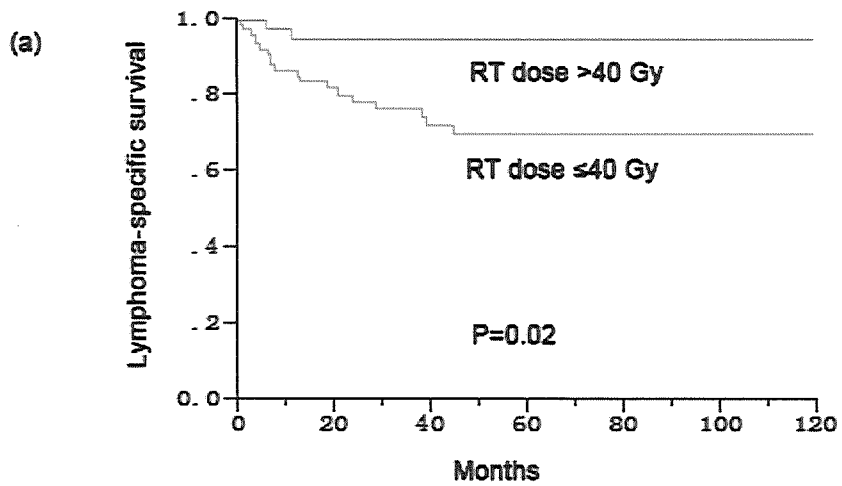
CXT cycles ≥ 6	67	55	39	31	26	18	10
CXT cycles < 6	49	24	20	16	11	9	9



No. at risk

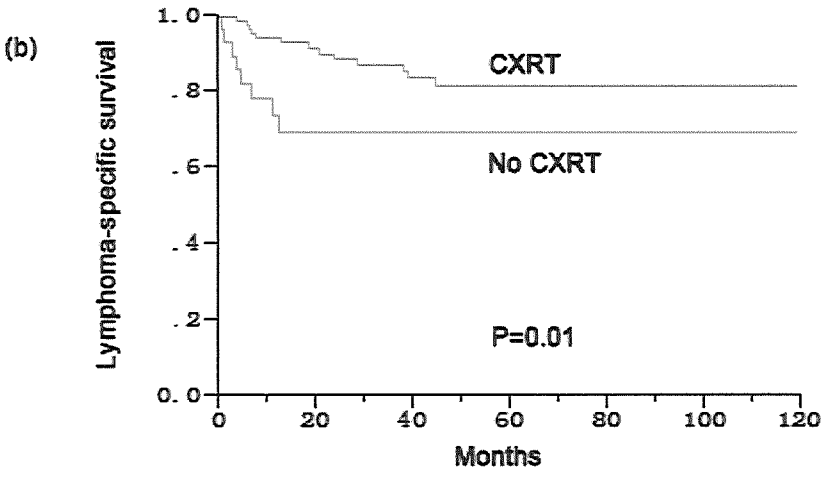
CR	86	69	54	44	33	24	16
No CR	30	9	4	3	3	2	2

Cai. Figure 2



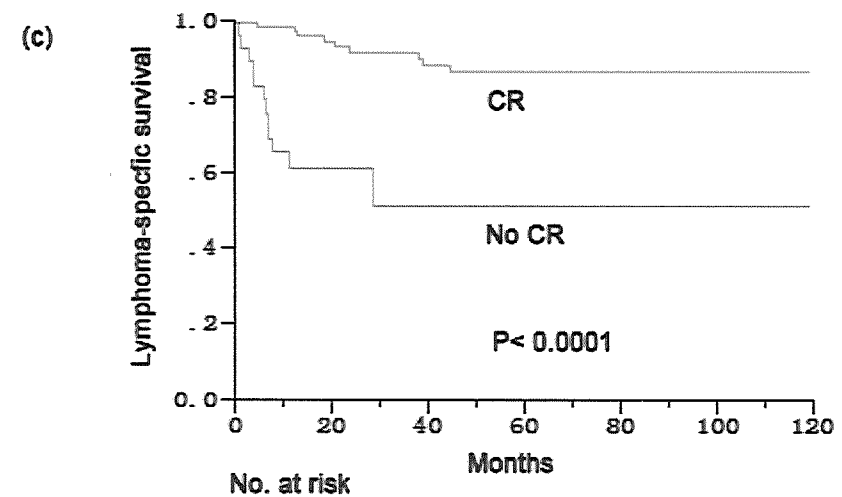
No. at risk

RT dose >40 Gy	39	30	24	19	14	12	8
RT dose ≤40 Gy	77	48	34	28	22	15	11



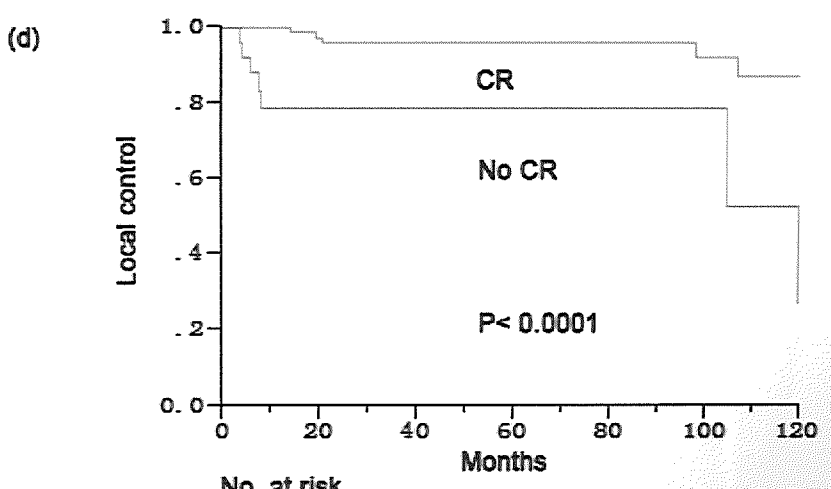
No. at risk

CXRT	87	66	49	38	29	21	13
No CXRT	29	13	10	9	7	6	6



No. at risk

CR	86	69	54	44	33	24	16
No CR	30	9	4	3	3	2	2



No. at risk

CR	86	69	54	44	33	24	16
No CR	30	9	4	3	3	2	2