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Results of consolidative radiotherapy for relapsed diffuse B-Cell lymphoma

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Abstract

Background: Recurrent diffuse large B-cell lymphoma (DLBCL) is a disease with high mortality. The standard of care involves autologous stem-cell transplantation (ASCT), which is not always feasible. We investigated the impact of radiotherapy as part of the salvage treatment for patients with relapsed disease.

Materials and methods: retrospective study of patients with recurrent DLBCL after chemotherapy and consolidative radiotherapy at a single institution. All patients were included if radiation was part of the first treatment.

Results: Of 359 patients assessed between 2010 and 2017, 65 (18.1%) presented a recurrence, but only 62 received further treatment and were included in the study. Mean overall survival was 18.6 months since diagnosis and progression-free survival after first progression (PFS2) was 7.7 months. Patients were divided into two groups according to whether they did (24.8%) or did not (75.8%) receive radiation as part of their salvage treatment. Patients that did not receive R-CHOP (rituximab plus cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone) in the first line were treated more

with radiation in the second line (p = 0.02). Six patients with in-field relapse were re-irradiated. Only 4 patients received ASCT as part of their treatment for relapsed disease. There was no difference in outcomes.

Conclusion: There is a place for radiotherapy in the treatment of relapsed DLBCL, particularly when patients do not receive ASCT. Radiotherapy is well-tolerated. More trials to assess the role of radiotherapy for these patients are needed.

Key words: non-Hodgkin lymphoma; refractory lymphoma; radiotherapy

Introduction

Disease relapse is still an important outcome for patients treated for diffuse large B-cell lymphoma (DLBCL). Almost one quarter of patients will have disease progression after the completion of the first treatment and will be treated for relapsed disease [1], and treatment is not always curative [2]. The standard of care for these patients, which is high-dose chemotherapy followed by autologous stem-cell transplantation (ASCT), with or without irradiation, is not feasible for a large portion of patients [3], even in controlled trials.

In this setting, radiotherapy can be used either for local control or as a palliative treatment. The role of radiation in the standard treatment for these patients was established almost thirty years ago [3], in the first PARMA trial. In addition, radiation has been investigated in the setting before [4] and after [5, 6] ASCT, with good results. Even after other important randomized trials that omitted radiotherapy, such as the CORAL trial [7], the use of radiation has been recurrently investigated, since that trial presented high rates of relapse in sites that would have been treated with radiotherapy.

This study was designed to assess the use of radiotherapy for relapsed DLBCL in a single university hospital and to describe the population for whom this treatment has been favored.

Materials and methods

This was a retrospective study of patients diagnosed with DLBCL and treated with radiotherapy between July 2010 and July 2017 who presented recurrent disease. Patients that did not receive second line / salvage treatment were excluded.

Demographic and treatment characteristics were assessed. Demographic variables included age, performance status (Eastern Cooperative Oncology Group — ECOG scale), stage, the presence of bulky disease, B symptoms, extranodal disease and human immuno-deficiency virus (HIV) status. The revised International Prognostic Index (R-IPI) was applied and updated in all patients. Treatment variables included the use of radiotherapy in second-line treatment, doses and fields, second-line chemotherapy, autologous stem-cell transplantation (ASCT) as consolidative treatment and the use of total body irradiation (TBI) as a conditioning agent. Afterwards, patients were divided in two groups for subsequent analyses: one including those patients that received radiotherapy for the recurrence, and the other including those who did not.

Overall survival (OS) was assessed from the date of diagnosis. Second progression-free survival (PFS2), considered as any recurrence after salvage treatment, was assessed from the date of first progression to the date of second progression.

Statistical analysis consisted of descriptive, and frequencies analyses, with comparisons between groups by the Fisher's Exact test. For the oncological outcomes and survivals, the Kaplan-Meier method was used with the Log-rank test for univariate analysis. Significance was set at 5% ($p \leq 0.05$).

Results

In the studied period, 359 patients were retrieved and, after charts evaluation, 65 (18.1%) presented disease progression, but only 62 (17.3%) that received further treatment were included in the study. Most patients were male (61.3%) and mean age at first diagnosis was 56.7 years. The most common chemotherapy regimens used as second line were ICE (ifosfamide, carboplatin, and etoposide) and IVAC (etoposide, cytarabine, ifosfamide, mesna and methotrexate). Table 1 and table 2 describe, respectively, demographic and treatment characteristics. The respective characteristics and comparisons of the two groups: one that received radiotherapy as part of second line treatment and the other that did not are presented in Table 3. The use of radiation in the second-line setting was correlated only to the use of chemotherapy regimens other than R-CHOP (rituximab plus cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone) in the first-line treatment ($p = 0.020$).

With a mean follow-up of 32.8 months, median overall survival was 18.6 months (1.3 – 121.0). There were 47 (75.8%) deaths reported. The mean first progression-free survival

(PFS) was 16.4 for the sample that did progress, but it was 48.5 months for the first initial 359 patients. Median PFS2 was 7.7 months (0.2–88.6) with 19 (30.6%) second recurrences in the period (Fig. 1 and 2). **None of the studied variables with OS or PFS2 in the univariate analysis [Something seems to be missing in this sentence. Please, verify.
] (Table 4, Figures 3 and 4).**

Discussion

Recently, the International Lymphoma Radiation Oncology Group (ILROG) [8] addressed the need for a review and consensus on the use of radiation for relapsed and refractory non-Hodgkin lymphomas. Even though we observe a consistent decrease in the use of radiotherapy for lymphomas [9], patients have been referred to radiation oncology departments particularly after treatment regimens without radiation have failed. In our sample, patients that were not treated with the standard R-CHOP regimen at first, were most suitable to need radiotherapy as part of the salvage treatment ($p = 0.02$). Our results show a trend to use radiotherapy when usual protocols were not applied.

It is important to stress that radiotherapy has already been compared to regimens containing ASCT in the PARMA trial. Without new evidence for the use of radiation instead of other consolidation regimens it cannot be favored. Nevertheless, this study shows data that raise two important questions. First, the investigation arm for this trial used radiotherapy, even in larger fields, with less technology and lower dose (26 Gy) than is currently used. Second, even amongst highly selected patients for a randomized trial, a fraction of patients received ASCT.

We compared the use of radiotherapy in this setting with other published data. In our sample, 24.2% of relapsed patients did receive radiotherapy. The decrease in the use of radiotherapy is consistent with global trends. It is important to stress that technology has evolved, and patients would have been treated differently from those in the PARMA trial, with smaller volumes and more technology invested into radiation delivery quality assessment [10].

Not every patient that relapses receives ASCT. In the PARMA trial, 41.9% of patients did not respond after high-dose chemotherapy and in the investigation arm, 11% of patients randomized to receive ASCT did not. Our numbers are consistent with this setting, since only four patients did receive ASCT. Even though guidelines stress the importance of ASCT in the relapsed setting, patients usually don’t reach that far. New prospective trials should be

designed to investigate the use of radiation as a consolidative treatment after second-line chemotherapy in the setting where ASCT is not possible or feasible.

There is a growing body of evidence in the treatment of recurrent DLBCL with CAR-t cells. This cellular immunotherapy could have a synergy with radiotherapy [11]. As it has been investigated for ASCT, with CAR-T cell treatments the correct order to offer radiotherapy has also been under investigation [12]. This is, nevertheless, a growing application for radiotherapy [13] and new, prospective data is needed.

Radiotherapy for DLBCL has been correlated with toxicities. Even though acute and long-term toxicities are rare [10], particularly with advanced technology, secondary neoplasms are always possible. In the setting of relapsed disease, nevertheless, this is a minor issue compared to the chance of death from the relapsed lymphoma. In special settings, such as patients living with HIV for whom ASCT is not always possible [14], radiotherapy should be more largely used, even with the risk of increased toxicities [15].

Re-irradiation is possible. This study was designed to assess whether patients that receive radiotherapy in the first line regimen would be exposed to radiation again. The chances of in-field relapse for patients treated with radiotherapy in the first line are very small, less than 2% [16]. In our sample, six (9.7%) patients had in-field relapses and were treated with re-irradiation to a dose of 30 Gy, in 2 Gy fractions. No outstanding toxicities were found. Data on re-irradiation for these patients are scarce and our experience may represent a modest but interesting highlight of our study.

Furthermore, there is a paucity of data for patients that have partial response or progress to second-line regimens. Radiotherapy has been investigated before and after ASCT transplantation, with better results when patients receive ASCT with as little residual disease as possible [5]. There is also a place for radiotherapy in the palliative setting. Nevertheless, all those situations haven’t been investigated in prospective trials.

Conclusion

Radiotherapy can be an important tool in the treatment of relapsed DLBCL patients, but its underused. Since the preferred regimen of ASCT regimen is not always feasible, irradiation should be considered mostly in patients that will not undergo ASCT. New trials should be designed to address the role of radiotherapy in the relapse setting as it deserves further studies, mainly in prospective trials.

Ethics approval and consent to participate

Ethics committee authorization was obtained in the local ethics committee according to Brazilian law and the Declaration of Helsinki. All patients have given written consent to participate.

Consent for publication

The author grants the publisher the sole and exclusive license of the full copyright. The authors guarantee that this manuscript has not been previously published elsewhere. The authors declare that any person named as co-author of the contribution is aware of the fact and has agreed to being so named.

Availability of supporting data

data on this research is available on request to the corresponding author

Competing interests

The authors do not have any conflict of interest to declare.

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Authors contributions

G.M. was responsible for study design. G.M. was responsible for ethics committee approval. G.M. was responsible for data collection. G.M. and M.N. have written project's final draft. G.M. was responsible for statistical analysis. H.C. was responsible for overall orientation and manuscript review.

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Table 1. Overall demographic description

Variable	**Number (n)**	**(%)**
Age at diagnosis (years), mean (range)		
	56.7 (24–72)	
Age (at diagnosis)		
< 60	36	58.1
≥ 60	26	41.9
Sex		
Male	38	61.3
Female	24	38.7
ECOG performance status at diagnosis		

0–1	51	82.3
2–4	11	17.7
Stage (Lugano system at first presentation)		
1	4	6.5
2	7	11.3
3	10	16.1
4	41	66.1
R-IPI (at diagnosis)		
Very good	2	3.2
Good	22	35.5
Poor	38	61.3
Bulky disease		
Present	48	77.4
Absent	14	22.6
Extranodal disease		
Present	52	83.9
Absent	10	16.1
B symptoms		
Present	49	79.0
Absent	13	21.0
HIV		
Negative	56	90.3
Positive	6	9.7

ECOG — Eastern Cooperative Oncology Group; R-IPI — revised International Prognostic Index; HIV — human immuno-deficiency virus

Table 2. Treatment characteristics

Variable	**Number (n)**	**(%)**
First-line		
First-line chemotherapy regimen		
R-CHOP	50	80.6
Others	12	19.4
Number of chemotherapy cycles in the first line		
≤ 6	24	38.7
> 6	38	61.3
Toxicity to first-line chemotherapy		
0–3	41	66.1
4	21	33.9
Response to first-line chemotherapy		
Complete response	15	24.2
Partial response	42	67.7

Unidentified	5	8.1
First-line consolidative RT technique		
Mantle and/or inverted-Y	2	3.2
Involved-field RT	10	16.1
Involved-site RT	14	22.6
Bulky disease or PR site only	36	58.1
Second-line		
Second-line chemotherapy		
Cytarabine-based	48	77.4
Others	14	22.6
Second-line RT		
Yes	15	24.2
Yes, as consolidative treatment	5	-
Yes, and as re-irradiation to primary site	6	-
No	47	75.8
Second-line RT dose [Gy]		
30	8	53.3
> 30	7	46.7
ASCT as consolidation for second-line chemotherapy		
Yes	4	6.5
No	58	93.5

R-CHOP —rituximab plus cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone; RT — radiotherapy; ASCT — autologous stem-cell transplantation

Table 3. Demographic description and treatment protocol according to delivery or not of second-line radiotherapy (RT) (p-values stand for the correlation between each variable and the use of RT)

Patients characteristics	**Second-line RT**		**p**
	No N = 47 (75.8%)	**Yes N = 15 (24.2%)**	
Age			
< 60 years	25 (53.2%)	11 (73.3%)	0.169
> 60 years	22 (46.8%)	4 (26.7%)	
ECOG			
0–1	38 (80.9%)	13 (86.7%)	0.608
2 or more	9 (19.1%)	2 (13.3%)	

R-IPI Very good Good Poor	2 (4.3%) 15 (31.9%) 30 (63.8%)	0 7 (46.7%) 8 (53.3%)	0.080
Bulky disease Absent Present	12 (25.5%) 35 (74.5%)	2 (13.3%) 13 (86.7%)	0.325
Extranodal disease Absent Present	8 (17.0%) 39 (83.0%)	2 (13.3%) 13 (86.7%)	0.735
B symptoms			
Absent	8 (17.0%)	5 (33.3%)	0.177
Present	39 (83.0%)	10 (66.7%)	
HIV Negative Positive	42 (89.4%) 5 (10.6%)	14 (93.3%) 1 (6.7%)	0.651
First-line chemotherapy regimen R-CHOP Other	41 (87.2%) 6 (12.8%)	9 (60.0%) 6 (40.0%)	**0.020**
Second-line chemotherapy regimen			
Cytarabine-based	24 (51.1%)	8 (53.3%)	0.878
Other	23 (48.9%)	7 (46.7%)	

ECOG — Eastern Cooperative Oncology Group; R-IPI — revised International Prognostic Index; HIV — human immuno-deficiency virus; R-CHOP —rituximab plus cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone

Table 4. Univariate analysis of variables related to overall survival (OS) and second progression-free survival (PFS2)

Variable	**Categories**	**Univariate analysis (OS)**		**Univariate analysis (PFS2)**	
		n (events)	**p**	**n (events)**	**p**
Age	< 60 years > 60 years	27 20	0.99	13 6	0.37
ECOG	0–1	39	0.57	17	0.34

	2–4	8		2	
R-IPI	Very good Good Poor	1 16 30	0.57	2 5 12	0.08
Bulky disease	Present Absent	35 12	0.58	15 4	0.89
Extranodal disease	Present Absent	39 8	0.44	19 0	**0.03**
B symptoms	Present Absent	36 11	0.96	6 13	0.06
HIV	Negative Positive	42 5	0.70	15 4	0.08
First-line chemotherapy	R-CHOP Other	9 38	0.76	7 12	0.41
Second-line chemotherapy	Cytarabine-based Other	25 22	0.70	8 11	0.74
Second-line RT	No Yes	34 13	0.30	13 6	0.08

ECOG — Eastern Cooperative Oncology Group; R-IPI — revised International Prognostic Index; HIV — human immuno-deficiency virus; R-CHOP —rituximab plus cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone; RT — radiotherapy

Figure 1. Overall survival (median 18.6 months)

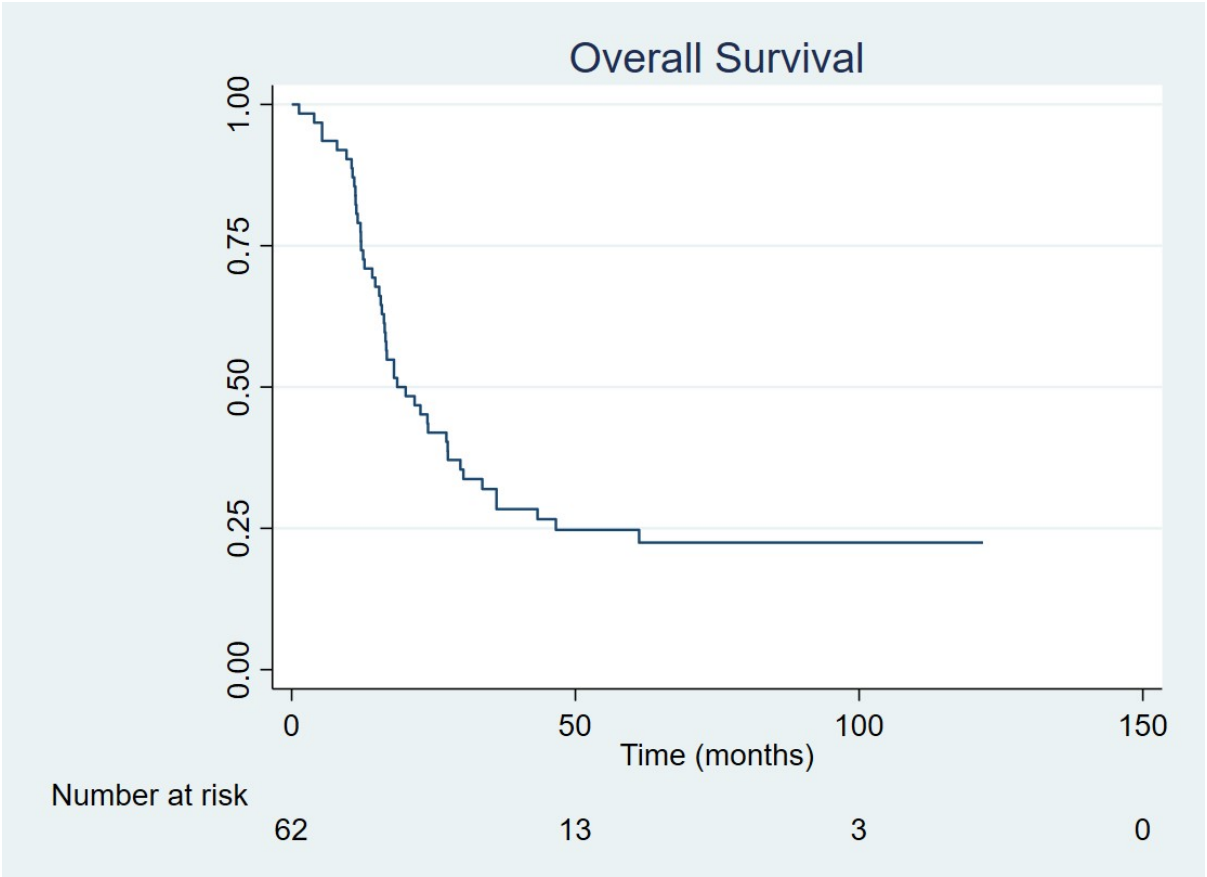

Overall Survival
1.00
0.75
0.50
0.25
0.00
0
50
100
150
Time (months)
Number at risk
62
13
3
0

Figure 2. Survival free from second progression (PFS2, median 7.7 months)

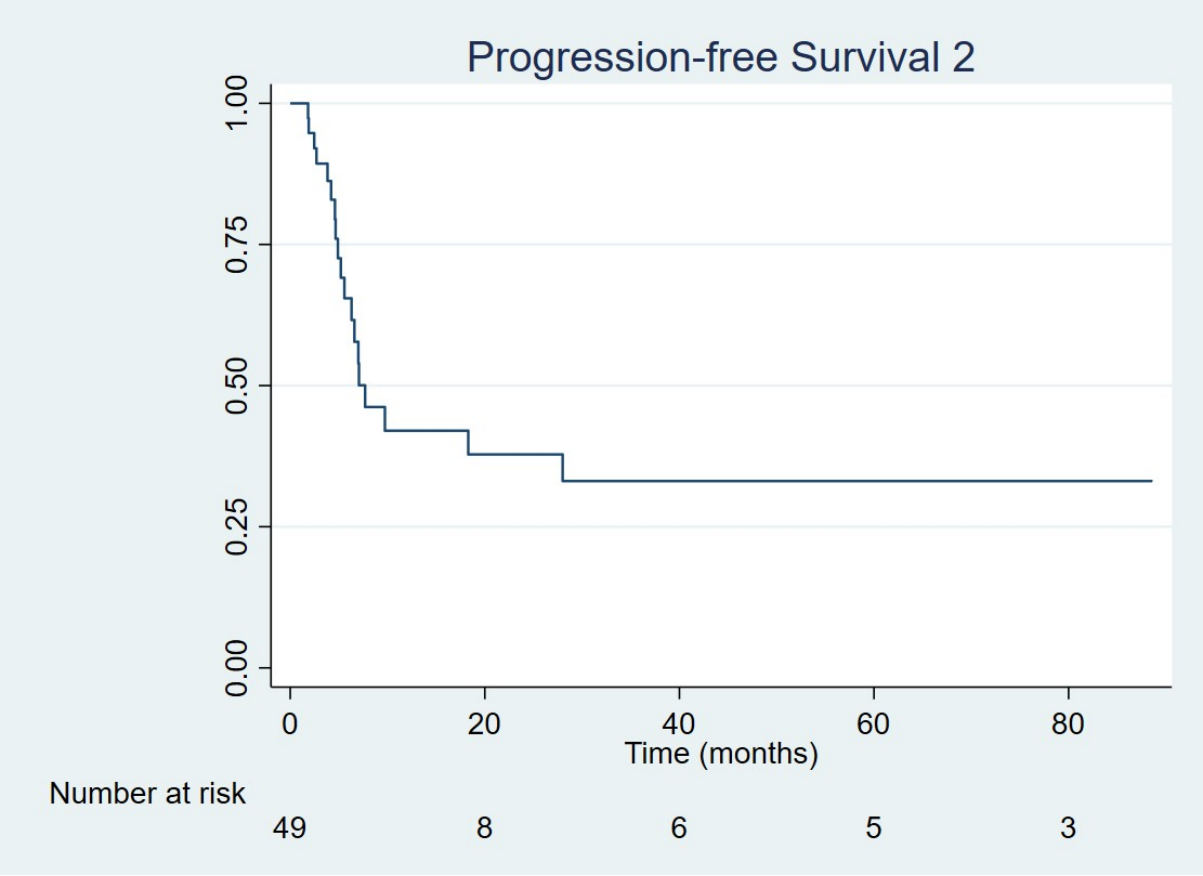


Figure 3. Overall durvival by second-line radiotherapy (median value was 23.9 months for the non-second-line radiotherapy (RT) group and 16.8 months for the second-line RT group, p = 0.30)

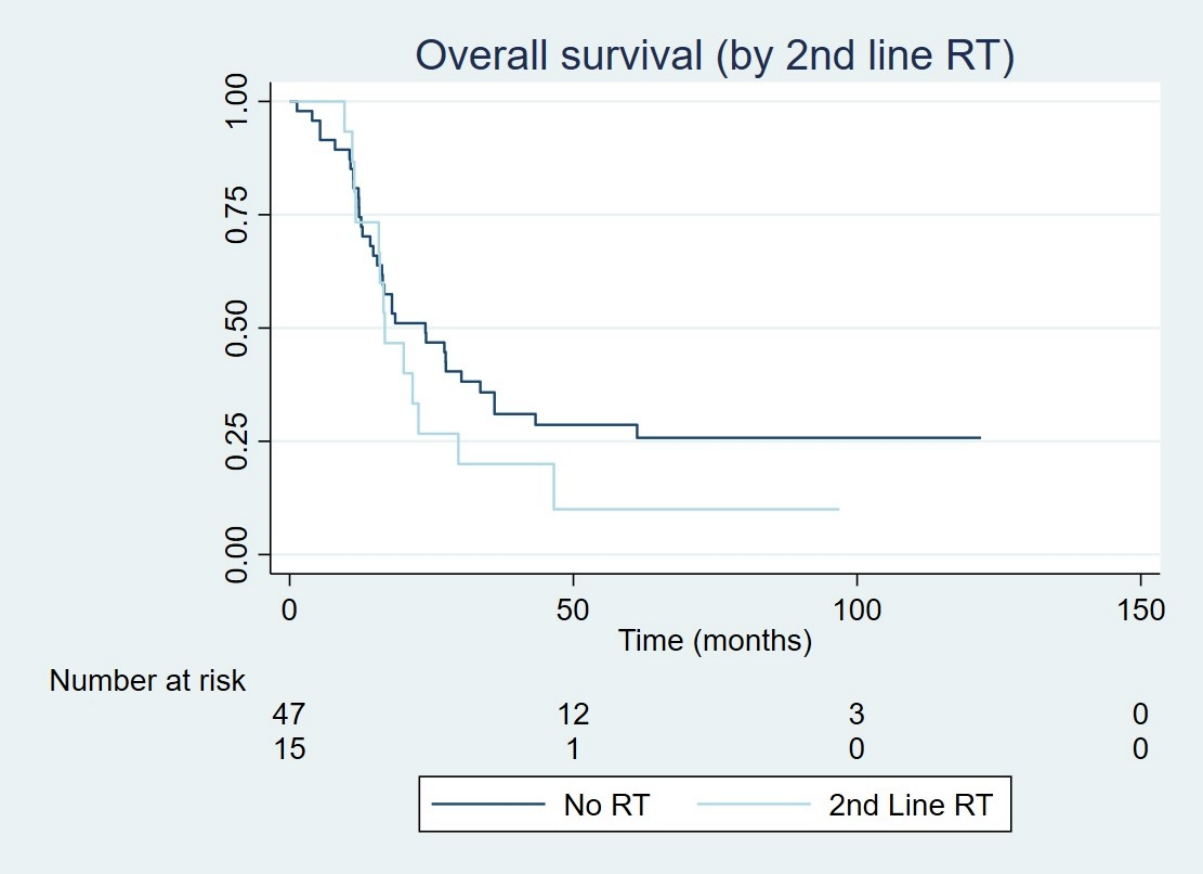
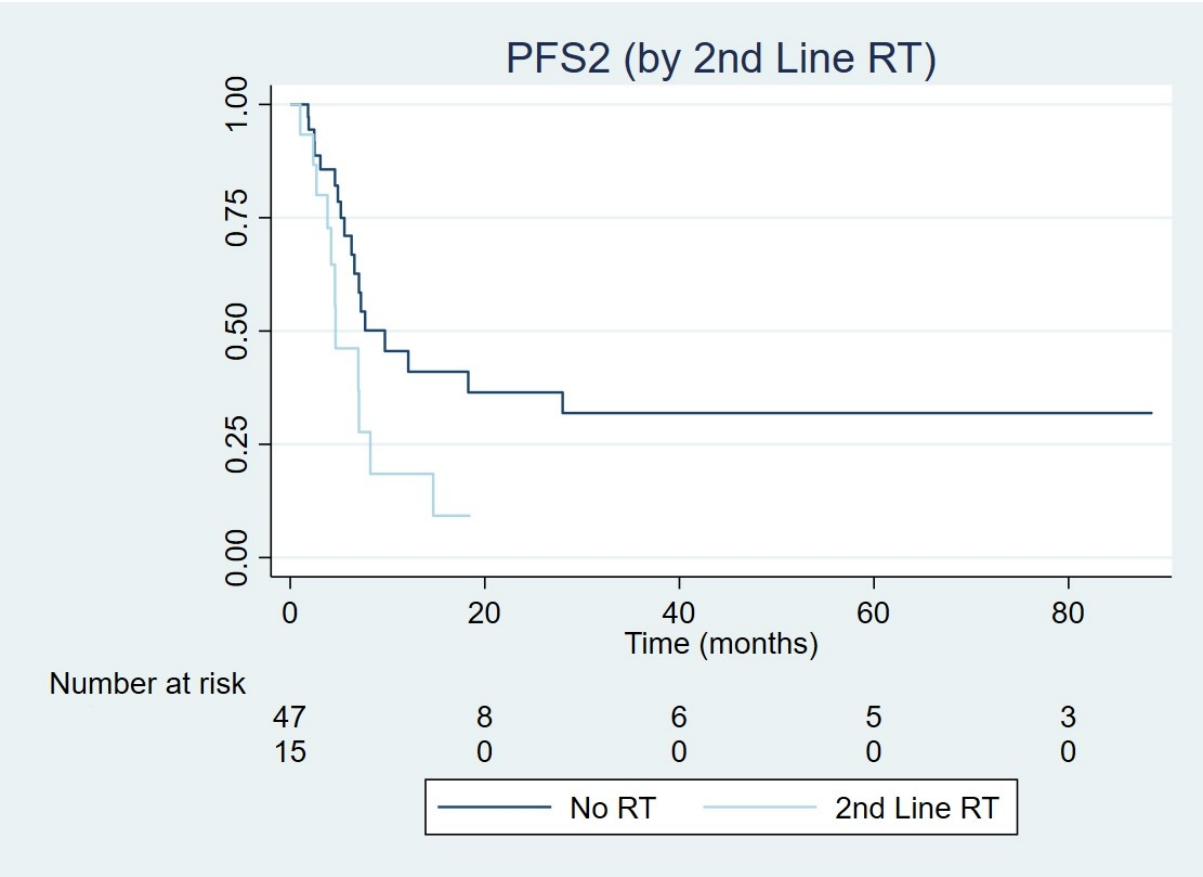


Figure 4. Second progression-free survival by second-line radiotherapy (median value was 18.3 months for the non-second-line radiotherapy (RT) group and 4.7 months for the second-line RT group, p = 0.08



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