Irinotecan Based Chemotherapy in Extrapulmonary Neuroendocrine Carcinomas: Survival and safety data from a Multicentric Italian Experience

Camilla Bardasi (camilla.bardasi@gmail.com)
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena https://orcid.org/0000-0002-0692-2546

Andrea Spallanzani
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena

Stefania Benatti
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena

Francesca Spada
IEO: Istituto Europeo di Oncologia

Alice Laffi
IEO: Istituto Europeo di Oncologia

Antonuzzo Lorenzo
University of Florence Department of Experimental and Clinical Medicine: Universita degli Studi di Firenze Dipartimento di Medicina Sperimentale e Clinica

Daniele Lavacchi
University Hospital Careggi: Azienda Ospedaliero Universitaria Careggi

Marconcini Riccardo
Pisa University Hospital: Azienda Ospedaliero Universitaria Pisana

Ferrari Marco
Pisa University Hospital: Azienda Ospedaliero Universitaria Pisana

Margherita Rimini
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena

Francesco Caputo
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena

Chiara Santini
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena

Krisida Cerma
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena
Andrea Casadei-Gardini
San Raffaele Hospital: IRCCS Ospedale San Raffaele
Kalliopi Andrikou
IRST: Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori Srl
Massimiliano Salati
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena
Federica Bertolini
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena
Annalisa Fontana
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena
Massimo Dominici
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena
Gabriele Luppi
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena
Fabio Gelsomino
Azienda Ospedaliero-Universitaria di Modena Policlinico di Modena: Azienda Ospedaliero-Universitaria di Modena

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Research Article

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Abstract

Purpose: Neuroendocrine carcinomas (NECs) are a rare subgroup of neuroendocrine neoplasms that occasionally originate from gastro-entero-pancreatic (GEP) tract. Evidence of the effectiveness of chemotherapy is scarce. Platinum plus Etoposide regimens are currently the standard treatment in first-line, while little data are available on second-line treatments. The aim of this study is to evaluate the efficacy and safety of Irinotecan (IRI)-based chemotherapy in a series of extrapulmonary NECs.

Methods: Patients with NEC diagnosis treated at University Hospitals of Modena, Florence, Pisa, and European Institute of Oncology of Milan with an IRI-based regimen (FOLFIRI or XELIRI) after progression to a first-line platinum-based therapy were enrolled. Objective responses were assessed according to RECIST criteria. Progression-free survival (PFS) and overall survival (OS) were calculated.

Results: 34 patients, 16 males, and 18 females, median age of 59 years (range 32-77), with metastatic NEC were included. Twenty-seven pts had Ki-67 ≥ 55% and 4 pts Ki-67 of < 55% (for 3 pts data was not available). The median number of treatment cycles of the IRI-based regimen was 7.5 (range 1-16). Six partial responses (17.6%) and 9 stable diseases (26.5%) were observed, with a disease control rate of 44.1%. Median PFS and OS were 4.4 and 5.9 months, respectively. Neutropenia, anemia, and nausea were the only G3-G4 toxicities reported.

Conclusion: Despite the relatively small sample size, IRI-based therapy demonstrated to be a valid option for patients with pre-treated extrapulmonary NEC.

Introduction

Neuroendocrine carcinomas (NECs) are a rare, aggressive variant of neuroendocrine neoplasms (NENs), with poorly differentiated histology and high proliferative index (Ki-67 > 20%). Roughly 35–55% of NEC originate from lungs but occasionally they can also arise from the gastro-entero-pancreatic (GEP) tract [1] [2], from bladder, and, in a further minimal percentage, from other districts like head and neck, breast, and prostate. GEP-NECs represent about 10% of all GEP-NENs and show a dismal prognosis with a median survival of approximately 5 months without treatment [3] [4].

Due to their low incidence, therapies for NECs have not robust evidence beyond: the available data derive from old, retrospective analyses with small samples, different schedules, and not designed to answer this specific unmet medical need. Therefore, platinum plus etoposide is the most common chemotherapeutic regimen used in clinical practice as first-line treatment (ref. Moertel et al.), resulting in a gain in median overall survival (OS) of 15 months [5]. Unfortunately, in the second-line setting, there is no consensus regarding further treatment. Hentic et al. from the French group has proposed irinotecan-based chemotherapy (IRI-CT) as a valid second-line strategy [6] as compared to other agents tested like amrubicin [7], temozolomide [8] [9], S-1 [7], FOLFOX [10], and taxanes [7].

However, the exiguous sample size of the study prevents us from drawing definitive conclusions about the efficacy of this regimen.

With this study, we retrospectively evaluate the efficacy and safety of IRI-CT in a cohort of patients with metastatic extrapulmonary (EP) NEC progressing after first-line platinum-based treatment.

Patients And Methods

Study population

This is a retrospective multicentric population-based study. We collected data from four oncological centers across Italy (Department of Oncology and Hematology of University Hospital of Modena; European Institute of Oncology of Milan, IEO IRCCS; Medical Oncology Unit of Careggi-Florence, Department of Clinical and Experimental Medicine of University of Pisa).

Thirty-four consecutive patients with a diagnosis of EP-NEC according to 2010 WHO Classification as reported by expert pathologists in this field in each center and treated with an IRI-CT after platinum plus etoposide chemotherapy failure were included.

The study was approved by the local Ethic Committee (n° 473/2020). All patients provided written informed consent.

Selection criteria and treatment regimens

Patients with a diagnosis of EP-NEC who received at least one cycle of IRI-CT were considered eligible for the study.

All patients were treated with one of the following regimens:

- FOLFIRI: Irinotecan 180 mg/mq over 60 minutes on day 1, followed by calcium levofolinate 100 mg/mq over 120 minutes, FU 400 mg/mq bolus, and FU 600 mg/mq continuous infusion over 22 hours on day 1 and 2 every 14 days.

- modified FOLFIRI plus or minus bevacizumab: Irinotecan 180 mg/mq IV over 60 minutes, calcium levofolinate 200 mg/mq IV over 2 hours, followed by FU 400 mg/m2 bolus on day 1 and FU 2400 mg/mq continuous infusion over 46 hours every 14 days. Bevacizumab was administered at the dose of 5 mg/Kg over 30 minutes before modified FOLFIRI

- XELIRI: Irinotecan 250 mg/mq infusion on day 1 plus Capecitabine 1000 mg/mq orally twice daily on days 1 to 14, every 3 weeks.

All patients received intravenous premedication with dexamethasone, chlorphenamine, and ondansetron. Administration of granulocyte clone-stimulating factors (G-CSF) was considered only as secondary

prophylaxis. Treatment was continued until disease progression, patient refusal, or occurrence of unacceptable toxicity.

Efficacy and safety assessment

Although a follow-up program was not standardized due to the retrospective design, response rate (RR) was assessed by Computer tomography (CT) scan of chest, abdomen, pelvis, and brain approximately every 3 months according to RECIST criteria. Progression-free survival (PFS) was calculated from the date of the first IRI-CT administration to progression. OS was defined as the time from starting chemotherapy until death. Disease control rate (DCR) was defined as the percentage of patients who have achieved complete response, partial response, and stable disease achieved to IRI-CT. Adverse events were evaluated using common terminology criteria for adverse events version 5.0 [11].

Statistical analysis

Quantitative data were expressed as medians (range). Survival rates were calculated according to the Kaplan–Meier method. All statistical analyses were performed using SPSS statistical software. STIMA CAMPIONE!!

Results

Patients' characteristics

From April 2008 to April 2020 a total of 34 patients with advanced NEC who had already received first-line Platinum-based chemotherapy were included in the analysis. The median age at diagnosis was 59 years (range 32-77y). The majority of patients was female (18/34, 53%) and the most common primary tumor location was colon-rectum (10/34, 29.4%), followed by pancreas (5/34, 14.7%), liver/gallbladder (5/34, 14.7%), stomach (4/34, 11.8%), head and neck (2/34, 5.8%), anus (1/34, 2.9%), cervix (1/34, 2.9%), upper esophagus (1/34, 2.9%), small bowel (1/34, 2.9%) and bladder (1/34, 2.9%). The primary location was undetermined in 3 patients. Ki-67 was ≥ 55% in 27 patients (79.4%) and < 55% in 4 patients (11.8%). Data was not available in 3 patients.

Other patients' characteristics are resumed in Table 1.

Efficacy outcomes

The median OS was 14 months (range 5–46 months) as reported in Fig. 1. All patients received a Platinum-based regimen as first-line treatment: 20 patients (58.8%) received cisplatin plus etoposide, while the remaining 14 patients (41.2%) received carboplatin plus etoposide. Three complete responses (CR) (8.8%), 14 partial responses (PR) (41%), 3 stable diseases (SD) (8.8%) and 14 progressive diseases (PD) (41%) were observed as best response. Median PFS to first-line treatment was 4.4 months with a median duration of 4.7 cycles (range 2–9)/3.1 months (range 1–9). Data about first-line treatment are reported in Table 2.

In the second-line setting, all patients received IRI-CT: 19 patients received FOLFIRI, 11 patients mFOLFIRI, 1 patient mFOLFIRI + bevacizumab, 2 patients XELIRI and 1 patient FOLFIRI infused every 3 weeks. Data on second-line treatment are summarized in Table 3.

Overall, 6 patients achieved a PR (17.6 %) and 9 patients showed SD (26.5%) as the best response to treatment, with a DCR of 44.1%. Four of 6 patients with PR to irinotecan had a high proliferative index (Ki-67 ≥ 55%), although there was no statistically significant difference in terms of response rate according to Ki-67 cut-off (OR = 0.69; 95% CI: 0.084–5.642).

The median PFS and OS to IRI-CT were 4.4 (range 0.9–21.4) and 5.9 (range 1.2–32.5) months, respectively. Patients showing disease control with IRI-CT demonstrated to have a better PFS ($p < 0.0001$) and OS ($p < 0.0001$) (Fig. 2a, b).

Patients presenting with liver involvement showed worse survival outcomes: PFS to IRI-CT was 3.5 months compared to 5.2 months ($p = 0.290$, 95%CI: 0.27–1.48) observed in the patients without liver metastases; also OS was modestly different (5.7 vs 7.9 months; $p = 0.293$, 95%CI: 0.27–1.49). However, the data did not reach statistical significance, probably due to an exiguous sample of patients without liver involvement.

In our analysis, we evaluated the association of selected inflammatory biomarkers with risk of death and progression disease: while lymphocyte-platelet ratio (PLR) and neutrophil-lymphocyte ratio (NLR) seems not to impact OS and PFS, low lymphocyte-monocyte ratio (LMR) demonstrate to be associated with a significantly worse PFS ($p = 0.041$) (Fig. 3), with no effects on OS.

Furthermore, primary tumor location seems to partially impact survival: colorectal NECs tend to show worse OS to IRI-CT than NECs arising from other districts (3.4 vs 7.3 months; $p = 0.102$).

It should be noted that, at the time of the drafting of this paper, 2 patients were steel receiving Irinotecan-based treatment.

Among all included patients, 21 (65.6% 21/32) could receive third-line treatment consisting of avelumab (1 pt), capecitabine/temozolomide (1 pt), dacarbazine/doxorubicin (1 pt), FOLFOX (4 pts), gemcitabine (1 pt), paclitaxel (2 pts) and temozolomide (11 pts).

Safety

During IRI-CT, only 12 patients (35.3%) showed grade 3 or 4 adverse events (7 neutropenia, 1 febrile neutropenia, 1 neutropenia plus transaminase elevation, 2 anemia, and 1 nausea) resulting in minor treatment delay (< 2 weeks). There were no chemotherapy-related deaths.

Hematological toxicity (n = 26), fatigue (n = 19), transaminase elevation (n = 8), hyponatremia (n = 7) and nausea (n = 5) were observed as most common minor toxicities as reported in Table 4.

Discussion

Patients with advanced EP-NECs are usually treated with platinum-based chemotherapy regimens in first-line setting. However, many options have been evaluated in second-line setting, but none with robust literature evidence, with data mainly coming from several small retrospective studies in which amrubicin [7], temozolomide [8] [9], S-1 [7], oxaliplatin [10], irinotecan [6], EpiCO (epirubicin, cyclophosphamide, and vincristine) [12] and taxanes [7] have been tested.

Hentic et al described the efficacy of irinotecan in this setting of patients retrospectively analyzing a population of 19 patients affected by PD-NEC and observing DCR of 62% with 31% partial response, 31% of stable disease, PFS and OS of 4 and 18 months, respectively. However, in that context, only 5 patients presented a Ki-67 ≥ 55%, while the majority of the population (14 patients, 74%) had a Ki-67 < 55% [6]. A recent analysis demonstrated Ki-67 = 55% as the best cut-off value concerning response rate and survival. Besides, data from the NORDIC NEC trial showed that patients with Ki-67 < 55% had a lower response rate (15% versus 42%, P < 0.001), but paradoxically better survival than those with Ki-67 ≥ 55% [13]. Based on this evidence, no consistent data concerning the impact of IRI-CT on EP-NECs with higher Ki-67 are available in the second-line setting.

To the best of our knowledge, this is the largest study aiming at evaluating the efficacy and feasibility of IRI-CT in a cohort of patients with pretreated NEC. In the last 12 years, in the four cancer centers that participated in this retrospective analysis, 34 patients affected by EP-NECs received IRI-CT after progression to first-line platinum plus etoposide chemotherapy. Twenty-seven of them had a Ki-67 ≥ 55% while four had Ki-67 < 55% (for three patients data was not available). Our population showed a DCR of 44.1% with 17.6% PR and 26.5% SD with median PFS and OS of 4.4 months and 5.9 months respectively. According to the retrospective nature of this study, survival outcomes appear significantly worse than literature evidence [6]. This difference should be probably attributed to the different populations of patients enrolled, with a higher proliferative index and probably a more aggressive disease. Nevertheless, our results show the anti-tumor activity of irinotecan also in patients with higher Ki-67, but without an important gain in OS, underling the worse prognosis of this subgroup of patients.

Besides the Ki-67 value, also liver involvement and colorectal primary location tend to negatively impact survival: data showed a moderately difference in OS between patients with and without liver metastases and worse prognosis in patients with NEC arising from the colorectal district, as already demonstrated by Sorbye et al. [13]. However, data did not reach statistical significance, probably due to an exiguous sample of patients analyzed.

This is the first study in which the prognostic significance of serum inflammatory biomarkers is evaluated in patients with NECs. While PLR and NLR did not impact OS and PFS, in our casuistry, lower LMR seems to be associated with poorer PFS, although it did not correlate with poorer OS. This data must be deeply explored in a larger and dedicated trial in order to assess possible major impact on outcome and clinical medical history.

As far as safety is concerned, adverse events were predominantly graded 1–2, and no treatment-related deaths were observed. As described by Sugiyama et al [14], our data support the good tolerance of IRI-CT with only minor treatment delay.

An interesting point is that, despite a cohort of patients affected by such an aggressive disease, 66% of patients received further systemic treatments, thus demonstrating the feasibility of a third-line treatment.

We have also to outline that the limitation of our study may be related to the retrospective nature of the analysis with relatively small sample size and without an independent pathological review.

However, we presume the reported data may have value due to the rarity of the disease prompting larger studies on irinotecan as second-line treatment for PD-NECs, particularly in those patients with high Ki-67 which still have an unacceptable prognosis.

Currently, there are several ongoing prospective trials aiming at evaluating the most efficacious chemotherapy schedule for second-line PD-NEC: SENECA trial (ClinicalTrials.gov Identifier: NCT03387592) in which FOLFIRI is compared to a combination of capecitabine and temozolomide; BEVANEC trial (ClinicalTrials.gov Identifier: NCT02820857) testing the efficacy of bevacizumab in combination with FOLFIRI vs FOLFIRI alone; NET-02 trial (ClinicalTrials.gov Identifier: NCT03837977) in which the standard second-line for SCLC (docetaxel) is compared to liposomal irinotecan (nal-IRI) and 5-fluorouracil/folinic acid; the EVINEC trial (ClinicalTrials.gov Identifier: NCT02113800) designed to test everolimus in NEC and NET G3 after the failure of first-line platinum-based chemotherapy; cabozantinib in combination with nivolumab/ipilimumab (ClinicalTrials.gov Identifier: NCT04079712) and avelumab (AVENEC ClinicalTrials.gov Identifier: NCT03147404) have been recently evaluated. Final data of the above studies should clarify the best clinical approach to such aggressive carcinomas.

Conclusion

In conclusion, IRI-CT seems to be a feasible and well-tolerated therapeutic option in second-line treatment of EP-NECs, but these findings warrant further confirmation in larger prospective studies.

Declarations

Funding: This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector. Conflicts of interest: The authors declare that they have no conflict of interest. Data availability The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Author contributions Material preparation and analysis were performed by C.B., F.G., and A.S. The first draft of the paper was written by C.B and F.G.; and all authors commented on previous versions of the paper. All authors read and approved the final paper. Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The studies were approved by the

regional ethic committee. This study has the following ethic number: 473/2020. Informed consent
Informed consent was obtained from all individual participants included in the study

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Tables

Table 1: Baseline Patients characteristics.

No. of Patients	34	
Modena	18	
Milan	6	
Florence	8	
Pisa	2	
Men	16	
Women	18	
Median age, y, (range)	59 (32-77)	
Primary tumor		
Colorectum	10	
Pancreas	5	
Liver/gallbladder	5	
Stomach	4	
Head and neck	2	
Anus	1	
Cervix	1	
Upper Esophagus	1	
Small Bowel	1	
Bladder	1	
Unknown	3	
Site of Metastases		
Lymph nodes	24	(70.6%)
Liver	26	(76.5%)
Lung	6	(17.6%)
Peritoneum	4	(11,8%)
Bones	2	(5.9%)
Thyroid	1	(2.9%)
Retroperitoneum	1	(2.9%)
Colon	1	(2.9%)
Bladder	1	(2.9%)
No. of metastasis sites		
1	11	
2	14	
≥ 3	9	
Ki-67%		
< 55%	4	(11.8%)
≥ 55%	27	(79.4%)
Unknown	3	(8.8%)

Table 2: First-line treatment characteristics.

First-Line Chemotherapy:	Cisplatin/Etoposide	Carboplatin/Etoposide
No. of Patients	20 pts (58.8%)	14 pts (41.2%)
Median duration (cycles/months)	4.4 2.8	5.1 4
Best Response **CR** **PR** **SD** **PD**	 1 11 / 8	 2 3 3 6
ORR **DCR**	60% (12/20) 60% (12/20)	35.7% (5/14) 57.1% (8/14)
PFS1 (months)	3	6

CR= Complete Response; PR= Partial Response, SD= Stable Disease, PD= Progressive Disease, ORR= Objective Response Rate, DCR= Disease Control Rate, PFS1=Progression Free Survival from start of first-line treatment

Table 3: Second-line treatment characteristics.

Irinotecan-based second-line chemotherapy: mFOLFIRI/FOLFIRI XELIRI mFOLFIRI + Bevacizumab FOLFIRI q21	**No.of Patients** 30 pts 2 pts 1 pt 1 pt
Median Duration Cycles Months	 7.5 (range 1-16) 4.3 (range 0 - 20.3)
Best Response CR PR SD PD	 / 6 (17.6%) 9 (26.5%) 19 (55.9%)
ORR **DCR**	17.6% (6/34) 44.1% (15/34)
PFS2 (months)	4.4
OS (months)	5.9

CR= Complete Response; PR= Partial Response, SD= Stable Disease, PD= Progressive Disease, ORR= Objective Response Rate, DCR= Disease Control Rate, PFS2=Progression Free Survival from start of second-line treatment, OS= Overall Survival

Table 4: Grade 1 to 4 Adverse Events attributed to the treatment combination.

TOXICITY (n° pts)	mFOLFIRI/FOLFIRI (n = 31 pts)		XELIRI (n = 2 pts)		mFOLFIRI + bevacizumab (n = 1 pts)	
Grade	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4
Hematological						
Neutropenia	10 (32%)	9 (29%)	2 (100%)			
Anemia	22 (71%)	2 (6.5%)	1 (50%)		1 (100%)	
Thrombocytopenia	5 (16%)		1 (50%)			
Gastrointestinal						
Nausea	5 (16%)	1 (3%)				
Vomiting	4 (13%)					
Diarrhea	4 (13%)					
Mucositis	2 (6.5%)					
Constitutional						
Fatigue/asthenia	17 (55%)		1 (50%)		1 (100%)	
Weight loss	1 (3%)					
Dermatologic						
Hand-foot-mouth syndrome						
Laboratory						
Alkaline phosphatase elevation						
Amylase elevation	1 (3%)					
Hyperbilirubinemia	1 (3%)					
Hyponatremia	6 (19%)				1 (100%)	
Hypokalemia						
Transaminase elevation	6 (19%)	1 (3%)	1 (50%)		1 (100%)	

Figures

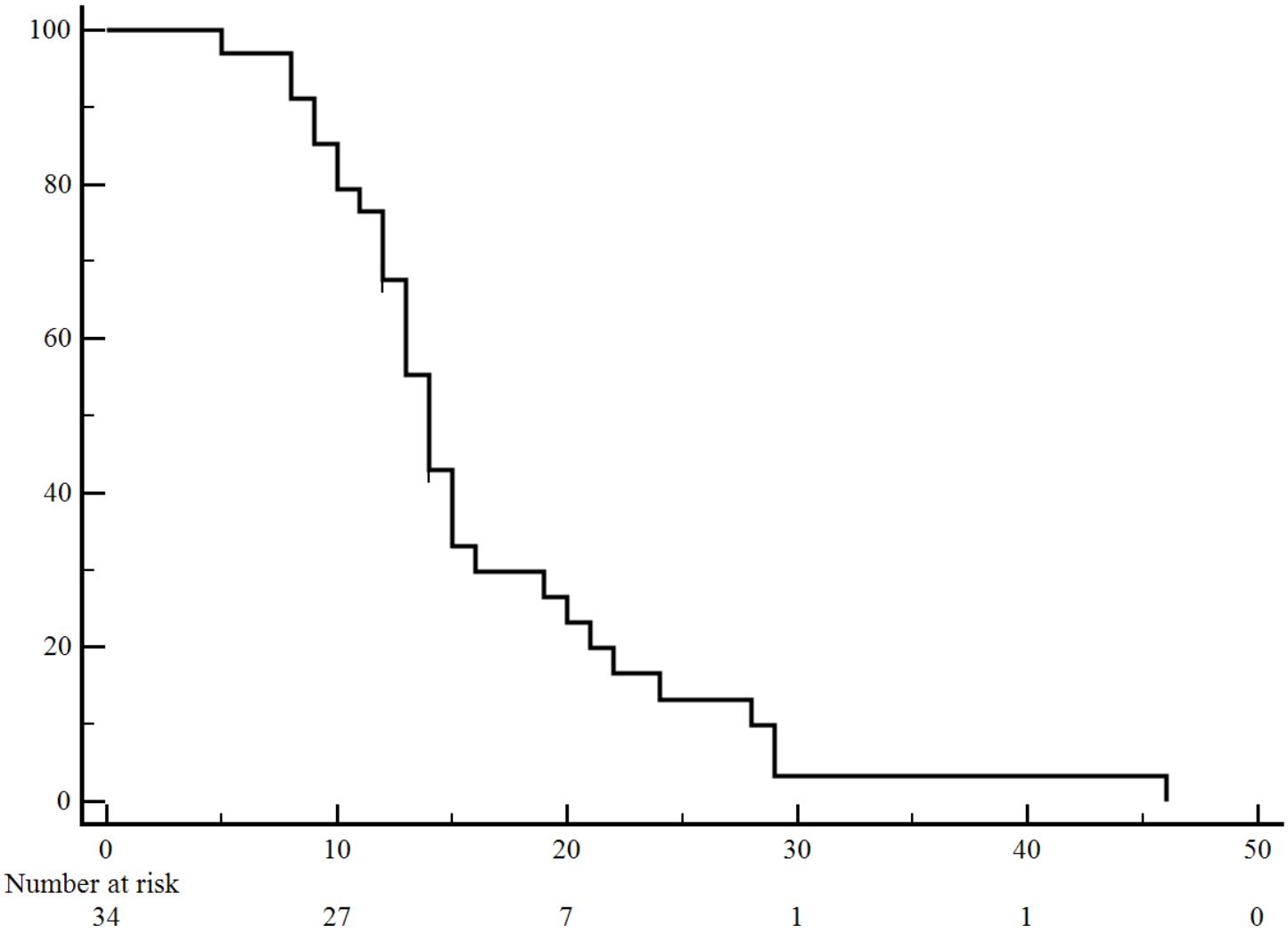
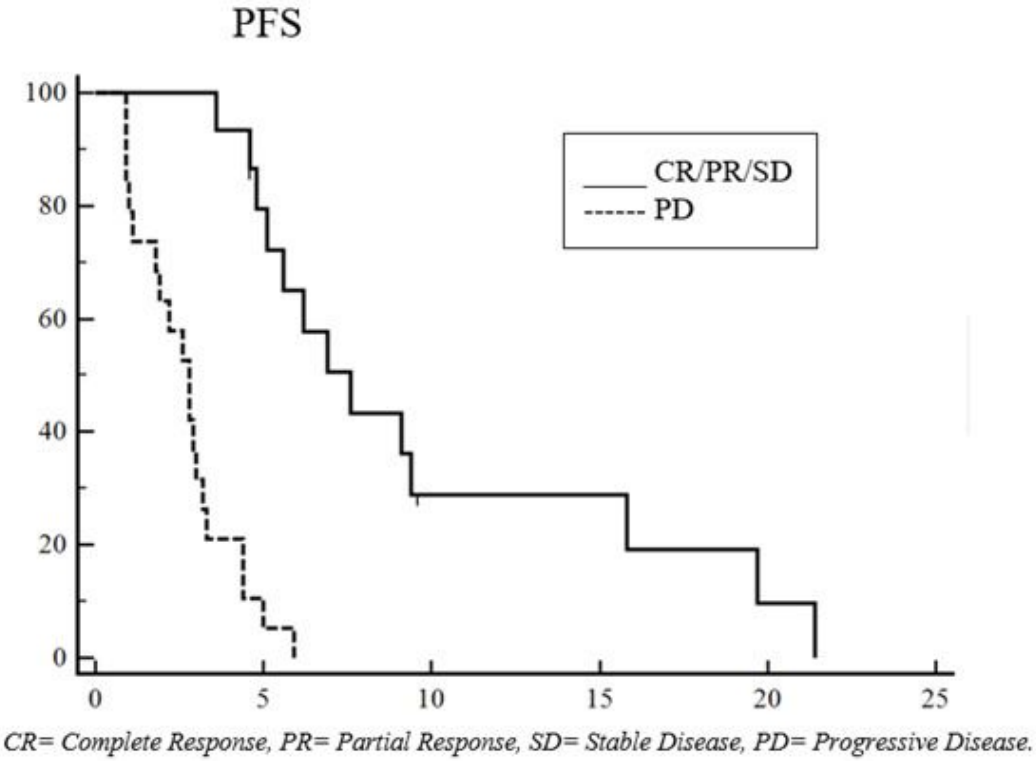


Figure 1

Kaplan-Meier curve of OS.



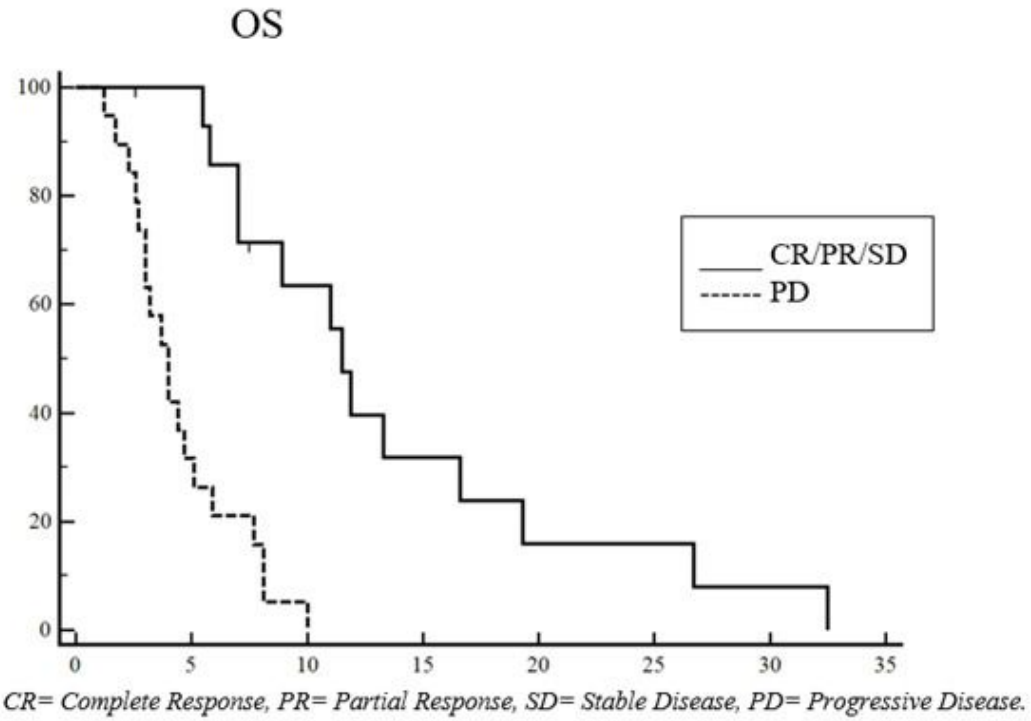


Figure 2

(Top panel) a. Kaplan-Meier curves of PFS. Curves include patients with PD and CR/PR/SD to second-line therapy as the best response, respectively. (Bottom panel) b. Kaplan-Meier curves of OS. Curves include patients with PD and CR/PR/SD to second-line therapy as the best response, respectively.

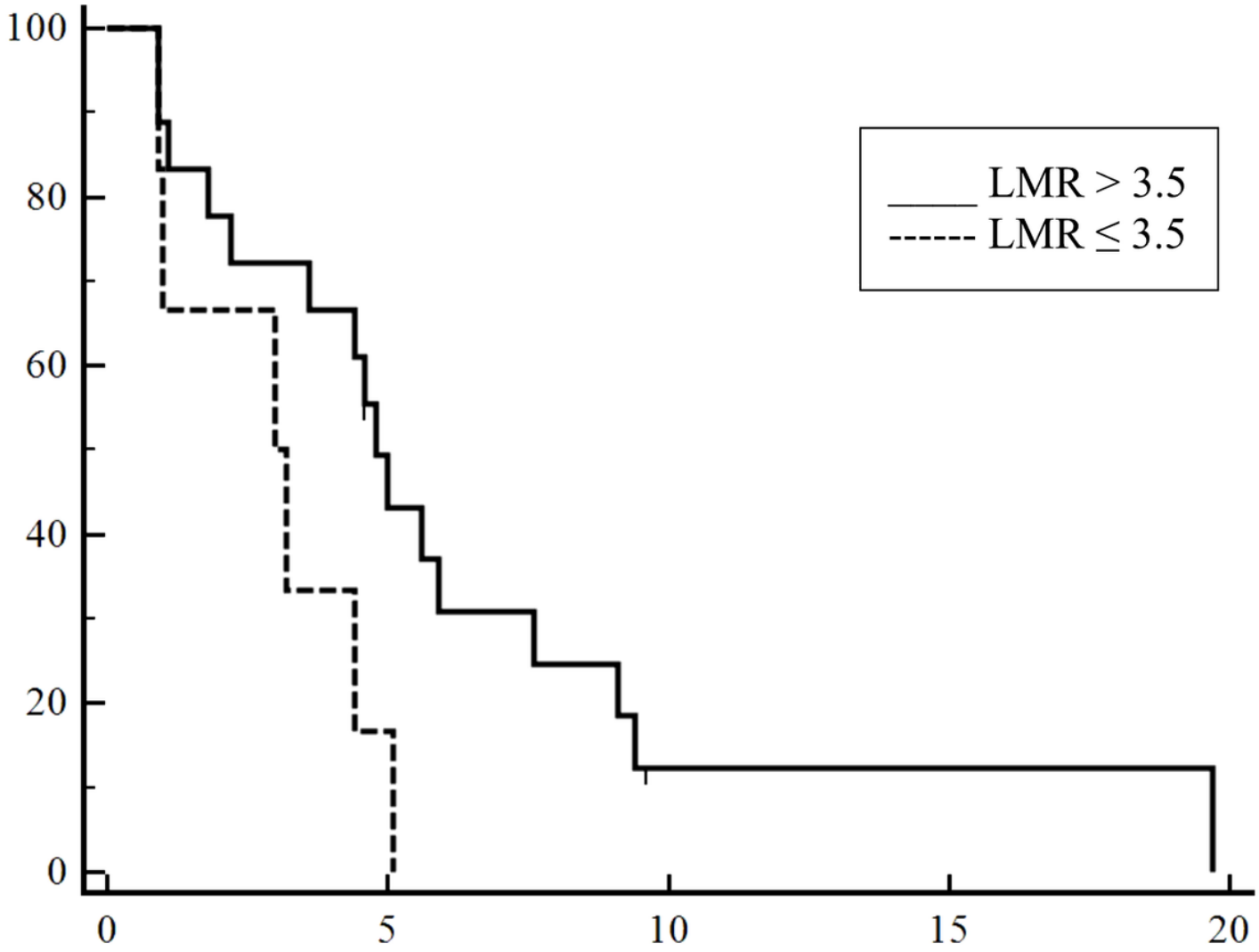


Figure 3

Kaplan-Meier curves of PFS. Curves include patients with LMR > and ≤ the cut-off value of 3.5 consisting in the 75th percentile