The Addition of Mifamurtide To Adjuvant Chemotherapy For Early Osteosarcoma: A Retrospective Analysis From Greece.

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Research Article

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Abstract

Background: Current treatment recommendations for high grade non-metastatic osteosarcoma include perioperative chemotherapy and surgery. Despite this intensive protocol, approximately 40% of patients will relapse. The addition of mifamurtide to adjuvant cytotoxic chemotherapy was associated with a significant improvement in 6-year overall survival (OS) in young patients with resectable osteosarcoma, leading to its approval in Europe and other countries. Very limited real-world data are reported on its use.

Methods: We retrospectively evaluated data from osteosarcoma patients who received mifamurtide in the adjuvant setting. Data were obtained from medical records in 2 high-volume bone sarcoma centers. The aim of this study was to collect real-world data on mifamurtide safety and efficacy in Greece.

Results: We identified 15 patients with completely resected osteosarcoma who received mifamurtide from September 2015 to January 2020. Median age at diagnosis was 24 years old (16-76). Osteosarcoma arose in the lower extremities (n=12), in the upper extremities (n=2) or in the ilium (n=1). The majority of patients (n=13) received cisplatin/doxorubicin/methotrexate as perioperative chemotherapy and the remaining patients cisplatin/doxorubicin. After a median follow-up of 46.9 months (range, 32.8-61.1), the median recurrence-free survival was 58.7 months (range, 18.5-98.8) and the median OS 64.1 months (range, 25.6-102.6). Except for fever and chills, the only adverse event probably related to mifamurtide was pericarditis (n=1).

Conclusions: Mifamurtide was well tolerated in a Greek osteosarcoma population, including patients older than 30 years. The small sample size and the non-comparative design do not allow drawing conclusions on the drug benefit in terms of survival.

Introduction

Although osteosarcoma is the most common primary bone tumor, it is considered an ultra-orphan cancer. It affects children and adolescents with a peak incidence between an age of 15 and 19 years; there is a second peak incidence though at 75-79 years [1]. Approximately 20% of patients present with metastatic disease and have a poor prognosis. Patients with localized high-grade osteosarcoma are managed with multimodal therapy, including neoadjuvant chemotherapy, surgery and adjuvant chemotherapy, with curative intent. The introduction of chemotherapy in the treatment algorithm of these patients dramatically improved their prognosis, with a long-term survival of approximately 16% with local therapy versus approximately 60-70% in patients treated with surgery plus chemotherapy [2–4]. It is believed that the majority of patients with localized disease at presentation have subclinical micrometastases, elucidating this survival benefit conferred by systemic therapy. The optimal chemotherapy regimen in early disease is yet to be defined, as there is no head-to-head comparison of the different drug combinations. However, the three-drug regimens have been shown to be superior to two-drug regimens [5] and the MAP (high-dose methotrexate, adriamycin, cisplatin) protocol is the most commonly used. Despite this intensive protocol, approximately 40% of patients will relapse. Prognosis of patients depends

on pathological response to neoadjuvant chemotherapy, with a 5-year overall survival (OS) of 55.5% in poor responders (necrosis <90%) versus 77.8% in good responders [6].

Muramyl tripeptide (MTP) phosphatidylethanolamine (MTP-PE), marketed as mifamurtide, is a fully synthetic analog of muramyl dipeptide (MDP), a component of the cell wall of Bacille Calmette-Guerin. Through encapsulation in liposomes mifamurtide is selectively delivered to mococytes and macrophages, acting as a non-specific immune modulator. There are preclinical data on the efficacy of the drug in spontaneous canine osteosarcoma and rodent xenograft models[7, 8]. The addition of mifamurtide to adjuvant cytotoxic chemotherapy was associated with a statistically significant improvement in 6-year OS in young patients with newly diagnosed, resectable high-grade osteosarcoma [9], leading to its approval in 2009 by the European Medicines Agency in this setting. It is reimbursed in many countries in Europe, Central and South America, Israel, and Turkey, whereas in the USA it remains an investigational drug.

Apart from the pivotal randomized phase III Intergroup study 0133 (Int-0133), only few data on mifamurtide use in early osteosarcoma are available, including two real-world studies [10, 11]. Here we present our experience regarding osteosarcoma patients treated with mifamurtide in the adjuvant setting in Greece. Given the existing controversy on the drug's benefit, we aimed to summarize patients' characteristics, as well as treatment outcome and safety in our country. Our results indicate that mifamurtide is a safe drug in the Greek population, including patients older than 30 years, and compare favorably to large randomized studies of early osteosarcoma in terms of clinical outcome.

Methods

We performed a retrospective study in two high-volume sarcoma centers in Greece, in which the majority of patients with bone sarcomas ≥16 years old are managed. All patients with newly diagnosed osteosarcoma in Greece between January 2015 and December 2020, who received mifamurtide, were included in the study. Osteosarcoma diagnosis was confirmed by tissue pathological examination both during the initial biopsy and surgery of the primary tumor. Mifamurtide (MEPACT) was scheduled twice/week × 12 weeks then weekly for 24 weeks for a total of 48 doses, at a dose of 2 mg/m^2 and it was administered after premedication with paracetamol.

Data were retrieved from the medical records. We analyzed the histopathological and clinical data, as well as the treatment regimens and outcomes. Variables of interest were: histological subtype and localization of the primary tumor, age at diagnosis of osteosarcoma, perioperative chemotherapy protocol, number of mifamurtide cycles, patterns of recurrence and survival.

Continuous variables were summarized using descriptive statistics, including me-dian and range values. Categorical variables were summarized using descriptive statistics, including counts and percentages. The Kaplan-Meier method was used for survival analysis and correlations between survival and potential prognostic features were analyzed using the log-rank test. OS was defined as the time between

osteosarcoma diagnosis and death of any cause. Patients who were still alive were censored at the last follow-up date. Recurrence-free survival (RFS) was defined as the time between osteosarcoma diagnosis and disease recurrence or death of any cause. Due to the small sample size we did not perform univariate and multivariate analysis using the Cox proportional hazards model. Statistical analyses were computed using SPSS 26 (IBM Corp., Armonk, NY). Significance was defined at $p<0.05$.

Results

Patients' characteristics

We identified 15 patients with completely resected osteosarcoma who received mifamurtide from September 2015 to January 2020. Table 1 summarizes their main clinicopathological characteristics. Median age at diagnosis was 24 years (16-76). The tumor was located in the lower extremities (n=12), in the upper extremities (n=2) and in the ilium (n=1). The most common osteosarcoma subtype was conventional osteoblastic (n=10), followed by chondroblastic or mixed chondroblastic and osteoblastic (n=2).

Table 1
Patients' clinicopathological characteristics.

Characteristics	No. (%)
Age at diagnosis	
Median (range)	24 (16-76)
Gender	
Male	7 (46.7)
Female	8 (53.3)
Primary tumor localization	
Femur	5 (33.3)
Knee	5 (33.3)
Tibia	2 (13.3)
Elbow	2 (13.3)
Ilium	1 (13.3)
Osteosarcoma subtype	
Osteoblastic	10 (66.7)
Chondroblastic or mixed chondroblastic/osteoblastic	2 (13.3)
Low-grade	1 (6.7)
Extraskeletal	1 (6.7)
Telangiectatic	1 (6.7)
Response to neoadjuvant chemotherapy	
Good (necrosis ≥90%)	5 (33.3)
Poor (necrosis <90%)	8 (53.4)

Treatment

MAP was the chemotherapy regimen in 13 patients and was administered in both the neoadjuvant and adjuvant setting, according to the protocol (Marina 2016). Neoadjuvant therapy was scheduled over a 10-week and adjuvant therapy over a 18-week period (week 12-29); supportive care with myeloid growth factor, dose reductions and therapy delays were decided by the treating physicians according to local practice. The remaining two patients (a 47-year old male with extraskeletal osteosarcoma and a 76-year old male with telangiectatic osteosarcoma) received only adjuvant therapy consisting of cisplatin and

doxorubicin. All patients underwent complete surgical removal of the primary tumor (R0). The patient with extraskeletal osteosarcoma received also radiation therapy.

Mifamurtide was initiated during adjuvant chemotherapy in six patients and at the end of adjuvant chemotherapy in nine patients. Twelve patients completed 48 cycles of mifamurtide, two patients interrupted the drug after 20 and 40 cycles due to recurrence and one patient died after 19 cycles of hemorrhagic stroke (not related to mifamurtide treatment).

Outcome and prognostic factors

After a median follow-up time of 46.9 months (range, 32.8-61.1), six patients experienced disease recurrence and five patients were deceased. At the time of the analysis, eight patients are alive with no evidence of disease and two patients are alive with disease recurrence. Of the five patients who died, four are dead of the disease and one of hemorrhagic stroke. The patterns of recurrence are depicted in Table 2. Median RFS was 58.7 months (range, 18.5-98.8), as shown in figure 1. Two-year-RFS and 3-year RFS rates were 73.3% and 66.7% respectively. The median OS was 64.1 months (range, 25.6-102.6) (figure 2). Two-year-OS and 3-year OS rates were 86.7% and 66.7% respectively.

Table 2
Patterns of recurrence in the six relapsed patients.

Patient No.	Site of recurrence	Recurrence-free survival (months)
1	Local recurrence (left ilium)	17
2	Lungs	29
3	Lungs	58.7
4	Lungs, liver	36.7
5	Lungs, pelvis	18.9
6	Lungs, bones	11.2

We performed subgroup analysis of the RFS and OS by the following variables: gender, age at diagnosis (>30 versus <30 years), response to neoadjuvant chemotherapy (good versus poor), location of the primary tumor (lower extremities versus upper extremities versus ilium) and osteosarcoma subtype (conventional osteoblastic versus other). Both RFS and OS were significantly reduced in poor responders to neoadjuvant chemotherapy (p=0.013 and p=0.038 respectively), as shown in figure 3, whereas the other factors were not found to have a statistically significant association with survival. Furthermore, location of the primary tumor influenced RFS, without reaching statistical significance (p=0.062).

Safety

There was no treatment-related death during mifamurtide treatment. Principal adverse events related to chemotherapy were leucopenia, neutropenia, anemia, thrombocytopenia, infections and transaminasemia. Mifamurtide administration was associated mostly with fever and chills, especially

during the initial doses, requiring symptomatic treatment in some patients. In one female patient mifamurtide treatment was delayed, due to investigations for persistent fever, which was finally attributed to the drug. Another female patient presented with chest pain after the 4th cycle of mifamurtide; cardiac ultrasound revealed pericarditis. The adverse event was considered probably related to mifamurtide and the patient received symptomatic treatment with pain relievers, while the drug was interrupted for 2 weeks. She did not report any more chest pain and ultrasound controls showed regression of pericarditis.

Discussion

Mifamurtide is the only approved immunotherapy in sarcomas. Its mechanism of action involves regulation of the balance between the proinflammatory and immunomodulatory function of macrophages [12]. Activation of the macrophages and monocytes leads to rapid induction of proinflammatory cytokines and cytotoxicity towards tumor cells, with no effect on non-cancer cells [8, 13–15]. Furthermore, the observation of improved survival in osteosarcoma patients after postoperative infection provides evidence for a role of the immune system activation in the outcome of the disease [16].

Notwithstanding the different new drugs that were found beneficial in relapsed/advanced osteosarcoma, such as the tyrosine kinase inhibitors sorafenib [17], regorafenib [18] and cabozantinib [19], the same chemotherapeutical agents are used in early disease since 30 years. Attempts to reverse the dismal prognosis of poor responders have been made by adding ifosfamide and etoposide (MAPIE protocol) [20] or pegylated interferon alfa-2b [21] to the postoperative regimen. No survival prolongation was achieved, whereas there are concerns for increase in secondary malignancies with alkylating agents [22].

A small phase II study of metastatic osteosarcoma patients demonstrated the biological effect of mifamurtide in lung metastases [14, 23], including inflammatory cell infiltration, through activation of alveolar macrophages [8]. The large Int-0133 study demonstrated that the addition of mifamurtide in patients ≤30 years old with early osteosarcoma conferred a 6-year OS rate of 78% versus 70%, with a hazard ration (HR) of 0.71 and a 6-year event-free survival (EFS) rate of 67% versus 61% (HR=0.8) [9]. A similar reduction in the risk of disease progression (HR=0.7) was also observed in the metastatic cohort, but it did not achieve statistical significance, probably due to the small sample size [24]. The rationale for mifamurtide administration after surgery in the Int-0133, concomitantly with adjuvant chemotherapy, relies on the minimal tumor burden of the disease at this time, with only eventual lung micrometastases. The patients in our analysis received the drug either concomitantly or at the end of adjuvant chemotherapy, mainly for practical reasons (availability of the drug). Some patients presented multiple toxicities related to neoadjuvant chemotherapy (mainly cytopenias and infections) and they received mifamurtide after completing adjuvant chemotherapy to avoid additional adverse events (fever), at the discretion of the treating physician. It is not known whether this different timing of the drug affects the patients' outcome.

The population in our study includes patients 16-76 years of age, with four patients >30 years, although mifamurtide was assessed in patients 2-30 years in the adjuvant setting. However, the drug was also

studied in metastatic osteosarcoma patients until 59 years old in the phase II study and in a patient-access protocol [13, 23] and it was found safe and beneficial. Given the age distribution of osteosarcoma, we decided to include mifamurtide in the treatment algorithm of older patients with a good performance status, as well. As expected, the primary tumor arose in the lower extremities in the majority of our patients (77%), similarly to the registration trial Int-0133 [9]. Sixty-seven percent of the patients in our series had a high-grade osteoblastic osteosarcoma, whereas all patients in the Int-0133 study had a high grade osteosarcoma. A small minority in our series had chondroblastic and low-grade osteosarcoma, two rare subtypes whose optimal treatment is yet to be defined. Due to the extremely small number of cases, mifamurtide benefit in these subtypes cannot be assessed. Finally, approximately half of our patients were poor responders to neoadjuvant chemotherapy, similarly to the Int-0133 study.

We report a median RFS of 58.7 months and a 2-year and 3-year RFS rates of 73.3% and 66.7% respectively, which are equivalent to historical control in the EURAMOS trial with the MAP regimen (3-year EFS rate of 77%) [21] and slightly inferior to the results of the Int-0133 study (4-year EFS rate of 69% with mifamurtide) [9]. Older age has been associated with worse prognosis in high-grade osteosarcoma [6, 25] and this could partially explain our results. Our study is the only one published reporting data on mifamurtide use in early osteosarcoma including patients >30 years (27%). In addition, we performed a retrospective real-world analysis of an osteosarcoma series, consisting of a different population from the randomized phase III trials. Real-world data are valuable tools for a more thorough drug benefit-risk ratio evaluation; they originate from a broader population representing the real clinical setting. Another two real-world studies on patients with localized osteosarcoma treated with mifamurtide from Turkey and Czech Republic have recently been published, including 19 and 23 patients respectively [10, 11]. These studies reported a 43-month OS rate of 87.5% and 3-year EFS of 87.4% respectively.

Our study demonstrated that mifamurtide has a manageable safety profile, in line with previous reports [9, 13, 24, 26], not only in young, but also in older patients. Its rapid clearance from the blood after intravenous administration and the absence of toxicity in non-cancer cells support this finding [13]. Apart from fever and chills, the only adverse event that we observed is mild pericarditis in a 26-year old female with no medical history. Rare cases of pericardial effusion or pericarditis, related to mifamurtide have been described, resolved after drug discontinuation or colchicines treatment [13]. A possible hypersensitivity reaction has been hypothesized, based on pleural biopsy in a patient who presented with pericardial and pleural effusion 11 months after mifamurtide discontinuation [27].

Our study has several limitations: i) the retrospective design and the absence of control arm, to compare the outcomes with and without mifamurtide ii) the small sample size, that fits with the ultra-rare disease setting and iii) the different timing of mifamurtide initiation among patients (concomitantly to adjuvant chemotherapy initiation or after its completion), hindering the analysis of its effect.

Conclusion

Notwithstanding the multimodality treatment in localized osteosarcoma, 30-40% of patients will die of the disease. Mifamurtide is the only “new” agent approved in some countries for localized high-grade osteosarcoma in over 30 years, targeting lung micrometastases through activation of the innate immunity. This small real-life observational study further confirms the registration phase III trial and indicates that mifamurtide is well tolerated as an add-on to multiagent adjuvant chemotherapy after macroscopically complete surgical resection. Our series is unique as it includes osteosarcoma patients in the two age peaks (until 76 years old), reassuring about the use of the drug in the oldest age group. The favorable toxicity profile coupled with its administration on an outpatient basis, make it an attractive agent. The non-comparative design and the small sample size do not allow drawing conclusions on the enhancement of DFS and OS. Given the existing debate on mifamurtide benefit and the need for further evaluation of its use, a French randomized phase III clinical trial in newly diagnosed high-risk osteosarcoma is ongoing [28]. Additional real-life data are also warranted, to offer clinical guidance in diseases where large randomized trials are difficult to conduct.

Declarations

Author Declarations

Ethics approval: Ethics committee approval was waived due to its retrospective, non-interventional nature.

Consent for publication: Patient consent was waived due to its retrospective analysis of standard routine management. Furthermore, the data were provided in an anonymised format and patients cannot be identified.

Availability of data and material: The data used and/or analyzed during the current study are available from the corresponding author upon request.

Conflicts of interest/Competing interests: S.K., I.K., A.P. and A.A. received honoraria from Genesis Pharma outside the scope of this study.

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Authors' contributions: S.K., A.A. and A.P. participated in study conception and drafting of the manuscript. I.K., E.M., T.K., G.D., S.T. and N.S. participated in data acquisition and interpretation, and in critical revision. All authors have read and agreed to the published version of the manuscript.

Acknowledgements: Not applicable

Code availability: Not applicable.

Compliance with Ethical Standards

Research involving Human Participants and/or Animals: The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Informed consent: Patient consent was waived due to its retrospective analysis of standard routine management. Furthermore, the data were provided in an anonymised format and patients cannot be identified.

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Figures

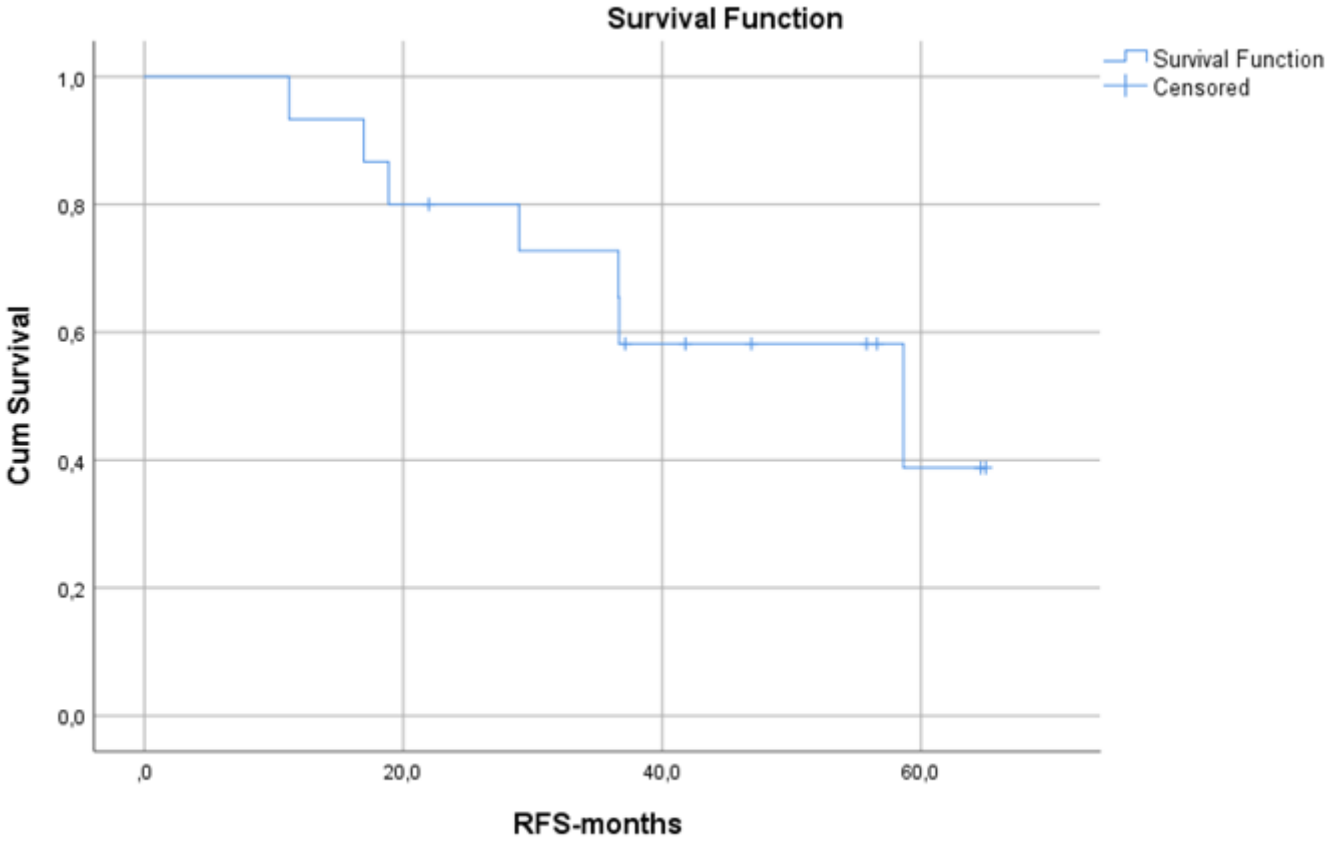


Figure 1

Kaplan-Meier estimation of recurrence-free survival in the total cohort

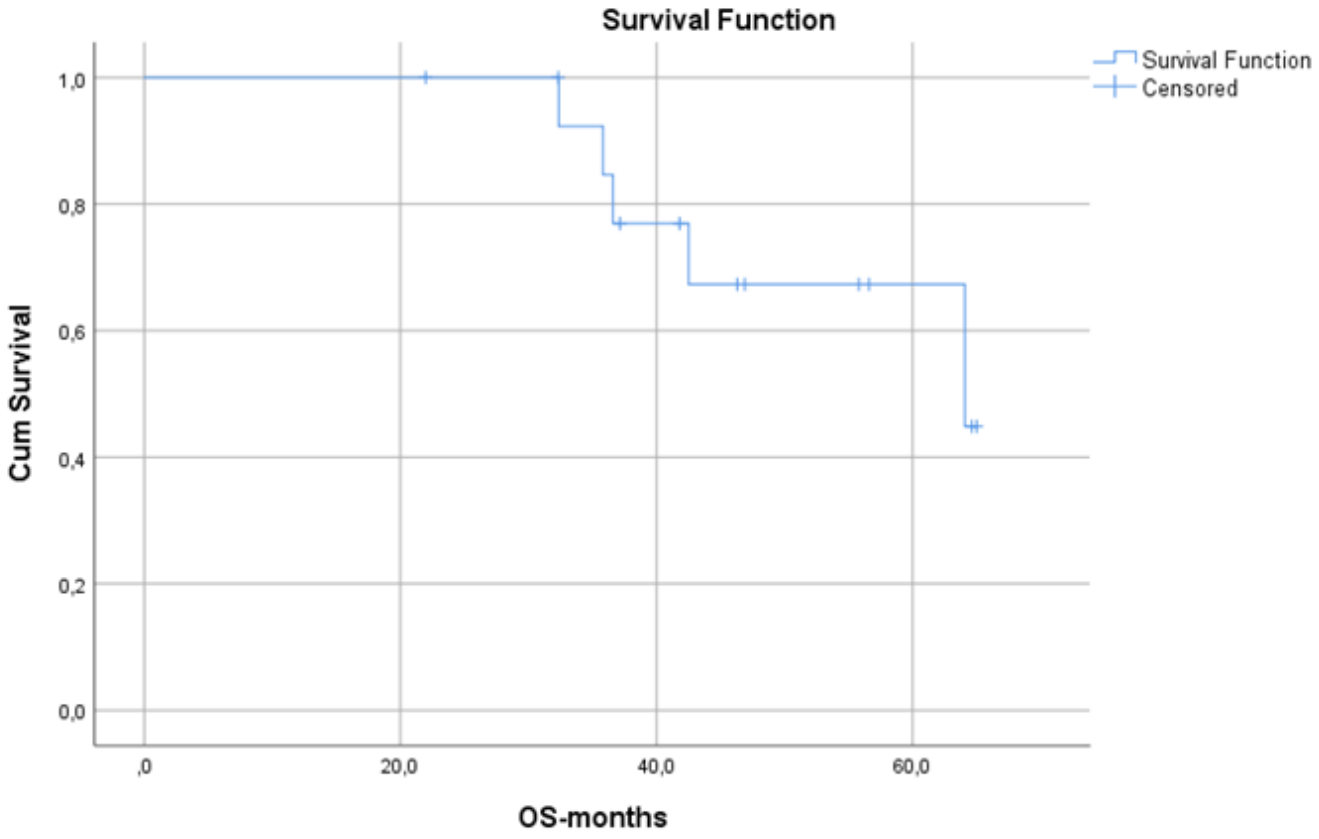
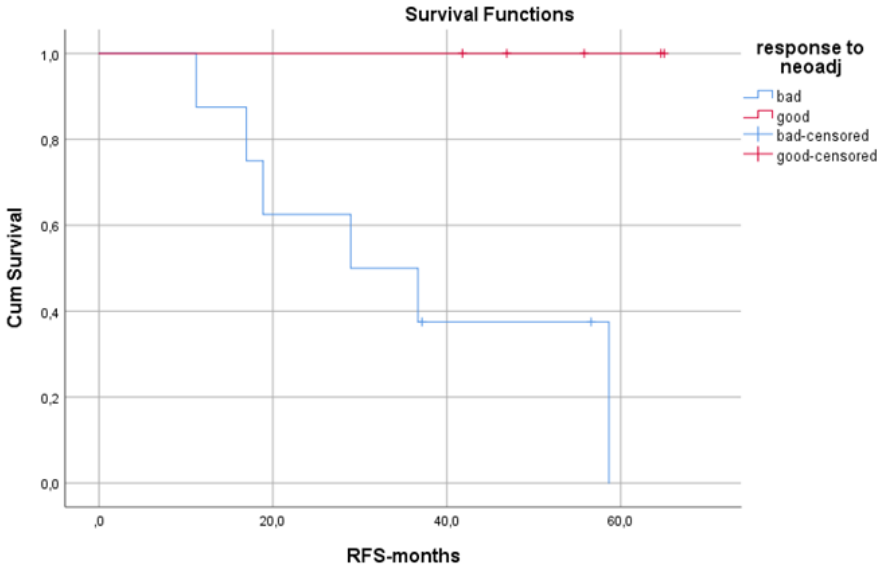


Figure 2

Kaplan-Meier estimation of overall survival in the total cohort

(a)



(b)

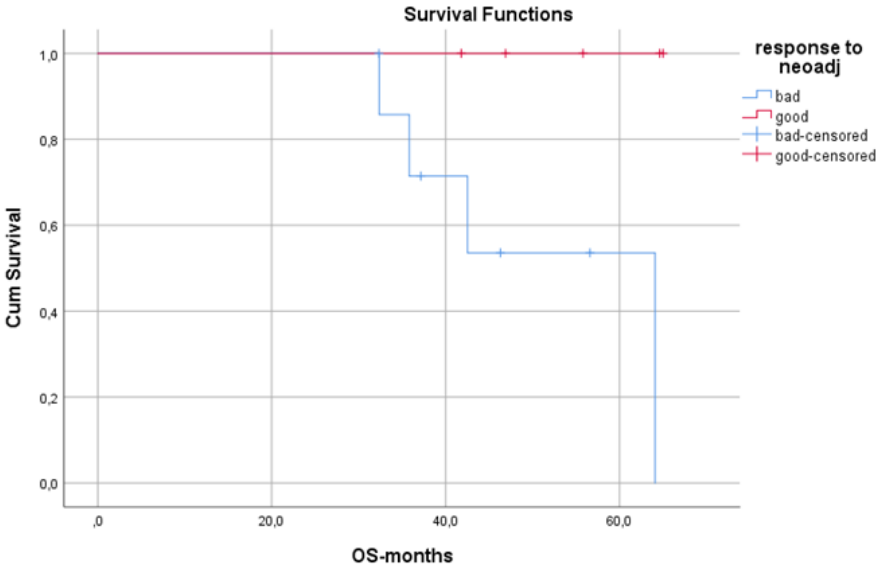


Figure 3

Kaplan-Meier estimation of a) recurrence-free survival and b) overall survival in the total cohort divided into two groups by response to neoadjuvant chemotherapy