Immune Checkpoint Inhibitor Therapy for Recurrent Meningiomas: A Retrospective Chart Review

Priya Nidamanuri (nidamanurip2@upmc.edu)
UPMC Hillman Cancer Center Shadyside https://orcid.org/0000-0003-2693-9684
Jan Drappatz
UPMC Hillman Cancer Center Shadyside

Research Article

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Abstract

Introduction: Meningiomas that progress after surgery and radiotherapy represent an unmet medical need. Expression of PD-1 and PDL-1 has been demonstrated in meningiomas and is proportional to tumor grade, suggesting a potential role for anti-PD-1/anti-PDL-1 inhibitor therapy. We explored the efficacy of immune checkpoint inhibitor therapy for recurrent meningiomas with primary endpoints of progression-free survival (PFS) and overall survival (OS).

Methods: This is a retrospective chart review of patients with meningioma who were treated with PD-1 inhibitors at UPMC Hillman Cancer Center. Any patient over age 18 who received immunotherapy was included in this study. Patients received treatment until development of disease progression, intolerable toxicities or adverse events, death, or oncologist decision. Serial radiographic assessments were made every 3-6 months.

Results: Between January 2015 and November 2021, eight patients received anti-PD-1 therapy. All patients underwent tumor resection and radiosurgery, and four patients received prior systemic therapy. Six out of eight patients experienced symptomatic perilesional edema and three patients experienced exacerbation of seizures. Median PFS was 7 months (95% CI 1-24) and median OS was 1.75 years (95% CI 1.5-4.0). In patients with positive PD-1 or PD-L1 expression, median PFS was 2 years and median OS was 3 years.

Conclusion: Anti-PD-1 therapy was associated with a manageable safety profile in patients with recurrent meningiomas. Patients with WHO Grade III tumors and positive PD-1/PD-L1 expression were noted to have increased PFS and OS, suggesting a potential role for immunotherapy in this specific subset of patients. Further studies are needed to investigate this in a larger patient population.

Introduction

Meningiomas represent one third of all central nervous system tumors and are the most frequently diagnosed primary intracranial tumors [1]. They originate from arachnoid cap cells within the arachnoid mater. Although the majority of these tumors are benign, their size and location intracranially can lead to significant morbidity and mortality [2]. The World Health Organization (WHO) classification of meningiomas includes three grades; I (benign), II (atypical), and III (malignant) [3]. The OS and PFS of each grade are 80-90% and 75-90%, 53-79% and 23-78%, and 14-34% with rapid progression, respectively [4]. Although surgical resection +/- radiotherapy serve as the initial therapeutic approach and are typically able to control disease in patients with benign meningiomas, higher-grade tumors (WHO Grade II/III) are more likely to recur following this initial treatment. Many alternative agents, including chemotherapeutic agents, targeted drugs, angiogenesis inhibitors, and somatostatin analogues, have been studied but have not displayed clear evidence of lengthening PFS or OS in this subset of patients [5].

Checkpoint-inhibitors, along with other forms of immunotherapy, have been investigated as a potential treatment option in recent years [6]. Meningiomas are known to exhibit several immune checkpoint

proteins, notably PD-1 and PD-L1 [4]. PD-L1-positive tumor cells bind onto PD-1 receptors on T cells and B cells to inhibit T-cell activation [6]. It has been discovered that the expression of these proteins, specifically PD-L1, is proportional to tumor grade, meaning that higher grade meningiomas express a greater amount of PD-L1 [7]. In addition, it has been shown that PD-L1 is predictive of poor overall survival and is associated with disease progression and recurrence [6, 8]. These findings suggest a potential role for anti-PD-1/anti-PD-L1 inhibitor therapy in the treatment of recurrent, high-grade meningiomas. Most studies regarding this topic have demonstrated the presence of immune checkpoint proteins that may suggest the role of these therapies, but there are very few individual case reports of patients with observed regression of meningioma with immune checkpoint inhibitor therapy [9]. This retrospective chart review aims to clarify the effectiveness of anti-PD-1 inhibitor therapy in the treatment of recurrent meningiomas by investigating primary endpoints of PFS and OS.

Patient Selection And Methods

The records of patients at University of Pittsburgh Medical Center Hillman Cancer Center between January 2015 and November 2021 were reviewed retrospectively between April 2021 and November 2021. The study was reviewed and approved by the University of Pittsburgh Institutional Review Board and designated as exempt under section 45 CFR 46.104(d)(4). Funding for use of anti-PD-1 therapy was provided by patients' insurance or through the manufacturer's patient assistance programs in patients whose insurance coverage was denied.

All patients above age 18 who were treated with anti-PD-1 therapy at any point in their disease course were included in this study. There was no limit on the number of prior or subsequent therapies. All patients had a tumor WHO grade of at least II or III at the time of immunotherapy initiation, received at least one dose of anti-PD-1 inhibitor therapy, and had at least one post-treatment radiographic follow-up. The immune checkpoint inhibitors used in this study were nivolumab and pembrolizumab, both of which are monoclonal IgG4 antibodies that target PD-1 [9]. Of the eight patients included in this study, seven patients received nivolumab 3mg/kg intravenously every 2-4 weeks, and one patient received pembrolizumab 2mg/kg every 3 weeks. Treatment was continued at these time intervals until development of PD, significant toxicity or adverse event, or physician decision. Toxicities were rated based on the Common Terminology Criteria for Adverse Events (CTCAE) [10]. Additionally, variables including tumor grade both at diagnosis and at immunotherapy initiation, comorbid conditions, tumor mutational burden and PD-1/PD-L1 status, and prior and subsequent therapies, performance statuses as defined by the Karnofsky Performance Status Scale (KPS) and the Eastern Cooperative Oncology Group (ECOG) were recorded.

The Response Assessment in Neuro-Oncology Working Group (RANO) criteria to assess for progression of disease was used in this chart review [11]. Progression of disease was defined as a radiographic increase in tumor size on MRI brain by greater than or equal to 25% or development of any new lesions, and stability of disease was defined as <25% change in tumor size and no development of new lesions. Based on these definitions, PFS was defined as the time from the first day of immune therapy to the date

of PD seen on MRI brain, and OS was defined as the time from the first day of immune therapy to the date of patient death. The primary endpoints of this study were to evaluate the PFS and OS of patients with recurrent meningioma who were treated with immunotherapy, and the secondary endpoints were to evaluate the toxicities and adverse outcomes associated with immunotherapy in these patients. Kaplan-Meier survival curves were created using MedCalc Statistical Software to illustrate PFS and OS and to calculate 95% confidence intervals.

Results

Patient characteristics

Between January 2015 and November 2021, eight patients with high-grade meningioma were treated with anti-PD-1 therapy. Seven patients were treated with Nivolumab, and one patient was treated with Pembrolizumab. Six of these patients were men (75%) and two were women (25%) with ages ranging from 38-79 (median 62.5). At the time of immunotherapy initiation, four patients had WHO Grade II tumors and four patients had WHO Grade III tumors. All target lesions at the start of immunotherapy initiation were >10mm in two dimensions. Three patients had tumors with positive PD-L1 expression, and one of these patients also had positive PD-1 expression. Two patients were PD-L1 negative, and the remainder were not tested. Patient characteristics are outlined in Table 1 and co-morbid conditions are outlined in Table 2.

Table 1: Patient characteristics

This table outlines data regarding patient characteristics including age, tumor grade and mutations, and prior therapies along with survival analysis of primary endpoints (PFS and OS).

Age: Median 62.5 (38-79)
Male to Female: 6:2
Grade III:

- Mutational burden (Ki-67):
  - <5%: 1
  - 15-20%: 1
  - 30-40%: 1
  - 50-60%: 1
- NF-2 mutation: 3
- PD-1/PD-L1 status: 2 PD-L1 strong positive, 1 PD-1 strong and PD-L1 focal weak, 1 negative

Grade II:

- Mutational burden (Ki-67):
  - 10-15%: 2
  - 15-20%: 2
- NF-2 mutation: 1
- PD-1/PD-L1 status: 1 PD-1 and PD-L1 negative, 3 not tested

Prior therapy:

- Surgery: 8
  - Repeat surgery: 5
- Radiotherapy: 8
  - Involved field radiation: 3
  - Stereotactic radiosurgery: 4
  - Gamma knife/CyberKnife radiosurgery: 4
  - Intensity-modulated radiation therapy: 1
- Systemic therapy
  - Bevacizumab: 1
  - Everolimus: 1
  - Bevacizumab + Everolimus: 1
  - Ipilimumab + Interferon: 1

Anti-PD-1 therapy

- Nivolumab: 7
  - Concurrent Bevacizumab: 3
  - Concurrent Ipilimumab + radiosurgery: 3
  - Monotherapy: 1
- Pembrolizumab: 1

Median time to start of immunotherapy from date of diagnosis: 6 years
Median duration of immunotherapy: 1.75 years
Survival analysis

- Median PFS: 7 months (1-42 months)
  - Grade III PFS: 15 months (2-42 months)
  - Grade II PFS: 5 months (1-18 months)
  - PD-1/PD-L1 + PFS: 2 years (6-42 months)
- Median OS: 1.75 years (1.5-4.5 years)
  - Grade III OS: 2.5 years (1.5-4.0 years)
  - Grade II OS: 1.5 years (1.5-4.5 years)
  - PD-1/PD-L1 + OS: 3 years (2-4 years)

Table 2: Co-morbid conditions

This table outlines the comorbid conditions of the patients included in this study.

Co-morbid conditions	Number of patients
Seizure disorder	7
Hypertension	5
Hyperlipidemia	2
GERD	2
Diabetes Type II	2
Depression	2
Hypothyroidism	1
Coronary artery disease	1
Childhood ALL s/p prophylactic cranial radiation therapy	1
Prostate cancer s/p prostatectomy	1
Metastatic melanoma	1
Stage I Lung adenocarcinoma	1

Prior therapies

All eight patients underwent craniotomy for tumor resection along with radiotherapy as part of standard initial treatment. Three patients underwent involved field radiation, four patients underwent stereotactic radiosurgery, four patients underwent gamma knife or CyberKnife radiosurgery, and one patient underwent intensity-modulated radiation therapy (IMRT). Five patients underwent multiple craniotomies throughout their disease course due to tumor recurrence. Prior systemic therapies included Bevacizumab (one patient), Everolimus (n=1), Everolimus with Bevacizumab (n=1), Octreotide LAR (n=1), and Ipilimumab with Interferon (n=1).

Anti-PD-1 therapy

One patient received Pembrolizumab and seven patients received nivolumab. Of the patients who received nivolumab, three were treated with concurrent Bevacizumab to minimize steroid requirements and control peritumoral edema, three were treated with concurrent ipilimumab and radiosurgery, and one received nivolumab monotherapy. The median time from date of diagnosis to date of immunotherapy initiation was 6 years, and the median duration of immunotherapy was 21 months. Three patients were noted to have radiographic progression within the first two months of immunotherapy initiation (37.5%); two of these patients received Nivolumab and were taken off treatment after development of radiographic and clinical progression, and one patient received Pembrolizumab and was continued on this despite development of interval radiographic progression because it was also being used for concurrent treatment of metastatic melanoma and lung adenocarcinoma in that patient. Seven out of

eight patients were noted to have radiographic progression following immunotherapy initiation, and one patient continues to have stable disease.

Survival analysis

The primary endpoints of this study were PFS and OS of patients with high-grade meningioma who were treated with immunotherapy. The median PFS was 7 months (95% CI 1-24) with a range of 1-42 months and the median OS was 1.75 years (95% CI 1.5-4.0) with a range of 1.5-4.5 years. Of the patients with WHO Grade III tumors at time of immunotherapy initiation, the median PFS was 15 months (range 2-42) and the median OS was 2.5 years (range 1.5-4.0). The remaining patients with WHO Grade II tumors had a median PFS of 5 months (range 1-18 months) and a median OS of 1.5 years (range 1.5-4.5 years). Three out of eight patients had tumors with positive PD-1 or PD-L1 expression; the median PFS for these patients was 2 years and the median OS was 3 years. Two patients died, and the other six patients remained alive by the time of data collection, with two patients continuing to receive active treatment with nivolumab. PFS and OS are displayed in Fig. 1 and Fig. 2, respectively.

Toxicities and Adverse Events

The most common treatment-related toxicities noted were symptomatic perilesional edema (n=6) and exacerbation of seizure disorder (n=3). Two patient experienced poor wound healing complicated by multiple infections at their craniotomy sites, and one of these patients suffered from right vertex and posterior left temporal lobe infarcts thought to be secondary to venous occlusion. Two patients experienced adverse effects of concurrent Bevacizumab treatment including lower extremity edema from proteinuria, cardiomyopathy, weight gain, and hypertension. Two patients died, one due to pneumonia and one due to multi-organ failure secondary to septic shock. Median ECOG score was 2 and median KPS score was 60. Graded treatment-related toxicities and adverse outcomes are outlined in Table 3.

Table 3
Toxicities and adverse outcomes

Co-morbid conditions	Number of patients
Seizure disorder	7
Hypertension	5
Hyperlipidemia	2
GERD	2
Diabetes Type II	2
Depression	2
Hypothyroidism	1
Coronary artery disease	1
Childhood ALL s/p prophylactic cranial radiation therapy	1
Prostate cancer s/p prostatectomy	1
Metastatic melanoma	1
Stage I Lung adenocarcinoma	1

This table illustrates the various toxicities and adverse outcomes experienced by patients included in this study with ratings based on the Common Terminology Criteria for Adverse Events [10].

Discussion

Meningiomas account for one third of all primary brain tumors and can be classified as WHO Grade I, II, or III [1, 3]. Typically, meningiomas are first treated with attempts at surgical resection and/or radiotherapy, though high-grade meningiomas are more likely to recur despite this initial treatment [5]. For these meningiomas that recur after surgery and radiotherapy, there is no effective salvage therapy [12]. Because meningiomas have been shown to exhibit immune checkpoint proteins, including CTLA-4, PD-1, and PD-L1, immune checkpoint blockade has become a potentially promising treatment option for high-grade meningiomas, particularly given evidence that PD-L1 expression is proportional to tumor grade [4, 6, 7, 12]. The PD-1/PD-L1 pathway mediates immune system evasion in these tumors, and blockade of this pathway has been shown to improve overall survival for multiple solid tumors including urothelial cancer, squamous cell head and neck cancer, non-small-cell lung cancer, and melanoma [12–16]. Most studies have demonstrated a potential role for immune checkpoint blockade in the treatment of high-grade, recurrent meningiomas given the increased expression of immune checkpoint proteins (notably PD-L1) on higher-grade tumors and their association with decreased OS, though few case reports have demonstrated tumor response with immune checkpoint inhibitor therapy. One case report by Gelerstein et al. describes a patient whose meningioma decreased in size following treatment with nivolumab [9]. Our

retrospective chart review, although a preliminary observation given the limited sample size, similarly suggests a potential role for immune checkpoint inhibitors in recurrent, high-grade, pre-treated meningiomas. The median PFS and OS for the entire sample was 7 months and 1.75 years, respectively. Of note, patients with WHO Grade III meningiomas exhibited a higher median PFS (15) and median OS (2.5 years) compared to those with WHO Grade II meningiomas (median PFS 5 months and median OS 1.5 years), and patients with positive PD-1 or PD-L1 expression had a median PFS of 2 years and median OS of 3 years. In addition, the three patients with positive PD-1/PD-L1 expression all had WHO Grade III tumors. These findings appear to affirm the correlation between tumor grade and PD-1/PD-L1 status and the potential increased benefit of immunotherapy in this specific subset of patients.

It is important to acknowledge several limitations of this study. Because it is a retrospective chart review of patients from a single institution, there is some degree of selection and sampling bias. In addition, the very small sample size makes it difficult to draw meaningful conclusions that are generalizable to a larger population. The patient sample chosen for this study was heterogeneous with varying prior, concurrent, and subsequent therapies that may have affected the efficacy of the immunotherapy. However, despite these limitations, this study demonstrates that immunotherapy is a potentially viable treatment option for patients with recurrent, pre-treated, high-grade meningiomas with a relatively manageable safety profile. Further studies are needed to investigate the use of immunotherapy agents in a larger sample of patients to determine which subset of patients would benefit most from immunotherapy and which specific anti-PD-1 inhibitors are most efficacious.

Declarations

The authors of this retrospective chart review declare that no funds, grants, or other financial support was received during the composition of this manuscript. The authors report no conflicts of interest.

Author Contributions

Both Dr. Nidamanuri and Dr. Drappatz contributed to the study concept and design. Data acquisition was performed by Dr. Nidamanuri, and data analysis was performed by both Dr. Priya Nidamanuri and Dr. Jan Drappatz. The first draft of the manuscript was written by Dr. Priya Nidamanuri, and both authors commented on and edited previous versions of the manuscript. Both authors read and approved the final manuscript.

Data Availability

All data recorded and analyzed during this study are included in this manuscript and the associated Figures and Tables.

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Figures

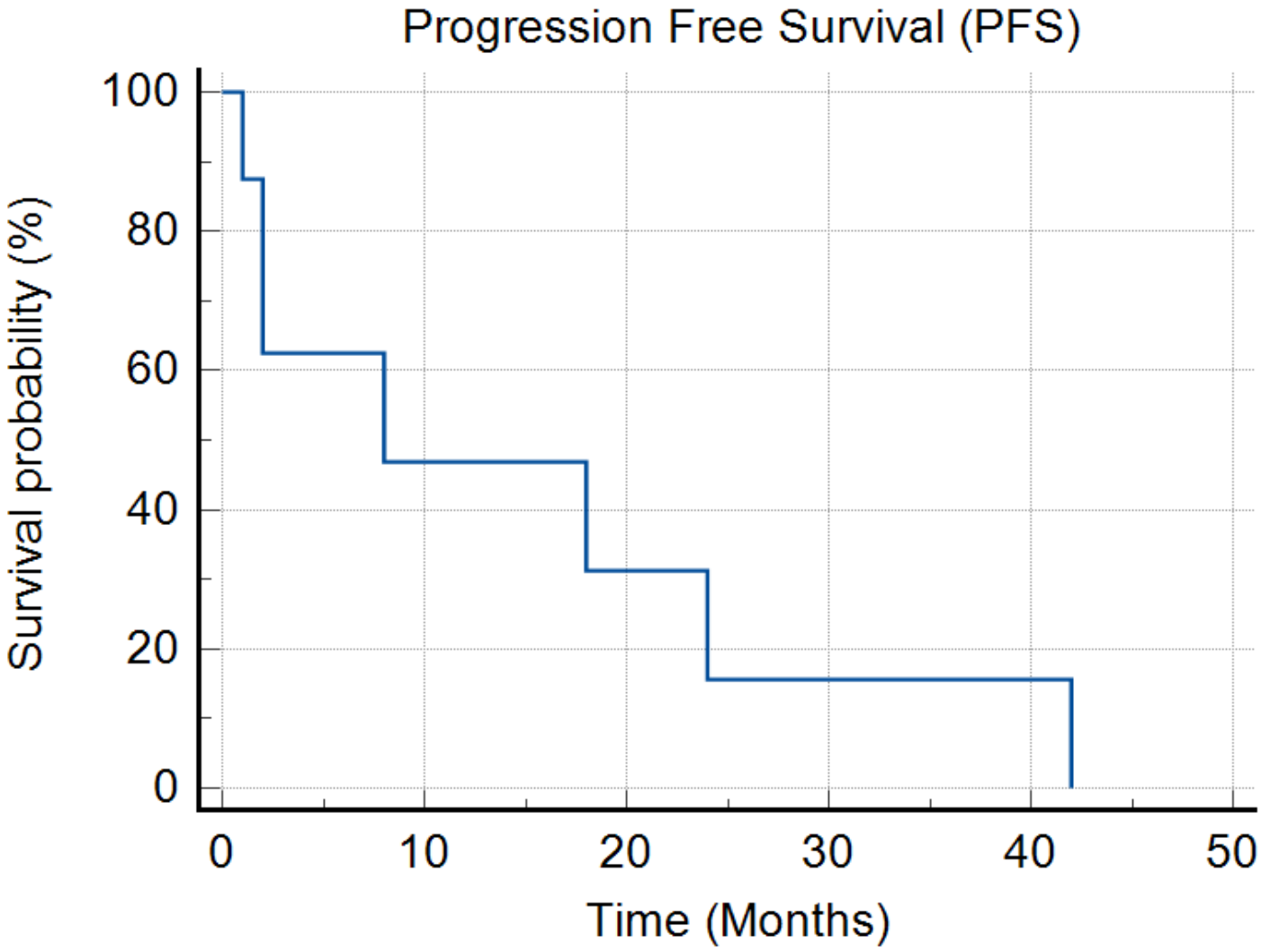

Figure 1

Kaplan Meier Progression Free Survival Curve. Median PFS 7 months (95% CI 1-24).

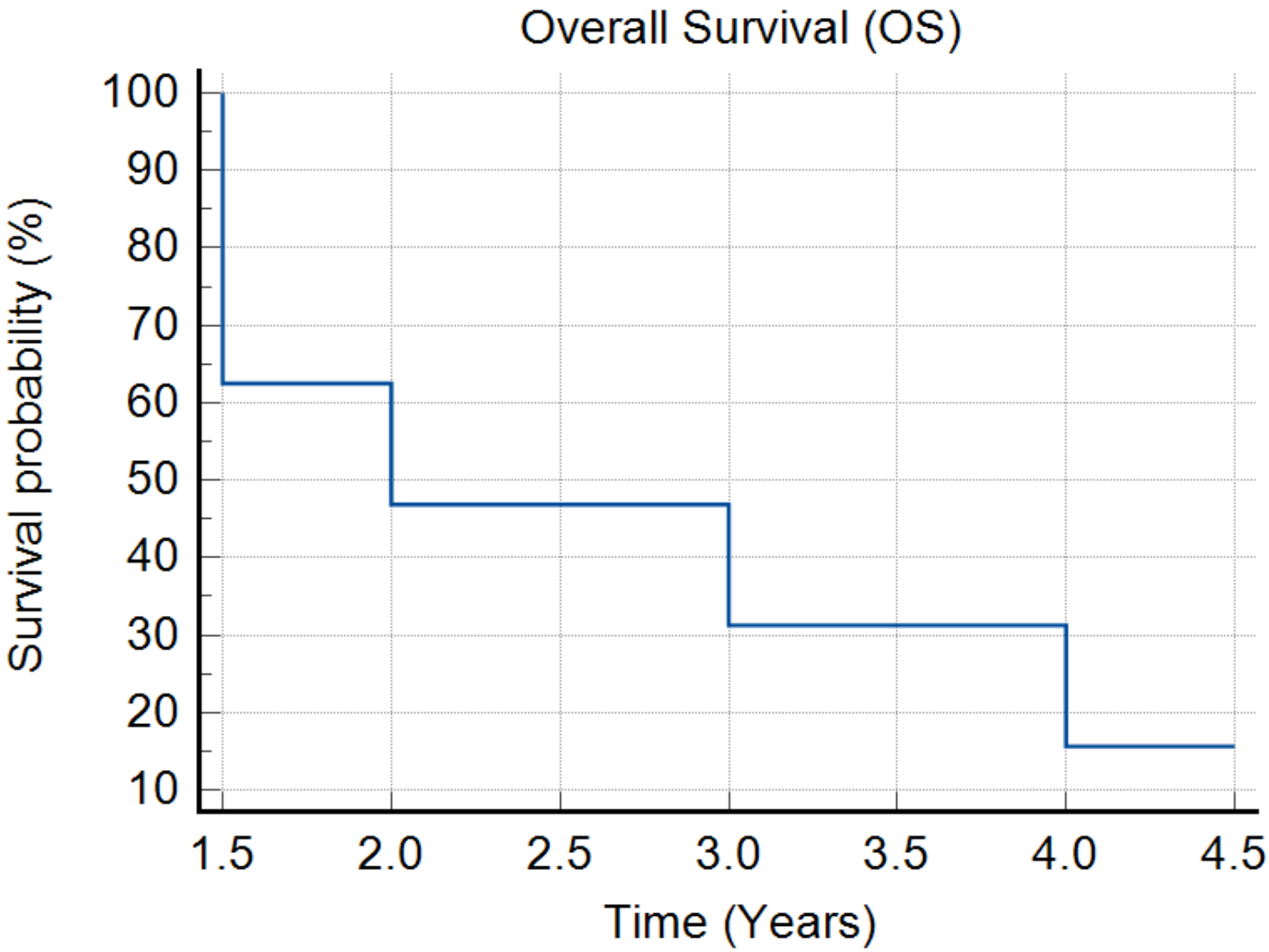

Figure 2

Kaplan Meier Overall Survival Curve. Median OS 1.75 years (95% CI 1.5-4.0).