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Biometric index and hormonal status in glioblastoma patients

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Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

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Ciências médicas e da saúde

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Biometric index and hormonal status in glioblastoma patients

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Paulo José Campos Linhares Vieira

COORIENTADOR (se aplicável)

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Faculdade de Medicina da Universidade do Porto, 28/03/2019

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À minha mãe e ao meu pai, pelo amor e carinho sempre presentes, por me terem apoiado nesta segunda corrida de fundo, pelo exemplo que são para mim.

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Title page

Title: Biometric index and hormonal status in glioblastoma patients

Short title: Biometric index and hormonal status in glioblastoma

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Summary

Biometric index and oestrogens exposure were assessed as prognostic biomarkers in glioblastoma patients. A retrospective review of glioblastoma patients submitted to surgical resection was performed, in which progression free survival and overall survival were primary endpoints. Our data suggest that in female patients obesity is a protective biomarker and in male patients being overweight is protective, whereas no relationship was found between oestrogens exposure and glioblastoma survival.

Abstract

Purpose: The impact of oestrogens and body mass index (BMI) in glioblastoma multiforme (GBM) is inconsistent. We assessed its potential as prognostic biomarkers in progression free survival (PFS) and overall survival (OS) of GBM patients.

Methods and materials: Retrospective review of GBM patients submitted to surgical resection, >18 years, with GBM diagnosis. Patients BMI at the beginning of postoperative treatment was classified as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) or obese (>30 kg/m^2). For female patients, age at menarche and menopause, history of oral contraceptive and hormone replacement therapy were additionally retrieved. Primary endpoints were PFS and OS. Kaplan-Meier method was used for estimating and comparing PFS and OS curves by log-rank test. Cox proportional-hazards models were fitted based on univariate and multivariate analyses.

Results: A total of 148 patients were included. For female patients, OS of overweight patients was significantly lower than OS of obese patients (13.37 months vs 23.23 months, p=0.017 by log-rank comparisons; unadjusted HR=2.27, 95% CI 1.05-4.90, p=0.038; adjusted HR=2.35, 95% CI 1.06-5.11, p=0.030). For male patients, OS of overweigh patients was significantly greater than OS estimated for normal weight patients (21.47 months vs 12.21 months, p=0.014 by pairwise log-rank comparisons). Other OS pairwise comparisons between patients in different BMI classes were not significant. BMI class was not a significant prognostic biomarker for PFS (p>0.05 for all log-rank pairwise comparisons). Neither patient gender nor other oestrogen exposure variables were significant prognostic biomarkers for OS or PFS.

Conclusions: Our study suggests that BMI has impact in GBM prognosis, with obesity as a protective biomarker in female patients and overweigh as a protective biomarker in male patients. No relationship between oestrogens exposure and GBM survival was found.

Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumour in the adult population, with a dismal prognosis. Despite best surgical and medical treatments, patients have a median progression free survival of 6.9 months and overall survival of 14.6 months (1, 2).

GBM incidence is significantly higher in men than in women (1.58 male to female ratio) (3). Since women have higher levels of oestrogens, this observation led to several studies on menstrual, reproductive and hormone therapy history in women in GBM epidemiology. Although most of these studies were inconsistent, later age at menarche was associated with higher risk of GBM (4).

Oestrogenic therapy has been used in neurocognitive disease, and evidence suggests oestradiol to be neuroprotective (4). Hormonal status may also have impact over glial cells and play a role in GBM development (5-7). Indeed, GBM cells express oestrogen receptors (ER), intracellular ERα and ERβ, although expression of progestogen receptors is not established (4). Oestradiol induces apoptosis in GBM, being an underlying possible mechanism through ER mediated JNK signalling (5). Oestradiol may also inhibit signalling pathways independent of oestrogen response elements (EREs). Specifically, oestradiol may inhibit transcription at cAMP response elements (CREs) in ERα-expressing GBM cells, modulating neuroinflammation (8). Oestrogens can also supress HIF1α accumulation, decreasing tumour angiogenesis (9). These effects translated in the hypothesis of using oestrogens in GBM therapy. 2-Methoxyoestradiol (2-ME2), a natural metabolite of oestradiol, induces GBM cells apoptosis and reduces tumour growth and angiogenesis (9).

Impact of hormonal status in GBM may be more complex though. In certain cancers, such as breast, endometrial and ovarian cancers, oestradiol induces cell proliferation (10). In GBM, although oestrogens can induce apoptosis, it may also increase GBM cells proliferation.

Thereby, reducing oestrogens would decrease tumour growth. In this context, GBM cells express aromatase, a key enzyme for converting androgens irreversibly to oestrogens (7). Preventing aromatase activity would eventually be useful in GBM therapy. Letrozole, an aromatase inhibitor, has been found to enhance the suppression of tumour growth by temozolomide (7).

Several prognostic factors have been recognised for GBM, ranging from patient age, performance status, degree of surgical resection (11), neurological function (12), glycemia (13), IDH mutation (14), *MGMT* silencing (15), *NFKBIA* deletion (16), c-*MYC* and *BMI1* expression (17), neutrophil-lymphocyte ratio (18) and MR imaging markers (19). Body mass index (BMI) has recently been implicated as a prognostic factor in GBM, with high BMI associated with increased survival (20).

Deeper knowledge on the impact of different factors over progression and survival in GBM patients is fundamental, both in improving prognosis evaluation as well as in therapeutic decision making. Here we assessed the impact of biometric index and oestrogen status in clinical evolution, progression free and overall survival of GBM patients.

Methods and Materials

Patients and retrieved data from medical records

Retrospective review of patients diagnosed with GBM submitted to surgical resection in the department of neurosurgery of a tertiary care hospital (Hospital São João, Porto, Portugal), between June 2012 and May 2016. Patients included were aged >18 years with GBM diagnosis (WHO grade IV) confirmed by anatomopathological analysis. Follow-up data was assessed until February 28th, 2019. Data retrieved from medical records included preoperative and postoperative clinical status (Karnofsky Performance Score (KPS), and Eastern Cooperative Oncology Group score (ECOG)); extension of surgical resection; postoperative complications;

postoperative treatment; height, weight and corresponding body mass index at the beginning of postoperative treatment; date of progression and death. Patients were classified as being underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2) or obese (BMI ≥30 kg/m^2). For female patients additional data retrieved included age at menarche and menopause, history of oral contraceptive and hormone replacement therapy. This study was approved by local Institutional Ethics Committee.

Progression free survival and overall survival

Progression free survival (PFS) was calculated from date of surgery to date of first imaging evidence of progression. Date of clinical progression was used as surrogate when imaging was not available. Overall survival (OS) was calculated from date of surgery to date of death from any cause or date of the end of this study.

Statistical analysis

Primary endpoints were PFS and OS. Secondary endpoints were postoperative KPS and ECOG at first and sixth months. Kaplan-Meier method was used for estimating and comparing PFS and OS curves by log-rank test. Cox proportional-hazards models were fitted based on univariate and multivariate analyses of potential prognostic factors. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics software (version 25).

Results

Patients

A total of 148 patients were included in this study, from which 68 (45.9%) were female and 80 (54.1%) were male (1.18 male to female ratio). One patient (0.8%) was underweight, 50

patients (41.7%) had normal weight, 51 (42.5%) were overweight and 18 (15.0%) were obese. Comparing BMI class distribution between female and male patients, less patients in female group were overweight (32.2% vs 52.5%) and more patients in female group were obese (22.0% vs 8.2%). Characteristics analysed for both female and male patients are described in Table 1. Beyond patient gender, for the study of oestrogen exposure variables, in 68 female patients, only 14 had menarche age registered in their medical records, 8 had registered menopause age, and 6 had registered oral anticontraceptive treatment. Four patients had hysterectomy surgery, 2 unilateral and 7 bilateral oophorectomies with or without hysterectomy. Female patients' characteristics are listed in Table 2.

Based on univariate analysis, patients age, extent of resection, eloquent areas of the brain affected, post-operative complications and post-operative treatment were all independent significant prognostic factors.

Analysis of BMI as biomarker for OS and PFS

At the time of final analysis 141 (95.3%) patients had died. From the seven patients alive, 5 had disease progression. For the 148 patients, mean PFS of 7.95 months (range 0-66) and OS of 15.01 months (range 0-77) were observed.

For female patients, OS estimated for overweight patients was significantly lower than OS of obese patients (13.37 months vs 23.23 months, p=0.017 by log-rank comparisons; unadjusted HR=2.27, 95% CI 1.05-4.90, p=0.038; adjusted HR=2.35, 95% CI 1.06-5.11, p=0.030) (Figure 1A). For male patients, OS estimated for overweigh patients was significantly greater than OS estimated for normal weight patients (21.47 months vs 12.21 months, p=0.014 by pairwise log-rank comparisons) (Figure 1B).

Focusing on female patients, by decrescent order, OS of obese patients was greater than OS of normal weight patients, which was greater than OS of overweight patients. However, this difference between OS of obese patients and normal weight patients was not statistically

significant (23.23 months vs 19.96 months, p=0.558 by pairwise log-rank comparison). Difference between OS of normal weight patients and overweight patients was also not significant (19.96 months vs 13.37 months, p=0.095 by pairwise log-rank comparison). Other OS pairwise comparisons between patients in different BMI classes were also not significant. For female patients, BMI class was not a significant prognostic factor for PFS (p>0.05 for all log-rank pairwise comparisons) (Figure 2A).

Focusing on male patients, by decrescent order, OS of overweight patients was greater than OS of obese patients, which was greater than OS of normal weight patients. However, this difference between OS of overweight patients and obese patients was not statistically significant (21.47 months vs 19.00 months, p=0.860 by pairwise log-rank comparison). Difference between OS of obese patients and normal weight patients was also not significant (19.00 months vs 12.21 months, p=0.173 by pairwise log-rank comparison). Other OS pairwise comparisons between patients in different BMI classes were not significant. For male patients, BMI class was not a significant prognostic factor for PFS (p>0.05 for all log-rank pairwise comparisons) (Figure 2B).

Analysing patients in total, by decrescent order, OS of obese patients was greater than OS of overweight patients, which was greater than OS of normal weight patients. However, these differences were not significant (22.06 months vs 19.07 months vs 16.24 months, p>0.05 for all pairwise comparisons by log-rank test). After fitting Cox hazard-proportional model to significant prognostic factors based on univariate analysis, lower OS observed for overweight patients in relation to obese patients was nearly significant (HR=1.79, 95% CI=0.985-3.256, p=0.056). BMI class was not a significant prognostic factor for PFS (p>0.05 for all pairwise comparisons by log-rank test).

Analysis of oestrogens exposure as biomarker for OS and OFS

Comparing OS of female patients in relation to male patients, patient gender was not a significant biomarker for OS (p=0.306 by log-rank test; HR=0.846, 95% CI=0.607-1.179, p=0.323) (Figure 3A). Comparing PFS of female patients in relation to male patients, patient gender was also not a significant biomarker for PFS (p=0.656 by log-rank test; HR=0.932, 95% CI=0.668-1.300) (Figure 3B).

Beyond patient gender, studying oestrogens exposure variables, we found no significant differences in OS or PFS in subgroups of female patients with registered menarche age, menopause age, oral anticontraceptive treatment, hysterectomy surgery, unilateral and bilateral oophorectomies with or without hysterectomy (p>0.05 for all comparisons by log-rank test).

Discussion

Recently, an association between increased BMI and increased OS was described (20). However, conflicting evidence exists, suggesting BMI classes in the low and high extremes as bad prognostic factors and normal BMI as a protective factor (21). Our data also suggest this association may be complex. Herein, OS was only significantly different between obese and overweight female patients, and between overweight and normal weight male patients. In female patients, our data suggest obesity is a protective biomarker for OS. In male patients, our data suggest being overweight is protective. We found no association between BMI class and PFS.

Although GBM is more frequent in men than women, in this study patient gender was not a significant prognostic biomarker for OS nor PFS. In female patients we found no association between age at menarche or at menopause, history of oral contraceptive therapy and previous oophorectomy with OS or PFS. In this context, we did not find an association between

exposure to oestrogens and survival in GBM patients. Given the reduced number of patients for whom data were available, more detailed gynaecology history of patients in future would allow further study of this potential prognostic biomarkers. In our study this reduced number could be an important bias. Previous review of GBM epidemiology reflected inconsistent findings regarding impact of hormonal status of GBM patients on survival (4). Multiple potential pathways with opposite effects may underly the mechanism of action of oestrogens in GBM (4, 5, 7-10), which might explain the inconsistency of studies on this matter. These multiple effects of oestrogens may also underly the lack of association found here between patient gender and PFS or OS.

This study had the advantage of including only patients with anatomopathological confirmation of GBM diagnosis, with BMI data based on measurements made at the beginning of post-operative treatment. This study was limited by its retrospective nature, and by reduced data available regarding gynaecology medical history and medication.

Conclusions

Our study suggests biometric index has a complex association with OS in GBM patients, and that obesity may be a protective factor in female patients and overweigh may be protective in male patients. No relationship was found between patient gender or exposure to oestrogens and survival. Further studies are needed to understand this relationships and potential underlying mechanisms.

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Figure captions

Figure 1. Kaplan-Meier estimated curves for overall survival in (A) female patients and (B) male patients, by BMI class.

Figure 2. Kaplan-Meier estimated curves for progression free survival in (A) female patients and (B) male patients, by BMI class.

Figure 3. Kaplan-Meier estimated curves for (A) overall survival (OS) and (B) progression free survival (PFS), by patient gender.

Table 1. Characteristics of patients.

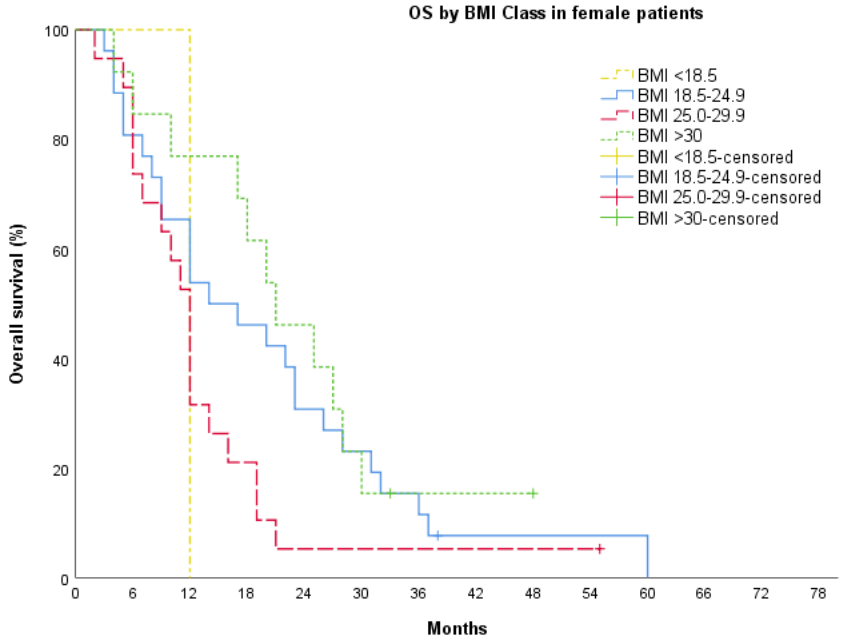
	Total	Female	Male
Number of patients - no. (%)	148 (100)	68 (45,9)	80 (54,1)
Characteristic			
Age – yr (mean, range)			
Mean	60,42	60,01	60,76
Range	26-86	26-86	26-85
Age - no. (%)			
<65	85 (57,4)	41 (60,3)	44 (55,0)
≥65	63 (42,6)	27 (39,7)	36 (45,0)
Pre-op KPS - no. (%)			
>70	114 (79,2)	52 (78,8)	62 (79,5)
≤70	30 (20,8)	14 (21,2)	16 (20,5)
Pre-op ECOG - no. (%)			
0-1	113 (78,4)	51 (77,3)	62 (79,5)
2	18 (12,5)	9 (13,6)	9 (11,5)
3-4	13 (9,1)	6 (9,1)	7 (9,0)
Extent of Resection - no. (%)			
Biopsy	25 (16,9)	12 (17,6)	13 (16,3)
Partial	33 (22,3)	13 (19,1)	20 (25,0)
Subtotal	25 (16,9)	16 (23,5)	9 (11,3)
Gross total	65 (43,9)	27 (39,7)	38 (47,5)
Eloquent areas - no. (%)			
Non-eloquent área	46 (31,1)	26 (38,2)	20 (25,0)
Pre or post-central sensorimotor area	19 (12,8)	7 (10,3)	12 (15,0)
Left fronto-temporo-parietal opercular área	30 (20,3)	13 (19,1)	17 (21,3)
Occipital visual córtex	8 (5,4)	2 (2,9)	6 (7,5)
Insula	25 (16,9)	11 (16,2)	14 (17,5)
Corpus callosum	20 (13,5)	9 (13,2)	11 (13,8)
Post-op complications - no. (%)			
No neurological deficit	107 (72,8)	51 (75,0)	56 (70,9)
Neurological deficit	40 (27,2)	17 (25,0)	23 (29,1)

Post-op treatment no. (%)			
Stupp	106 (74,6)	54 (81,8)	52 (68,4)
Bevacizumab + Irinotecan	1 (0,7)	-	1 (1,3)
Paliative	21 (14,8)	10 (15,2)	11 (14,5)
No treatment	11 (7,7)	2 (3,0)	9 (11,8)
Others	3 (2,1)	-	3 (3,9)
Body mass index (kg/m^2) - no. (%)			
<18,5 – underweight	1 (0,8)	1 (1,7)	-
18,5-24,9 – normal weight	50 (41,7)	26 (44,1)	24 (39,3)
25-29,9 – overweight	51 (42,5)	19 (32,2)	32 (52,5)
≥30 – obese	18 (15,0)	13 (22,0)	5 (8,2)

Table 2. Hormonal status variables in female patients.

	Female patients (N=68)
Hormonal status variable	
Age at menarch	
Patients with available data - no. (%)	14 (9,52)
Mean	12,93
Range	11-15
≤12	6
>12	8
Oral anticontraceptive treatment	
Patients with available data - no. (%)	6 (4,08)
Combined oestrogen-progestagen	4
Progestagen	1
Age at menopause	
Patients with available data - no. (%)	8 (5,44)
Mean	51,38
Range	47-57
≤52	4
>52	4
Hormonal substitution therapy	
Patients with available data - no. (%)	3 (2,04)
Gynaecology surgery - no. (%)	
No hysterectomy no oophorectomy	55 (80,9)
Hysterectomy only	4 (5,9)
Unilateral oophorectomy with/without hysterectomy	2 (2,9)
Bilateral oophorectomy with/without hysterectomy	7 (10,3)

A



B

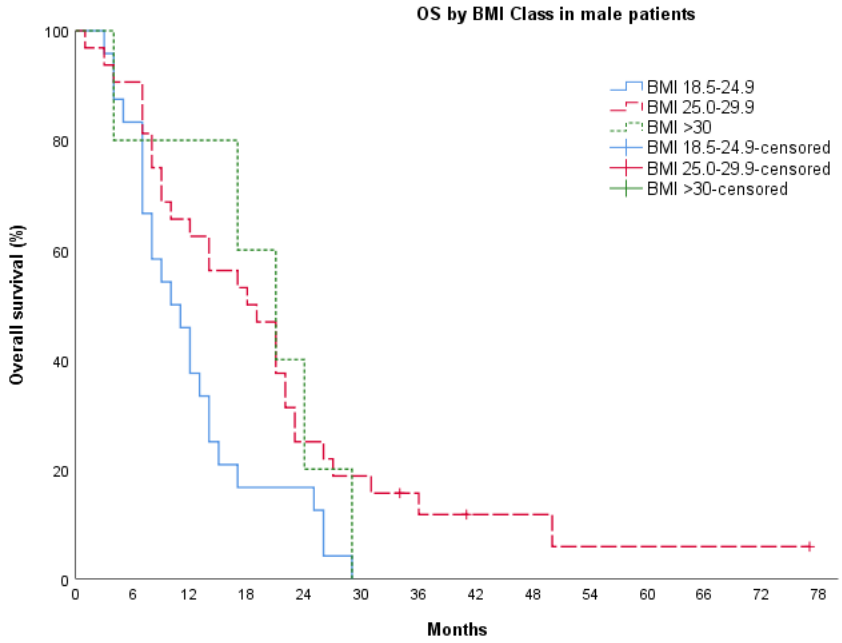
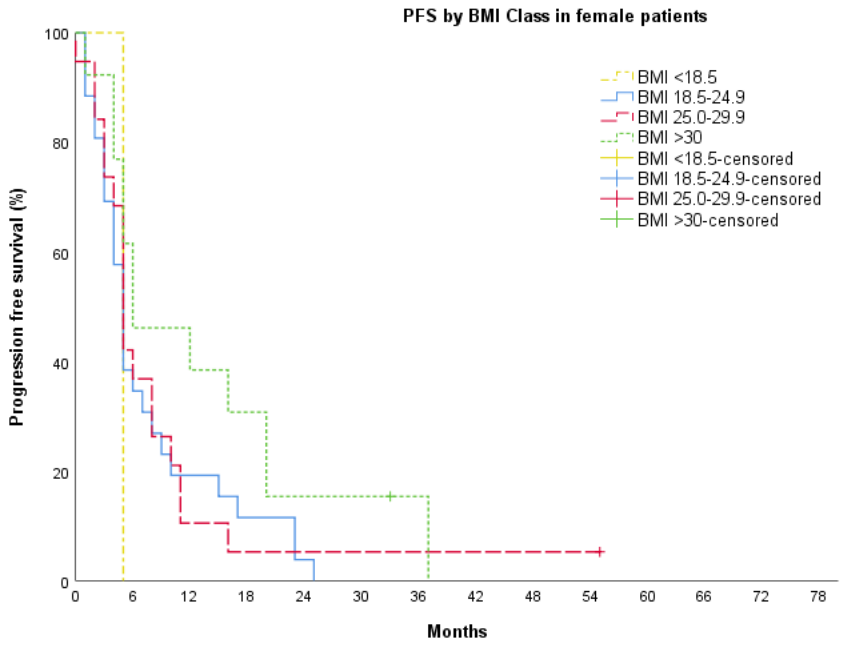


Figure 1. Kaplan-Meier estimated curves for overall survival in (A) female patients and (B) male patients, by BMI class.

A



B

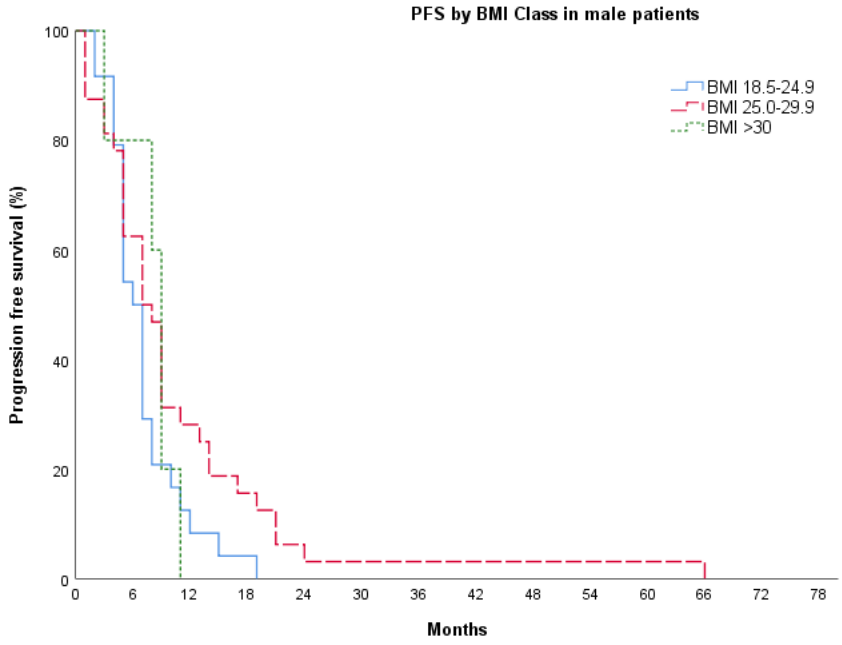
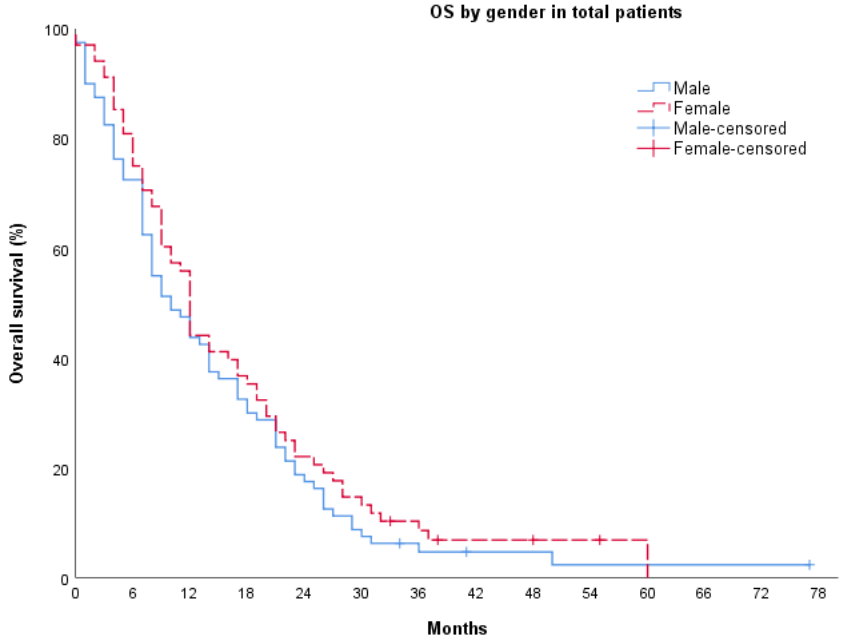


Figure 2. Kaplan-Meier estimated curves for progression free survival in (A) female patients and (B) male patients, by BMI class.

A



B

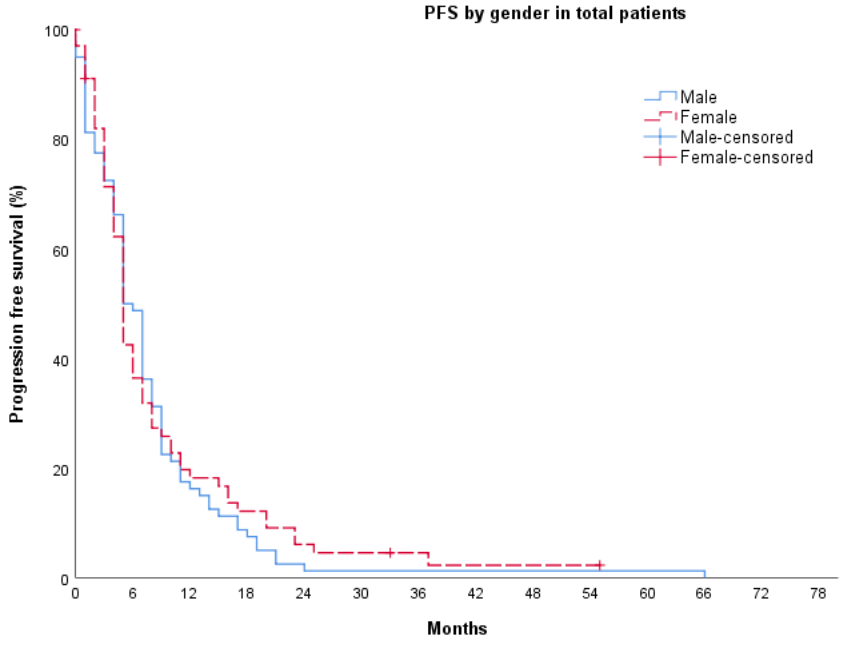


Figure 3. Kaplan-Meier estimated curves for (A) overall survival (OS) and (B) progression free survival (PFS), by patient gender.

Agradecimentos

Ao Professor Doutor Rui Vaz, por me ter permitido realizar este trabalho no Departamento de Neurocirurgia do Hospital São João.

Ao Professor Paulo Linhares, por me ter orientado ao longo deste trabalho e pela disponibilidade que teve no esclarecimento das dúvidas que foram surgindo.

Anexo 1

Red Journal: Instructions for Authors

Journal Information

Scope

International Journal of Radiation Oncology●Biology●Physics (IJROBP), known in the field as the Red Journal, publishes original laboratory and clinical investigations related to radiation oncology, radiation biology, medical physics and both education and health policy as it relates to the field.

This journal has a particular interest in original contributions of the following types: prospective clinical trials, outcomes research and large database interrogation. In addition, it seeks reports of high-impact innovations in single or combined modality treatment, tumor sensitization, normal tissue protection (including both precision avoidance and pharmacologic means), brachytherapy, particle irradiation, and cancer imaging. Technical advances related to dosimetry and conformal radiation treatment planning are of interest, as are basic science studies investigating tumor physiology and the molecular biology underlying cancer and normal tissue radiation response.

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4. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, eds. Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York, NY: RavenPress; 1995:465-478.

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