Health-Related Quality Of Life And Clinical Outcome After Radiotherapy of Patients With Intracranial Meningioma

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Abstract

Purpose: This retrospective, single-institutional study investigated long-term outcome, toxicity and health-related quality of life (HRQOL) in meningioma patients after radiotherapy.

Methods: We analyzed the data of 119 patients who received radiotherapy at our department from 1997 to 2014 for intracranial WHO grade I-III meningioma. Fractionated stereotactic radiotherapy (FSRT), intensity modulated radiotherapy (IMRT) or radiosurgery radiation was applied using a linear accelerator. A median total dose of 54.7 Gy (IQR 54.0-60.0 Gy) was prescribed in median single doses of 1.8 Gy (IQR 1.8-1.9 Gy). Overall survival (OS) and local control (LC) rates were obtained. In addition, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core questionnaire (QLQ-C30) and the EORTC Brain Cancer Module (QLQ-BN20) were completed for assessment of HRQOL. Results were compared with normal population and with already published data.

Results: OS for the entire cohort was 89.6% at 5 years and 75.9% at 10 years. LC at 5 and 10 years was 82.4% and 73.4%, respectively. Local recurrence was observed in 22 patients (18.5%). CTCAE grade ≥3 acute and chronic toxicities were observed in seven patients (5.9%) and five patients (4.2%), respectively. Global health status was rated with a mean of 59.9 points (SD 22.3) on QLQ-C30. HRQOL was lower after radiotherapy in comparison to normal population and to meningioma patients treated by surgery alone.

Conclusion: Radiotherapy resulted in very good long-term survival and tumor control rates with low rates of severe toxicities. Nevertheless, long-term HRQOL may be negatively affected by radiotherapy.

Introduction

Meningiomas are neoplasms derived from the arachnoidal cells of the leptomeninges and are the most common primary intracranial tumors in adults with 15-30% [1]. Women are twice as often affected as men, however, men tend to develop more aggressive forms of meningiomas [2]. Meningiomas are classified in three groups by the World Health Organization (WHO) according to histological characteristics. Approximately 80-85% of all meningiomas are categorized as non-malignant meningiomas (WHO grade I), which commonly exhibit a slow growth rate and a noninvasive expansion. Only 5-15% of meningiomas are considered as atypical meningiomas (WHO grade II) and only 1-3% are malignant meningiomas (WHO grade III) with a tendency of brain invasion [3, 4]. A novel meningioma classification is based on molecular markers to predicted clinical outcomes more accurately [5]. Multimodal meningioma treatment is dependent on WHO grading as well as resection status and may include surgery, radiotherapy, peptide receptor radionuclide therapy (PRRT) or watchful waiting [6]. Radiotherapy is commonly applied as adjuvant or primary therapy option and may be conducted in terms of intensity modulated radiotherapy (IMRT), fractionated stereotactic radiotherapy (FSRT) or radiosurgery [7]. Although modern radiation techniques have decreased the amount and severity of acute and late toxicity, previous publications observed high-grade adverse effects after radiotherapy of the brain such as visual field deficit, neuropathy, cerebral necrosis, pituitary dysfunction and cerebrovascular events [8–13].

Cognitive impairment, memory loss and personality changes might be objectively difficult to quantify, but have a huge impact on daily life of individuals [9, 14]. Consequently, any acute or late side effect may lead to a significant deterioration in health-related quality of life (HRQOL) [15]. Up to date, few data has been published for toxicity and HRQOL after radiotherapy in meningioma patients. Therefore, the present retrospective single-center analysis aimed to provide data on long-term HRQOL, side effects and efficacy after radiotherapy in a large cohort of meningioma patients.

Materials And Methods

Patients characteristics

We retrospectively analyzed data from 119 consecutive meningioma patients who were treated at our department between 1997 and 2014. The primary endpoint of our study was HRQOL, assessed by EORTC QLQ-C30 version 3.0 and the EORTC QLQ-BN20. Secondary endpoints were treatment related toxicity, 5- and 10-year local control (LC) and overall survival (OS). LC was defined as the time between initiation of radiation and the occurrence of first progression at the treated site on imaging. OS was defined as the time between diagnosis and the last documented follow-up or death from any cause. Included were all patients with meningioma who were treated with radiotherapy in the given time period and who showed no signs of spinal infiltration. In case of multiple treatment series, we analyzed one series only. Patients with history of a different cancer, independently of previous treatment, were included in the database. All cases were discussed in an interdisciplinary neuro-oncological review board before treatment. Meningioma was histologically determined in 76 patients (63.9%). In 43 patients (36.1%) diagnosis was based on radiologic signs after magnetic resonance imaging (MRI) examination by at least two (neuro)radiologists. Radiation was administered in 56 patients (47.0%) at initial diagnosis with 41 patients (34.5%) being irradiated within a year of diagnosis. The other 63 patients (52.9%) were treated at time of meningioma relapse. Median tumor axial size was 2.5 cm (IQR 1.5-3.8 cm) in the longest orientation at the start of radiotherapy. Three patients received a concomitant or sequential chemotherapy. All patients' characteristics are summarized in Table 1.

Treatment planning

FSRT, IMRT and radiosurgery alone were performed in 67 (56.3%), 48 (40.3%) and four (3.3%) patients, respectively. Sequential boost radiation was administered in 38 patients (31.9%). For normofractionated radiotherapy, the gross tumor volume (GTV) was expanded by 8-15 mm, depending on the WHO grade and tumor location, to generate the clinical target volume (CTV). The CTV was expanded by 3 mm resulting in the planning target volume (PTV). A median total dose of 54.0 Gy (IQR 54.0-58.5 Gy), 60.0 Gy (IQR 54-61.2 Gy) and 60.0 Gy (IQR 59.4-60.3 Gy) was administered for WHO grade I, II and III meningiomas, respectively. Dose was prescribed to the mean PTV dose. In case of stereotactic radiotherapy, a margin of 1-2 mm was added to the GTV for the PTV and a median total dose of 19.5 Gy (range 17.5-21 Gy) was prescribed to the 68% PTV encompassing isodose. IMRT was delivered as a step-and-shoot technique with 3–9 fields or as Volumetric Intensity Modulated Arc Therapy (VMAT) with two

dynamic arcs. One patient was treated with whole brain irradiation with 30.0 Gy and a sequential boost on the meningioma lesion with 15.0 Gy. All radiation therapies were conducted with photon beams using an ELEKTA Synergy® or a Siemens PRIMUS linear accelerator. GTV was contoured on CT with co-registered MR imaging using Pinnacle³ (Philips Radiation Oncology Systems, Fitchburg, WI, USA). In 26 patients (21.8%), (68)Ga-DOTATOC, (68)Ga-DOTATATE or (18)F-FET PET imaging was performed and fused for improved target volume definition. Nine patients (7.6%) received an additional PRRT using (177)Lu-DOTATOC with a mean dose of 7.5 Gy (SD ± 0.3).

Follow-up

Clinical and radiologic follow-up including contrast-enhanced MR imaging was performed 6-12 weeks after radiation therapy and thereafter once or twice per year, unless an earlier examination was considered due to suspected relapse. Imaging examinations were assessed by two independent (neuro)radiologists. Tumor dimensions were measured according to an axial T1-weighted contrast-enhanced MRI sequence or to a contrast enhanced CT scan. In case of multifocal occurrence, tumor location was defined by the site of the largest lesion. RANO criteria were used to evaluate tumor progression [16]. Tumor localization was categorized in skull base, cerebral falx, hemispheral convexity or optic nerve sheath.

Clinical examination included assessment of neurological status. For the evaluation of acute and late toxicity, the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used. Acute toxicity was assessed up to 90 days after the end of radiation. For HRQOL assessment, EORTC QLQ-C30 version 3.0 and the EORTC QLQ-BN20 were filled out at follow-up visits or were sent out to the patients. QLQ-C30 data was compared with reference data of German and European normal population as well as with already published data of historic cohorts [17–22]. Reference data from the normal population for the QLQ-BN20 questionnaire were not available, therefore, our data was compared with previous publications [19, 23].

Statistics

All data were analyzed with IBM SPSS Statistics 26.0. The threshold for statistical significance was set at a two-sided $p < 0.05$. Regarding the QLQ-C30 and BN20 questionnaires, a relevant clinical difference was defined when the point difference was greater than 10 points [24, 25]. OS and LC were calculated using Kaplan-Meier statistics. Log-rank testing was used to determine the statistical significance of the OS or LC difference between different groups. For multivariate analysis, Cox proportional hazard regression was performed. Mann-Whitney-U and Kruskal-Wallis tests were performed due to not normally distributed parameters according to the Shapiro-Wilk test. To correlate toxicity grades with radiation dose, volumes and tumor location, the significance of Kendall’s tau-b correlation coefficient was assessed.

Results

Quality of Life

Out of 82 questionnaires, 49 were filled out and returned, which is equivalent to a correspondence rate of 59.8%. The questionnaires were completed in median 4.8 years (IQR 2.7-9.2 years) after radiotherapy from patients with a median age of 64.4 years (IQR 59.0-72.5 years). In terms of self-assessment, the global health status was rated with a mean of 59.9 points (SD 22.3) on the QLQ-C30 with functional scales ranging between a mean of 55.6 and 71.2 points (Table 2). We could detect a relevant decrease on the functional scale for physical, role, cognitive and social functioning, which was accompanied by an increase on the symptom scale for fatigue, pain, dyspnea, insomnia, constipation and financial impact in comparison to reference data of normal population (Supplementary Fig. S1). On the QLQ-BN20, the most common impairments were drowsiness, uncertainty about the future and weakness of the legs (Table 2). Compared to previous cohort groups, our data showed partially worse results on the QLQ-C30 (Fig. 1) and on the QLQ-BN20 (Supplementary Fig. S2).

Side effects

Radiation-related acute toxicities with clinical significance (CTCAE grade ≥3) were recorded in seven patients (5.9%). These included one case of amaurosis with prior visibility impairment and three cases of dizziness. Other CTCAE grade 3 toxicities were nausea, headache, radiation dermatitis, fatigue and mucositis. In two cases, the irradiation had to be discontinued due to a deterioration of general health. Acute grade 1 and 2 side effects occurred in 52.9% and 37.8% of cases, respectively. Fatigue, alopecia, headache, radiation dermatitis, dizziness, as well as nausea and vomiting were the most common acute side effects reported. In 3.4% of all cases, no adverse effects were reported.

Severe chronic toxicities (CTCAE grade ≥3) were observed in five patients (4.2%). There was one case of surditas (CTCAE grade 4) and one case of amaurosis (CTCAE grade 4) with anterior pituitary insufficiency (CTCAE grade 3). The other three cases suffered from tiredness, exhaustion, confusion or headache (all CTCAE grade 3). Chronic side effects of CTCAE grade 1 and 2 were found in 11.8% and 20.2% of the patients, respectively. The most common chronic side effect was chronic headache, which occurred in 7.5% of all cases. In addition, circumscribed CNS toxicity (6.7%), memory and concentration disorders (5.9%) as well as fatigue (5.8%) were relatively common.

All mean dose values for organs at risk in our cohort were below recommended limits. Patients with toxicities grade ≤2 received a mean total dose of 54.9 Gy. The mean total dose in patients with toxicities grade ≥3 was 57.9 Gy. There was no statistically significant correlation between maximal toxicity grade and total dose ($p = 0.55$), PTV ($p = 0.86$), GTV ($p = 0.52$) nor tumor location ($p = 0.56$).

Local control

Median follow-up was 5.4 years (IQR 2.9-9.7 years). Estimated 5- and 10-year LC rates were 82.4% and 73.4%, respectively (Fig. 2a). The median time to recurrence was not reached at time of data analysis. In total, 22 patients (18.5%) had an in-field relapse, three patients with WHO grade I, six with WHO grade II and eight with WHO grade III meningiomas. A relapse also occurred in five patients without histologically confirmed meningioma. One patient with highly suspected neurofibromatosis type II was diagnosed with a meningioma relapse twice. The histological grade was significant and suggestive for influencing LC in

the univariate ($p < 0.001$) and multivariate analysis ($p = 0.05$), respectively (Fig. 2b). Simpson grade (I-III vs. IV-V) did not have a statistically significant impact on LC. Location of the tumor ($p = 0.032$) as well as GTV for the subgroup of patients with WHO grade II and III meningiomas ($p = 0.023$) were significant in univariate analysis, but not in multivariate analysis. No significant difference in LC could be observed when comparing a cumulative dose of ≥60 Gy versus <60 Gy for all patients ($p = 0.37$) nor for patients with WHO grade II and III meningiomas ($p = 0.46$).

Overall survival

Estimated 5- and 10-year OS was 89.6% and 75.9%, respectively (Fig. 2c). The median OS was 17.5 years. Survival rates significantly differed by WHO grade ($p = 0.002$). Karnofsky Performance Status (≥90% vs. <90%) ($p = 0.046$), GTV ($p = 0.001$), timing of radiation ($p = 0.005$) and age ($p = 0.001$) had a significant impact on OS in univariate analysis. After multivariate analysis, WHO grade ($p = 0.002$) and GTV ($p = 0.001$) remained significant for OS (Fig. 2d). OS was not significantly affected by gender, Simpson grade, location of tumor and tumor volume before treatment. As for LC, no significant difference in OS was found comparing radiotherapies with a dose escalation above 60 Gy for all patients ($p = 0.32$) nor for patients with WHO grade II and III meningiomas ($p = 0.08$).

Discussion

To the best of our knowledge, this study is the first one to assess HRQOL data using QLQ-C30 and BN20 questionnaires for exclusively meningioma patients who received radiotherapy. Our database search found only few publications evaluating HRQOL using QLQ-C30 and BN20 questionnaires in meningioma patients, mostly as unplanned subgroup analyses [17–19, 23]. Our HRQOL data shows that meningioma patients have lower QLQ-C30 and BN20 scores after radiotherapy than the general population (Supplementary Fig. S1) [20–22]. Moreover, our data shows slightly lower HRQOL results in comparison to already published data for meningioma patients, although comparability might be limited due to different data acquisition methods and patient group compositions [26]. For instance, Erharter et al. performed a preselection of patients excluding patients with severe cognitive impairment, which resulted in higher HRQOL scores [23]. No additional information about meningioma patient group composition is provided by Shin et al. [19]. Budrukkar et al. assessed HRQOL in a subgroup of patients with benign brain tumors, which was not limited to meningioma patients only [18]. Konglund et al. reported higher QLQ-C30 scores which is probably attributable to group differences as their cohort consisted to 94% of benign, resected meningiomas without radiotherapy [17]. Primary radiotherapy is often chosen for advanced, inoperable tumors and benign meningiomas should not be irradiated after complete resection according to the EANO guidelines for the diagnosis and treatment of meningioma [27, 28]. Our cohort predominantly consisted of patients with unfavorable tumor location or with incompletely resected meningiomas, prone to worse outcome with more clinically significant side effects and consequently lower HRQOL [13]. Furthermore, the rate of WHO grade II and III meningiomas was significantly higher with 31.9% in our study and 21 patients (17.6%) reported another malignant tumor before HRQOL assessment.

Another selection bias might result from the limited response rate of questionnaires (59.8%) in our study. Since only long-term HRQOL was assessed in our study, beneficial effects directly after radiotherapy or surgery resulting in functional gains and better HRQOL were not measured in contrast to the studies of Budrukkar et al., Konglund et al. and Bitterlich et al. [17, 18, 29]. HRQOL was determined with a median time of 4.8 years after treatment in our study providing the possibility of other diseases negatively influencing HRQOL, such as stroke or cognitive deterioration due to aging.

Physician-assessed severe acute toxicities appeared in only 5.9% of cases, confirming that radiotherapy has mild side effects when applied in meningioma patients. The one case of acute amaurosis could be attracted to tumor growth as the patient had severe visibility impairment prior to radiotherapy and received a palliative radiation with a lower dose. Albeit 36.2% of patients reported chronic toxicities, only 4.2% suffered from a chronic side effect CTCAE grade ≥3. Our findings are in line with previously published data in terms of acute and late toxicities (0-49.9%) [7, 10, 12, 14, 30, 31].

Our median applied dose of radiation was comparable with existing literature. Based on already published data, a dose of 54 – 60 Gy is indicated and well tolerated for WHO grade I meningiomas. In our WHO grade I meningioma cohort, a dose up to 66.0 Gy was accepted if histopathology specimens had angiomatous or fibrous components. For high-grade meningiomas (WHO grade II and III), a median total dose of 60.0 Gy was prescribed in our cohort. A minimum dose of 60 Gy is usually prescribed for WHO grade III meningiomas to ensure long-term local control [32, 33]. The dose prescription for WHO grade II meningiomas, however, is inconsistent throughout literature. Depending on the resection status, high dose radiation with 60 Gy or 70 Gy was prescribed for all WHO grade II meningioma patients in the EORTC 22042 study while newly diagnosed WHO grade II meningioma patients with gross total resection were treated with a lower radiation dose of 54 Gy in the RTOG 0539 study [34, 35]. Three-year progression-free survival (PFS) and OS were comparable in both studies. Long-term results for both studies have not been published yet. In retrospective analyses, dose escalation, however, is associated with improved clinical outcome and may be prescribed for WHO grade II meningiomas [32, 33, 36, 37].

Existing reports on factors influencing OS and LC for meningioma are inconsistent except for WHO grade [11, 15, 30, 38–41]. In line with these results, our data confirmed that the WHO grade had a significant impact on OS in univariate and multivariate analysis and affected local control as well. Due to the lack of studies with large patient numbers, statistics for OS and LC in WHO grade II and III meningiomas show a broad variance (0.0-89.0%) (Table 3) [30, 32, 33, 38, 40, 42, 43]. Our estimated 5-year LC for WHO grade II (66.7%) and WHO grade III (53.1%) meningiomas is compatible with the majority of published data (Table 3) [11, 13, 15, 30, 32, 33, 38, 40, 42, 44–47]. Our 5-year and 10-year OS rates for each WHO grade, however, seem to be more favorable in comparison to published ones. This might be due to our low number of high-risk meningioma patients limiting statistical information. In addition, histological grading in older samples was not updated to the revised WHO grading system from 2016 influencing the indication for radiotherapy, the target volume, applied dose and probably the outcome [48]. Although concordance for histopathological grading of meningioma is relatively high, there is still some interobserver and interinstitutional discrepancy, which might lead to a bias in outcome [49].

The lack of longitudinal assessment of HRQOL is a limiting factor of our analysis as HRQOL data was only assessed at a specific time point during follow-up. Hence, a pre-treatment survey is missing to compare if treatment had a beneficial or deteriorating effect on HRQOL.

Nevertheless, our data confirms that radiotherapy shows an excellent prognosis with regard to OS and LC in meningioma patients. In a cohort of mostly advanced or relapsed meningioma patients, radiotherapy lead to acceptable HRQOL and low toxicity. HRQOL deterioration should be considered and may guide decision making when opting for radiotherapy in meningioma patients. The considerable risk of recurrence in patients with high-grade meningiomas has to be taken in account. Prospective studies should aim for improvement of HRQOL without worsening outcome.

Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Authors' contributions

Study design: MF, BP, JTa. Material preparation, data collection: DL, JTr, PL, JTa, PH, VL. Data analysis and interpretation: DL, JTr. Writing the manuscript: DL. All authors contributed to revising the draft and approved its final version.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The Julius-Maximilians-University Würzburg Ethics Committee has confirmed that no ethical approval is required.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

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Tables

Due to technical limitations, tables 1,2 and 3 are only available as a download in the Supplemental Files section.

Figures

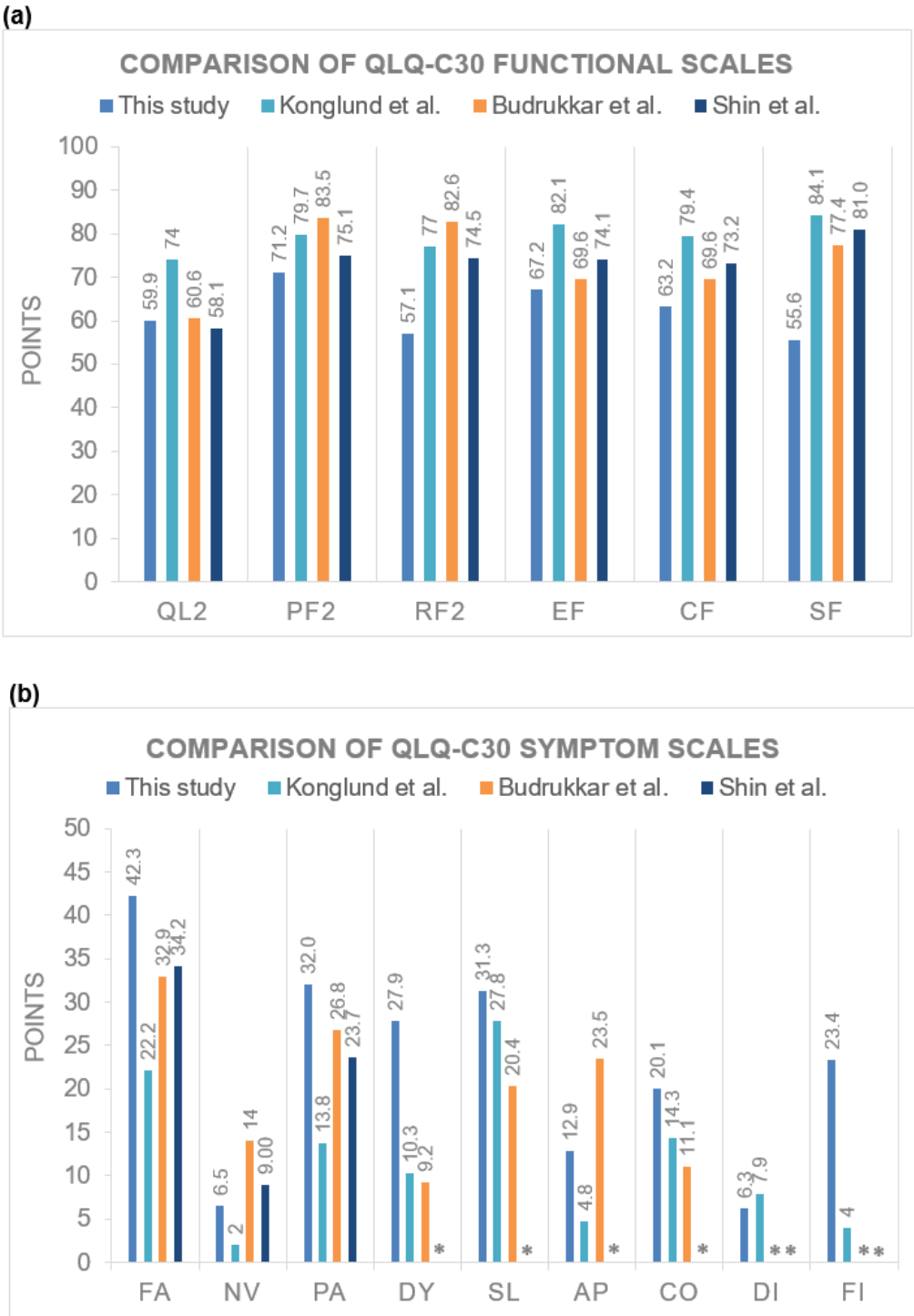

Figure 1

(a) Comparison of QLQ-C30 functional scales with previously published data. Higher scores in functional domains suggest higher level of functioning and better quality of life. *Abbreviations:* QL2 = Global health status (revised); PF2 = Physical functioning (revised); RF2 = Role functioning (revised); EF = Emotional functioning; CF = Cognitive functioning; SF = Social functioning.

(b) Comparison of QLQ-C30 symptom scales with previously published data. Higher scores in symptomatic domains suggest lower level of functioning and worse quality of life. *Abbreviations:* FA = Fatigue; NV = Nausea and vomiting; PA = Pain; DY = Dyspnea; SL = Insomnia; AP = Appetite loss; CO = Constipation; DI = Diarrhea; FI = Financial difficulties. *Data not published.

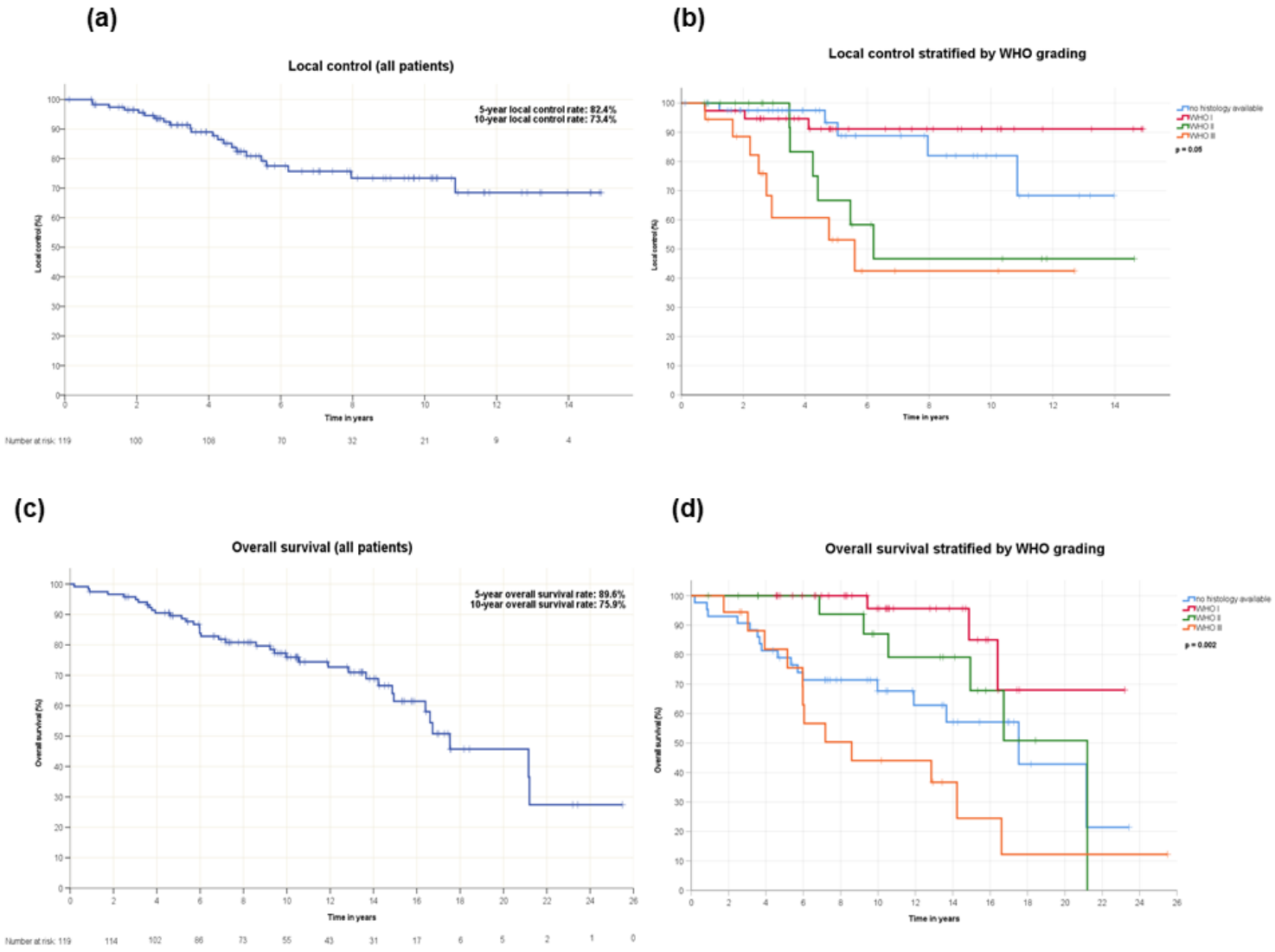

Figure 2

Local control shown by Kaplan-Meier analysis for all patients **(a)** and stratified by the WHO grading **(b)**. WHO grading was suggestive for influencing local control (p = 0.05). Overall survival shown by Kaplan-Meier analysis for all patients **(c)** and stratified by the WHO grading **(d)**. WHO grading was highly significant for overall survival (p = 0.002).

Supplementary Files

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