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5th Combined Gulf Cancer Conference
Sharjah, United Arab Emirates

**CONTINUUM OF CARE
IN CANCER CONTROL
& MANAGEMENT**

Awareness & Prevention | Early Detection & Screening | Diagnosis
Treatment | Palliative Care | Survivorship | Research

**SAVE
THE DATE** **21-23
NOV 2022**

The banner features a dark purple and teal background with a white circular seal containing the text '5th Combined Gulf Cancer Conference' and 'Sharjah, United Arab Emirates'. Below the seal, the main title 'CONTINUUM OF CARE IN CANCER CONTROL & MANAGEMENT' is written in bold black letters, followed by a list of topics: 'Awareness & Prevention | Early Detection & Screening | Diagnosis Treatment | Palliative Care | Survivorship | Research'. At the bottom, a white box with a teal border contains the text 'SAVE THE DATE' and a teal calendar icon showing '21-23 NOV 2022'.

Gulf Guidelines for Colorectal Cancer Workshop

**Updating
Colorectal Cancer
Guidelines**

8-9 November 2022

State of Kuwait

A circular graphic with a teal background and a white border. The text 'Updating Colorectal Cancer Guidelines' is written in bold yellow letters. Below it, a white box with a teal border contains the text '8-9 November 2022'. At the bottom, the text 'State of Kuwait' is written in white.

MONKEY POX
ALL YOU NEED TO KNOW

A graphic with a white background and a red border. The top half features several red, spiky virus particles of varying sizes. The bottom half contains the text 'MONKEY POX' in bold black letters on a white background, with 'ALL YOU NEED TO KNOW' in bold black letters on a black background below it.

The Official Journal of the Gulf Federation For Cancer Control

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Correlation of Ki-67 with Radiation Response and Grade in Meningiomas: A Systematic Review

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Abstract

Purpose: This systematic review aimed to identify the role of Ki-67 as a prognostic factor in estimating tumor grade and the radiation response in meningiomas.

Methods: A systematic search of the literature on meningiomas was carried out through the PubMed, Scopus, and EBSCOhost databases according to the PRISMA guidelines.

Results: Our search resulted in 465 collected articles, 15 of which satisfied the eligibility criteria. Twelve studies

reported the correlation between Ki-67 and meningioma grade. Two other investigations reported the relationship between Ki-67 and the radiation response in meningioma, and one failed to capture the association between Ki-67 and the radiation response in meningioma.

Conclusion: The Ki-67 proliferation index has a uniform correlation with meningioma grade. Two of the 3 studies on the correlation of Ki-67 with the radiation response in meningioma patients reported that patients with a higher Ki-67 responded better to radiation therapy.

Keywords: Ki-67, Meningioma grade, Radiation therapy response, Systematic review

Introduction

Meningiomas are the most common primary intracranial tumors. The majority are benign, slowly growing, and require surgery and/or radiation therapy. Gross total resection (GTR) is the main therapeutic option for meningioma. Radiotherapy plays a role as adjuvant therapy. Radiotherapy also plays a major role in managing difficult-to-reach intracranial meningiomas, e.g., skull-base meningiomas, which are close to the nervous and vascular structures. Radiation therapy results in various responses in meningiomas.

Ki-67 is a nuclear antigen associated with cell proliferation. It is expressed only in the cell division cycle: G1, S, G2, and M. It is known that there is a relationship between radiosensitivity and cell proliferation. Radiotherapy works efficiently in highly reproductive cells. The relationship between the radiotherapy response and Ki-67 index has not been widely studied. Ishibashi et al.⁽¹⁾ reported a correlation between the Ki-67 proliferation

index and the response of lung cancer cells to radiation dosing at 45–60Gy. A Ki-67 index $\geq 79.77\%$ correlated significantly with complete response ($P=0.04$). Oral squamous cell carcinoma patients with a low Ki-67 index develop recurrence within 27.5 months, whereas patients with a high Ki-67 index develop recurrence within 49.5 months ($p=0.048$). A retrospective study conducted by Adua et al.⁽²⁾ reported no correlation between the Ki-67 index and complete pathological response after neoadjuvant chemoradiation in rectal cancer.

A higher Ki-67 index lowers the survival rate of meningioma patients⁽³⁾. However, correlations of the

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Ki-67 index and responses to radiotherapy in meningioma are rarely studied. This systematic review aimed to aid in clinical decisions on the inclusion of radiotherapy in managing meningioma to improve local control.

Materials and Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁽⁴⁾. We assessed the correlation between the Ki-67 index and tumour grade and response to radiation in meningioma patients receiving radiation therapy. The literature search included three databases: PubMed, Scopus, and EBSCOhost. The investigators used the same MESH terms and their synonyms the same keywords during the literature search. The aim was to find a correlation of the Ki-67 proliferation index with the grade of meningioma. The keywords used for the search were (Meningioma OR Meningiomas) AND (Ki-67 OR KI-67 OR MIB-1) AND (Grade OR Grading) AND (Correlation). To establish a relationship between the Ki-67 proliferation index and the response to radiation in meningioma, the following keywords were used: (Meningioma OR Meningiomas) AND (Ki-67 OR KI-67 OR MIB-1) AND (guided radiotherapy OR (Radiation AND Therapy) OR Irradiation) AND (Response OR Outcomes OR Benefit OR Impact OR Effectiveness).

First, the search results were filtered to exclude duplicate entries, literature reviews/systematic analyses, and case reports. Then, the remaining articles were further filtered in accordance with the following inclusion criteria: (1) clinical studies; (2) meningioma patients as the subjects; (3) assessment of the Ki-67 index; and (4) description of the relationship of the Ki-67 index with the grade of meningioma or the response to radiation. The exclusion criteria were as follows: (1) no full text available; (2) not in English; and (3) not reporting the mean Ki-67 index.

Study selection and data extraction

All articles were reviewed by two persons independently who also extracted the data. Disagreements were discussed and resolved among the authors. The following study characteristics were extracted: first author, year of publication, country of study, year of study, type of study, number of patients, and patient age. Extracted Ki-67 data included the mean Ki-67 in 3 grades of meningioma, the cut-off Ki-67, and the correlation of the Ki-67 index with tumor grade or the radiation response. Extracted outcomes included local control and progression-free survival.

Results

1. Literature search results

The literature search was conducted in three databases, namely, PubMed, EBSCOhost, and Scopus, on December 16, 2020. For the search, keywords combined with MESH terms were used. Sourcing the three databases resulted in 235 articles concerning the relationship of the Ki-67 index and the grade of meningioma. After filtering duplicates and applying inclusion and exclusion criteria, the investigators ultimately obtained 12 articles. The initial result was 230 articles on the relationship of the Ki-67 index and radiation responses. After filtering duplicates and applying inclusion and exclusion criteria, the investigators ultimately obtained three articles. The four-phase flow chart shown in Figure 1 describes the systematic review reporting.

2. Study characteristics

The characteristics of the included studies in this systematic review are shown in Table 1. All reports were derived from a variety of countries in Asia, Europe, North America, and Africa. These studies were published between 2001 and 2020, with a total sample size of 2359. A total of 13 studies reported the distribution of meningioma grade, and we obtained a total of 1558 subjects with grade I, 375 with grade II, and 76 with grade III. The range of patient was 0–94 years. The average patient age was 52.9–64 years. Almost all articles were retrospective cohort studies. A report by Telugu et al.⁽⁵⁾ was the only report on retrospective and prospective cohorts.

Immunohistochemistry was used to assess the Ki-67 proliferation index in all included studies. The mean Ki-67 proliferation index in grade I, II, and III meningiomas ranged from 0.9–4.7%, 3.3–13.7%, and 8.7–34%, respectively. All studies demonstrated a significant correlation between Ki-67 and the grade of meningioma^(5–16). Table 2 shows the association between the Ki-67 proliferation index and tumor grade and other factors, such as meningioma subtype, recurrence, progesterone receptor expression, and brain tissue invasion.

All selected articles clearly described the method used to the Ki-67 proliferation index (using paraffin-embedded tissues and tissue microarrays). The proliferative index was expressed as a percentage of positively stained nuclei in tumor cells and was assessed from the areas of the greatest proliferation counts.

Table 3 shows three articles in which the correlation of the Ki-67 proliferation index with the response to radiation was assessed^(17–19). The total number of samples examined to analyse the relationship of Ki-67 with the

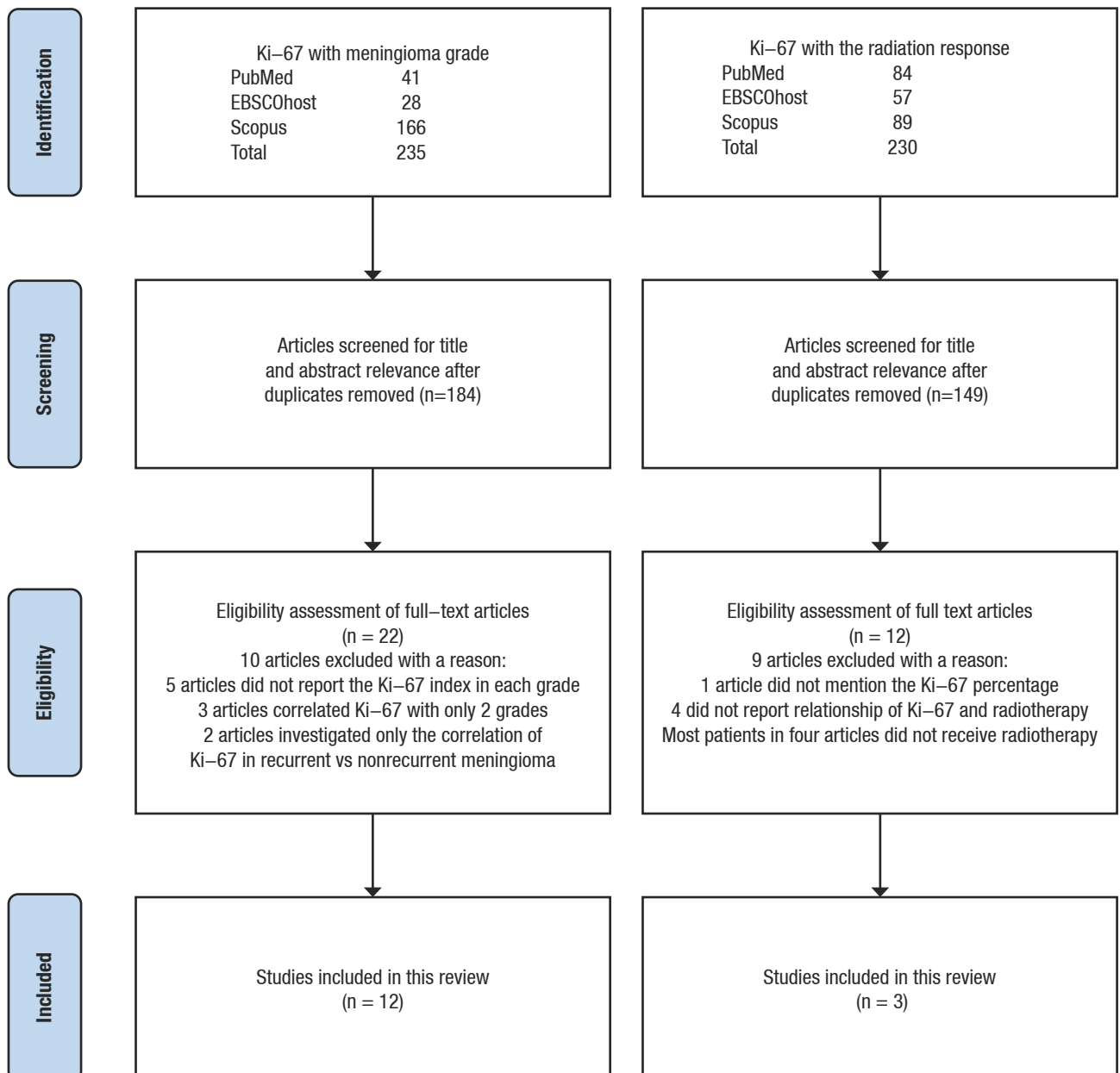


Figure 1: PRISMA flow diagram of study selection

response to radiation was 246. Two studies, one by Choi et al.⁽¹⁸⁾ and one by Liu et al.⁽¹⁹⁾, demonstrated a relationship of the Ki-67 proliferation index with local control after radiation therapy. However, Jensen et al.⁽¹⁷⁾ reported no relationship between the Ki-67 proliferation index and the response to radiation.

Choi et al.⁽¹⁸⁾ reported that radiotherapy after surgery improved local control in grade II meningioma with a Ki-67 index >13% (p<0.001). In the group of meningiomas with a Ki-67 index ≤13, radiotherapy after surgery did not significantly influence local control (p=0,412). Liu et al.⁽¹⁹⁾ reported that a group of meningioma patients with a Ki-67 index ≥5 who received adjuvant radiotherapy after subtotal

resection experienced significantly better PFS than those who did not receive adjuvant radiotherapy (p=0.014).

However, Jensen et al.⁽¹⁷⁾ reported no relationship between the Ki-67 proliferation index and local control of meningioma after stereotactic radiotherapy (SRT) (p=0.135). A Ki-67 index <5 was predictive of good OS after receiving SRT (p=0.020). The definition of local control in this study was the absence of an increase in the size of the tumor by 25%, in accordance with the MacDonald criteria. The size of the tumor was assessed by imaging for at least two months after radiation therapy. Local control and OS were calculated from the start of SRT/ stereotactic radiosurgery (SRS).

| Study | Year | Country | Study Design | No. of samples | Males / females | Age (range, yr) | Outcomes |
|---|------|---------|------------------------|----------------|-----------------|-----------------|---|
| Correlation of Ki-67 and grade of meningioma | | | | | | | |
| Amatya et al. [6] | 2001 | Japan | Cohort | 146 | 33/113 | 13– 86 | Correlations of Ki-67, p53, p21, and p27 with grade of meningioma |
| Roser et al. [7] | 2004 | German | Cohort retros | 580 | 189/391 | 15–94 | Correlations of Ki-67 with grades and recurrence of meningioma |
| Terzi et al. [8] | 2008 | Turkey | Cohort retros | 84 | 29/55 | 1–81 | Correlations of Ki-67 with grade and brain invasion of meningioma |
| Shayanfar et al. [9] | 2009 | Iran | Cohort retros | 78 | 25/53 | 22– 82 | Correlations of Ki-67 and progesterone receptor (PR) with grade of meningioma |
| Rao et al. [10] | 2009 | India | Cohort retros | 123 | 1/1.4 | 27–77 | Correlations of Ki-67 and p53 with grade of meningioma |
| Babu et al. [11] | 2010 | India | Cohort retros | 429 | 115/185 | 2–75 | Correlations of Ki-67 with subtypes and grade of meningioma |
| Pavelin et al. [12] | 2013 | Croatia | Cohort retros | 170 | 70/100 | 19 – 85 | Correlations of Ki-67 and p53 with grade and size of meningioma |
| Lee et al. [13] | 2014 | Korea | Cohort retros | 88 | 24/64 | 24 – 83 | Correlations of VEGF and Ki-67 with grade of meningioma |
| Narla et al. [14] | 2014 | India | Cohort retros | 79 | 30/49 | 10 – 75 | Correlations of EGFR and Ki-67 with grade of meningioma |
| Telugu et al. [5] | 2016 | India | Cohort pros and retros | 224 | 78/146 | 5 – 71 | Correlations of Ki-67 and p53 with grade of meningioma |
| Mostafa et al. [15] | 2017 | Egypt | Cohort retros | 40 | 13/27 | 12 – 75 | Correlations of CD44 and Ki-67 with grade of meningioma |
| Ikeri et al. [16] | 2018 | Nigeria | Cohort retros | 72 | 1/3.8 | 0 – 80 | Correlations of PR and Ki-67 with grade of meningioma |
| Correlation of Ki-67 and radiation response | | | | | | | |
| Jensen et al.[17] | 2012 | USA | Cohort retros | 162 | 38/124 | 12 – 90 | Local control and overall survival (OS) |
| Choi et al. [18] | 2015 | Korea | Cohort retros | 50 | 26/24 | 13 – 78 | Local control and OS |
| Liu et al. [19] | 2020 | China | Cohort retros | 34 | 17/17 | 14 – 72 | Progression-free survival (PFS) and OS |

Table 1. Baseline characteristics of the included studies

Discussion

Uncontrolled proliferation is a tumor characteristic. Immunohistochemistry can be used to assess the proliferative activity using specific markers such as Ki-67, proliferating cell nuclear antigen (PCNA), and minichromosome maintenance (MCM). Ki-67 and MCM are sensitive for detecting actively dividing cells, while PCNA is less specific because in addition to detecting actively dividing cells, PCNA also detects the process of DNA repair⁽²⁰⁾. Ki-67 is often associated with meningioma grade because both are related to proliferation.

Studies included in this systematic review included patients who were diagnosed with meningioma between

2001 and 2018 and used two WHO classification systems (those released in 2007 and 2016). There were overlapping values of the mean Ki-67 among different grades of meningioma in the twelve included investigations. The exact Ki-67 index for each grade was not determined, likely because of the heterogeneity and variability in each sample. Calculating of proliferation in a hotspot can depict a pathomorphological description and capture biological functions in the tumor so that the pattern converges to the source of malignancy. Digital calculation of the Ki-67 value in a hotspot is a suitable approach for assessing breast cancer⁽²¹⁾.

The effects of radiation on the tumors can be measured by several endpoints, including local tumor control, tumor

| Study | Sample size | Age | Mean Ki-67 (%) | | | P (Correlation of Ki-67 and tumour grade) | Other Findings | LoE |
|--------------------------------------|-------------|-------|-----------------------------|------------------------------|-------------------------------|---|---|-----|
| | | | No. of Patients Grade I (n) | No. of Patients Grade II (n) | No. of Patients Grade III (n) | | | |
| Amatya et al. ⁽⁶⁾ 2001 | 146 | 13–86 | 1.5 ± 1.3 (107) | 8.1 ± 9.9 (27) | 19.5 ± 13.5 (10) | <.001 | The difference in MIB-1, p53, p21, p27 was statistically significant between benign, atypical, and malignant meningiomas. | 3 |
| Roser et al. ⁽⁷⁾ 2004 | 580 | 15–94 | 3.54 ± 4.97 (526) | 11.9 ± 8.25 (45) | 18.2 ± 9.53 (9) | <0.0001 | The mean Ki-67 was significantly different in recurrent vs non-recurrent meningioma (p<0.0001), but not significantly correlated with tumour location (p=0.273) | 3 |
| Terzi et al. ⁽⁸⁾ 2008 | 84 | 1–81 | 0.9 | 3.3 | 8.7 | <0.001 | A high Ki-67 index had a strong correlation with decreased RFS in the univariate analysis (p<0.001), while the multivariate analysis revealed only tumour grade as a sole factor of recurrences | 3 |
| Shayanfar et al. ⁽⁹⁾ 2009 | 78 | 22–82 | 2.98 ± 2.27 (63) | 9.3 ± 5.79 (10) | 34 ± 5.47 (5) | <0.001 | Ki-67 negatively correlated with PR (P=0001). No statistically significant difference between Ki-67 and sex. | 3 |
| Rao et al. ⁽¹⁰⁾ 2009 | 123 | 22–77 | 3.8 | 13.7 | 19.4 | =0.000 | p53 had no relationship with the grade of meningioma | 3 |
| Babu et al. ⁽¹¹⁾ 2010 | 429 | 2–75 | 4.07 ± 3.83 (211) | 9.57 ± 7.43 (78) | 17.78 ± 7.18 (11) | 0.0001 | Ki-67 correlated significantly with invasion to the brain tissue (p=0.0083) and recurrences (p=0.0093). | 3 |
| Pavelin et al. ⁽¹²⁾ 2013 | 170 | 19–85 | 1.5 (142) | 6.2 (18) | 10.2 (10) | <0.001 | Correlation of Ki-67 and tumour subtype (p=0.009), no correlation of Ki-67 with tumour location or sex (p=0.174) | 3 |
| Lee et al. ⁽¹³⁾ 2013 | 88 | 24–83 | 2.4 (49) | 7.7 (33) | 16.0 (6) | 0.019 | Correlation of Ki-67 with mitosis (p=0.008), cellularity (p=0.032), and prominent nucleoli (p=0.036); no correlation of Ki-67 with location (p=0.616) or recurrences (p=0.797) | 3 |
| Narla et al. ⁽¹⁴⁾ 2014 | 79 | 10–75 | 3.13 ± 3.04 (46) | 6.46 ± 5.37 (28) | 16.4 ± 8.62 (5) | □0.001 | Reduced EGFR was statistically significant with an increase in grade. The increase in the p53 level was not significantly correlated with tumour grade. | 3 |
| Telugu et al. ⁽⁵⁾ 2016 | 224 | 5–71 | 3.1 (193) | 7 (24) | 14.2 (7) | <0.001 | Ki-67 correlated significantly with invasion to the brain tissue p<0.001. No significant difference between Ki-67 and meningioma subtypes | 3 |
| Mostafa et al. ⁽¹⁵⁾ 2017 | 40 | 12–75 | 2.9 (24) | 10.4 (13) | 19.0 (3) | <0.001 | Ki-67 was significantly correlated with the brain tissue invasion (p=0.01) and CD44 (p=0.01). No correlation between CD44 or Ki-67 with age, sex, or tumour recurrence (p>0.05). | 3 |
| Ikeri et al. ⁽¹⁶⁾ 2018 | 72 | 0–80 | 2.46±1.59 (62) | 7.24 ± 3.49 (8) | 21.00 ± 3.00 (2) | 0.000 | Decreased PR and increased Ki-67 expression correlated with tumour grade (P=0.000) | 3 |

Table 2: Correlation of Ki-67 with the grade of meningioma

LoE, Level of Evidence; RFS, Recurrence-free Survival; EGFR, Epidermal Growth Factor Receptor; PR, Progesterone Receptor

| Study | Sample | Males/ Females | Age (range, years) | Distribution of Samples | | | Ki-67 cutoff (%) | Correlation of Ki- 67 with Radiation Response | OS and Other Findings | LoE |
|--|--------|-------------------|--------------------------|----------------------------|-------------|--------------|------------------------|--|---|-----|
| | | | | Grade I | Grade II | Grade III | | | | |
| Jensen et al. ⁽¹⁷⁾ 2012 | 162 | 38/124 | 12–90 | 115 | 29 | 6 | 5 | Ki-67 <5 does not have a significant relationship with local control following SRT (P=0.135) nor SRS (P=0.104) | <ul style="list-style-type: none"> • Ki-67 <5 correlated with prolonged OS after SRT: HR: 0.18 ((p=0.020) • Ki-67<5 did not correlate significantly with OS following SRS (p=0.215) | 3 |
| Choi et al. ⁽¹⁸⁾ 2015 | 50 | 26/24 | 13–78 | 0 | 50 | 0 | 13 | <ul style="list-style-type: none"> • Local control PORT (n=14) was significant in meningiomas with Ki-67>13% in the multivariate analysis (P<0.001) • Local control PORT (n=29) did not significantly influence tumours with Ki-67<13% (P=0.412) | <ul style="list-style-type: none"> • Multivariate analysis revealed Ki-67 >13% (P=0.022) and PORT (P=0.006) as independent prognostic factors for local control. • The 3- and 5-year OS rates were 89.5% and 89.5% | 3 |
| Liu et al. ⁽¹⁹⁾ 2020 | 34 | 17/17 | 14–72 | 20 | 12 | 2 | 5 | <ul style="list-style-type: none"> • PFS was better for patients who received adjuvant RT STR with Ki-67\geq5 compared to Ki-67 <5 • Ki-67\geq5, EOR and without adjuvant RT were identified as risk factors for short PFS. • In the group of meningiomas with Ki-67\geq5, adjuvant radiotherapy significantly prolonged PFS • 3, 5, and 10-year PFS rates were 0.63, 0.47, and 0.47, respectively | The 3-, 5-, 10-year OS rates were 0.87, 0.80, and 0.80, respectively. The mean duration of OS was 111 months | 3 |

Table 3: Correlation of Ki-67 with the radiation response in meningioma

LoE, Level of Evidence; SRT, Stereotactic Radiotherapy; SRS, Stereotactic Radiosurgery; OS, Overall Survival; HR, Hazard Ratio; PORT, Postoperative Radiotherapy; EOR, Extent of Resection; PFS, Progression-free Survival

regrowth delay, and tumor regression. Two studies in this systematic review reported improved local control and PFS in meningioma patients whose Ki-67 proliferation index was high^(18,19). Nuclear antigen, detected by Ki-67 was expressed in almost all human cell lines, but not in cells with the resting phase. Therefore, Ki-67 can be applied to recognize nuclear antigens associated with proliferation⁽²²⁾. A meningioma with a higher Ki-67 and a better radiation response is in accordance with theory, which demonstrated a link between cell proliferation and cellular radiosensitivity. Cells that more often divide are more sensitive to radiation. Cells that rapidly proliferate are more sensitive to radiation than cells that are quiescent⁽²³⁾.

Another study failed to capture a relationship between Ki-67 and the response to SRT or SRS radiation⁽¹⁷⁾. The Ki-67 index, assessed by immunohistochemistry, is a conventional method used to assess the re-population aside from the potential doubling time (T-pot) of the tumor and S-phase Fraction (SPF) by flow cytometry^(24,25). No correlation between the Ki-67 index and local control was observed due to the presence of other factors affecting the rate of cell growth, i.e., cell loss. In solid tumors, cells undergo necrosis due to the lack of oxygen and nutrient supply in damaged blood vessels.

Studies on the Ki-67 proliferation index and radiotherapy response are most often associated with recurrence. Some studies reported that meningioma grade I after GTR with Ki-67 >4.5% had a similar recurrence rate as meningioma grade I post STR (18.8% vs. 18.6%). Ki-67>4.5% is a prognostic factor for the recurrence of meningioma grade I after GTR. It is necessary to impose a close follow-up or even consider prescribing an adjuvant radiotherapy⁽²⁶⁾.

In the study of Liu et al. (19), meningioma patients with Ki-67 ≥5 who received adjuvant radiotherapy had longer PFS than those who did not receive adjuvant radiotherapy. In the group of meningiomas with Ki-67 <5, radiotherapy adjuvant did not prolong PFS. The effectiveness of radiotherapy is observed in cells with strong proliferation ability, whereby the DNA of cells that are dividing is exposed to radiation.

Other factors are also reported to affect the response to radiation therapy in meningioma, including the meningioma grade, the size of the tumor, and tumor location. conducted by Lin et al.⁽²⁷⁾ assessed the meningioma reirradiation radiographic response (SRS or EBRT) and reported a response rate of 20% in WHO grade II/III and 8% in WHO grade 1 meningiomas. The response was assessed with MRI at least six months postradiotherapy.

The magnitude of the residual volume prior to radiotherapy in meningioma *grade* II also affects the response to radiation. A reported residual tumour volume greater than 8.76 cm³ is associated with a significantly low PFS rate ($p=0.0079$)⁽²⁸⁾. However, three studies in this review did not find any correlation between tumor size and location and local control after radiation therapy⁽¹⁷⁻¹⁹⁾.

Jensen et al.⁽¹⁷⁾ did not report a relationship of Ki-67 with local control by the administration of either SRT or SRS. Ki-67 <5 was related only to improved OS after SRT. The median dose of SRT provided was 5400cGy (2400–5400cGy), and the median dose of SRS was 1500cGy (1000–2000cGy).

The mechanism of DNA strand breaks and chromosomes aberrations by SRS with doses >10Gy per fraction was hypothesized to lead to vascular damage resulting in low perfusion and indirectly leading to cell death⁽²⁹⁾. This plausible mechanism could explain the lack of a relationship between Ki-67 and the response to SRS in the study by Jensen et al.⁽¹⁷⁾. In addition, one study showed that radiation could inhibit the proliferation of endothelial cells, triggering cell death, which then increases vascular permeability, and indirectly leads to tumor cell death⁽³⁰⁾.

Tumor cell death induced by radiation depends on a number of factors, such as the delivered dose and cell death pathways. Pinzi et al.⁽³¹⁾ found no data on meningioma cell death pathways different from apoptosis.

Conclusion

The Ki-67 proliferation index increased significantly as the grade of meningioma advanced. Two of 3 studies on the correlation of the Ki-67 proliferation index with the radiation response in meningioma reported that meningiomas with a higher Ki-67 responded better to radiation therapy.

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Conflict of Interest

The authors declare that they have no competing interests

Abbreviations

EBRT: External Beam Radiotherapy; EFS: Event-free Survival; EGFR: Epidermal Growth Factor Receptor; GTR : Gross Tumour Resection; MCM: Minichromosome Maintenance; PCNA: Proliferating Cell Nuclear Antigen;

PFS: Progression-free Survival; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RFS: Recurrence-free Survival; SPF: S-phase Fraction; SRS: Stereotactic Radiosurgery; SRT: Stereotactic Radiotherapy; STR: Subtotal Resection; VEGF: Vascular Endothelial Growth Factor

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