

Clinicopathologic Factors Related to Post-Operative Outcome of Pituitary Adenoma: a Meta-Analysis

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Abstract

Purpose: About 30% to 40% of patients with pituitary adenoma require surgery. About 25% to 40% of those who have had surgery will have an aggressive outcome. The purpose of this study was to see if certain clinicopathologic factors such as size, type/subtype, invasiveness, proliferative (ki-67, mitotic rate, and p53), and grade influenced the aggressiveness of postoperative pituitary adenomas.

Methods: The factors mentioned in the research objectives were examined as independent variables. Ten studies out of 736 were chosen. The 10 studies had 2727 participants and 632 cases. The monitoring lasted 3-11 years. The studies' quality ranged from fair to excellent.

Results: The results of the meta-analysis were: size ≥ 10 mm OR 1,79 (1,29-2,48), corticotroph OR 1,91 (1,41-2,58), invasive OR 3,67 (1,95-6,90), proliferative OR 4,78(3,61-6,32), Ki-67 $\geq 3\%$ OR 4,13 (2,94-5,81), mitotic rate > 2 OR 3,91 (2,74-5,57), p53 positive OR 1,92 (1,28-2,90), and grade 2b OR 4,56 (3,0-6,91).

Conclusions: Size, type/subtype, invasiveness, proliferative (ki-67, mitotic rate, and p53), and grade of postoperative pituitary adenoma influenced the postoperative aggressiveness outcome.

Introduction

Pituitary adenoma, also known as pituitary neuroendocrine tumor (PitNET)^{1,2} is a type of intracranial tumor that typically arises from the anterior lobe of the pituitary gland and accounts for 10–15% of all intracranial tumors.^{3,4} According to the Japan brain tumor registry center, 19.2% of 13,431 cases of brain tumors were histopathologically confirmed as pituitary adenoma.⁵ Pituitary adenoma was found to be prevalent in South Korea, with a prevalence of 62.9 cases per 100,000 people and an incidence of 26.1 cases per 100,000 people, according to a population-based study using data from the National Health Insurance.⁶ Data from the English city of Banbury shows 63 cases of pituitary tumors out of a total population of 89,334 people, with a population prevalence of 77 cases per 100,000.⁷

About 60–70% of pituitary adenomas are prolactinomas that respond well to medical treatment, though about 10–15% require surgery. With indications of macroadenoma invading surrounding tissue accompanied by visual disturbances or clinically due to hormone hypersecretion that does not respond well to medical therapy, approximately 30-40% of patients with pituitary adenoma require surgical management.^{8,9} About 25–40% of patients who had surgery had unfavorable outcomes, such as local invasion, resistance to conventional therapy, a high recurrence rate, and metastases.^{10,11} Pituitary adenomas are malignant in about 0.2–0.5% of cases. While mortality occurs in approximately 28% of aggressive pituitary adenomas and 42.5% of pituitary carcinomas over the median of 11-12 years.^{12,13} It is challenging and necessary to predict the nature of pituitary adenomas because early detection of potentially aggressive adenomas will lead to aggressive treatment, which is expected to improve patient outcomes.

The size of the adenoma, the type/subtype of the adenoma, the invasive nature of the adenoma (imaging), the proliferative nature of the adenoma (immunohistochemical examination (IHC) on Ki-67, mitotic activity, and p53), adenoma grade, and novel biomarkers are some of the factors that are thought to be involved in the outcome of pituitary adenoma analyzed in the past studies. These factors require healthcare providers to have adequate imaging, surgery, and anatomical pathology (in this case, IHC examination) modalities to support pituitary adenoma patients' specific management. The European Society of Endocrinology (ESE) guidelines for the management of pituitary adenoma cases, on the other hand, include recommendations for IHC examination with a very low level of evidence.¹⁴

Previous studies that looked at the prognostic factors above came up with varying significance values. According to Trouillas J et al.¹⁵ and Asioli S et al.¹⁶, when adenomas are classified as micro or macroadenomas, the odds ratio (OR) for an aggressive outcome is 3.2 consecutively (confidence interval (CI) = 1.64-6.26) and 1.81 (CI=1.099-2.979), respectively in macroadenomas. However, Raverot G et al.¹⁷ concluded that it lacked prognostic significance, with a hazard ratio (HR) of 1.34 (CI=0.65-2.76).

Atypical pituitary adenomas were classified as a special classification by the World Health Organization (WHO) in 2004 solely based on the adenomas' proliferative nature.¹⁸ However, it was later removed from the 2017 WHO classification since it did not provide patients with different prognostic values.¹⁹ This is because, as several studies have shown, assessing the level of aggressiveness of pituitary adenomas solely based on proliferative properties is insufficient; other clinical evaluations such as mass size and invasiveness are also necessary.^{15–20}

Existing studies have found conflicting results regarding the prognostic value of pituitary adenoma type; according to Asioli S et al.¹⁶, lactotrophs and corticotrophs have a worse outcome than other types, with HR of 2,968 (CI=1,672-5,27) and 2,336 (CI=1,233-4,426), respectively, whereas other studies found no difference in prognostic value in the type of adenoma.^{15,17,20} Although the data available to date is still limited, WHO emphasizes the high risk of aggressive pituitary adenoma in the five subtypes of pituitary adenoma. Sparsely granulated somatotroph adenoma, lactotroph adenoma in men, Crooke's cell adenoma, silent corticotroph adenoma, and pituitary-specific transcription factor 1 (Pit-1) positive adenoma are among the five subtypes.²¹

Another point of debate is the lack of consensus on the Ki-67 proliferative marker's threshold value. The percentages proposed range from 1.3–10%.^{22,23} The majority of studies, however, use a 3% threshold.¹⁴ While a value of more than 10% is considered to be a sign of malignancy.²³ All of these figures are only based on a limited number of case studies, a short observation period, or even expert opinions.

According to the findings, there are still few studies examining the importance of assessing prognostic factors in postoperative pituitary adenoma. Also, no systematic study has been attempted to collect all the studies out there. The main aim of this study was to see if clinicopathological factors influence the aggressiveness of postoperative pituitary adenomas.

Method

This research is a systematic examination that collects data from both electronic and manual sources. This study's inclusion criteria were as follows:

1. Adult participants in observational studies
2. The study included subjects with pituitary adenoma who had undergone surgery and had histological data.
3. Studies looked at adenoma size, invasiveness, proliferative qualities, adenoma type, adenoma subtype, ki-67, p53, mitotic rate, and adenoma grade as independent variables.
4. The study looked at the relationship between independent variables and aggressiveness (recurrence or advancement to conventional therapy (surgery, medicine, and/or radiation)) of pituitary adenoma as early as one year after surgery.

The following were excluded:

1. Only certain patients with pituitary adenoma were included in the study.
2. The study only assessed less than three independent variables.

The study protocol was registered using PROSPERO. With the help of the Covidence device, the search was carried out. PubMed, CINAHL, Scopus, ProQuest, and Science Direct were used to conduct a literature search using electronic-based data sources. Manual searches are also conducted using reference lists and citations from related journals (snowballing), as well as other search engines such as Google Scholar and Global Index Medicus, the results of theses and dissertations through the online libraries of Indonesia's major universities, and contacting endocrinologists, particularly in the field of pituitary adenoma, through related semi-structured interviews.

The literature search employs keywords to represent each PICO element and is tweaked with MESH terms, truncation, and proximity signs to match the desired data source. Keywords that were used were (((post operative pituitary adenoma) OR (post surgical pituitary adenoma) OR (post surgical pituitary neuroendocrine tumor) OR (post operative pituitary neuroendocrine tumor)) AND ((size) OR (type) OR (subtype) OR (invasion) OR (proliferation) OR (ki-67) OR (mitoses) OR (p53) OR (grade))) AND ((aggressive) OR (recurrence) OR (resistant) OR (progression)).

Data extraction for each study was completed with the help of Covidence and Excel, then grouped according to each independent variable, type, measurement estimation/conclusion, and study design, in which the information is presented in a tabular format later.

The Newcastle Ottawa Scale (NOS) is used to determine the quality of a study and the possibility of bias. Examined biases are baseline confounding, study participant selection bias, searching for missing data, and reported bias. The results of the assessments are tabulated and grouped according to the study's design. The study component's assessment results are then added together and concluded the quality of the study according to the score :

1. Between 7 and 9: good
2. Between 4 and 6: adequate
3. Between 1 and 3: poor

This evaluation will be used in concluding the study's findings. The study selection bias was assessed regarding how much data the independent variables had from the list of excluded studies. Two researchers worked independently on each stage of this systematic study. Any disagreements are worked out in collaboration with the third researcher. RevMan 5.4 was used to carry out the quantitative synthesis. If the I^2 value is greater than 60%, heterogeneity is considered significant. A narrative review is performed if data is unavailable or cannot be extracted, or heterogeneity is too high.

Result

The literature review took place between July 21 and August 9, 2020. In total, 736 studies were found, with limitations applied to each database in the form of studies in humans and adults, duplication of studies eliminated, and titles and abstracts screened. 568 studies were agreed to be excluded, leaving 22 studies. The search was continued by reading the full text of 22 studies. Both researchers agreed that 12 studies should be eliminated for the reasons listed in table L1. In the end, ten studies were analyzed qualitatively and quantitatively. Figure L1 illustrates the detailed search flow.

The studies took place in Europe, Asia, and the United States. There were a total of 2727 people in the study, with 632 people in the case group. The majority of studies had a monitoring period of 3 to 5 years, but one study had a monitoring period of up to 11 years. Table 1 lists the characteristics of each selected study.

All of the studies were of a good to an excellent standard. The poor-quality studies are:

1. Gejman et al.²⁴: too many sample candidates were excluded due to a lack of data.
 2. Trouillas et al.¹⁵: about 45% of the sample candidates were excluded due to a lack of data.
 3. Hasanov et al.²⁵: 18% of subjects dropped out without explanation.
 4. Raverot et al.¹⁷: has a poor adequacy component of follow-up because more than 30% of subjects dropped out without adequate explanation of their outcome.
- Tables 2 and 3 describe the study's quality in great detail.

Each independent variable on the aggressiveness of postoperative pituitary adenoma was subjected to meta-analysis. In the studies that looked at it:

1. Adenoma's size: The meta-analysis of the case-control study revealed that a size of ≥ 10 mm was significantly more aggressive, with an OR of 1.79 (1.29-2.48). (figure 1). Meanwhile, in a cohort meta-analysis study, the size ≥ 10 mm was significantly more aggressive, with an HR of 1.79 (1.08-2.96). (figure 2).
2. Adenoma type: Corticotroph-type adenoma was significantly more aggressive, with an OR of 1.88 (1.39-2.55), while the somatotroph-type adenoma was significantly less aggressive, with an OR of 0.65 (0.49-0.88)(Fig. 3).
3. Invasive trait: Invasive adenomas were found to be significantly more aggressive, with an OR of 2.59 (2.06-3.26)(figure 4).
4. Proliferative trait: Proliferative adenomas were found to be significantly more aggressive, with an OR of 4.78 (3.61-6.32)(figure 5).
5. Ki-67: With an OR of 4.13 (2.94-5.81), the meta-analysis revealed that adenomas with Ki-67 $\geq 3\%$ were significantly more aggressive (figure 6).
6. Mitosis rate: Mitotic rates >2 were found to be significantly more aggressive, with an OR of 3.13 (1.19-8.20)(figure 7).
7. p53: Aggressiveness has been found in adenomas with positive p53 in some studies. P53-positive adenomas were found to be significantly more aggressive, with an OR of 1.92 (1.28-2.90)(figure 8).
8. Adenoma grade: Grade 2b adenomas were found to be significantly more aggressive, with an OR of 4.56 (3.00–6.91)(figure 9).

Table 1
Basic characteristics of selected studies

No.	Study, Year	Number of Subjects (Case)	Study Design	Data Collection Period	Country	Outcome	Observation Period	Assessed Variable(s)	Funding
1	Hsu et al ²⁶ , 1993	62(30)	Case-control	1982-1992	USA	Recurrence	Mean 7.3 year	Size, invasiveness and postoperative residue	Public health service grant
2	Gejman et al ²⁴ , 2008	55(24)	Case-control	1984-2005	USA	Progression	5 year	Size, invasiveness, Ki-67, p53, and postoperative residue	University and government scholarships
3	Matsuyama et al ²⁷ , 2012	39(12)	Case-control	2001-2009	Japan	Progression	Mean 46.1 month	Size, invasiveness, Ki-67, and postoperative residue	-
4	Trouillas et al ¹⁵ , 2013	407(125)	Case-control	1987-2004	France	Recurrence /Progression	Median 11.14 (1.19-23.8) year	Size, types, dan grade	Government grant
5	Kim et al ²⁸ , 2016	167(28)	Case-control	2011-2013	South Korea	Recurrence	48 month	Size, invasiveness, mitosis, Ki-67, p53, and postoperative residue	Personal
6	Jang et al ²⁹ , 2016	331(92)	Retrospective Cohort	1998-2014	South Korea	Progression	Mean 65.3 (24.2-131.1) month	Size, invasiveness, Ki-67, and postoperative residue	Samsung Biomedical Research Institute grant
7	Raverot et al ¹⁷ , 2017	213(89)	Cohort	2007-2012	France	Recurrence	Mean 3.5 (+/-1.9) year	Size, types, dan grade	Government grant
8	Ly et al ²⁰ , 2018	270(77)	Case-control	2008-2016	China	Recurrence	Median 44 (5-111) month	Size, types, subtypes, invasiveness, proliferative properties, grade, and postoperative residue	Financial support from government hospitals
9	Hasanov et al ²⁵ , 2019	117(39)	Case-control	2001-2015	Turkey	Recurrence	Mean 49.7 +/-31.1 month	Size, types, invasiveness, mitosis, Ki-67, and p53	-
10	Guaraldi et al ³⁰ , 2020	1066(116)	Case-control	1998-2018	Italy	Recurrence	Mean 65.6 (1.0-160.2) month	Size, types, invasiveness, mitosis, Ki-67, p53, and grade	University grant

Table 2
Quality assessment of selected case-control study design using NOS

Study (year)	Selection		Comparability		Exposure			Total	
	Is the case definition adequate	Representativeness of the case	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls		Non-response rate
Hsu (1993)	*	*	*	*		*	*	*	7
Gejman (2008)	*		*	*	*	*	*	*	7
Matsuyama (2012)	*	*	*	*		*	*	*	7
Trouillas (2013)	*		*		*	*	*	*	6
Kim (2016)	*	*	*		*	*	*	*	7
Liang (2018)	*		*		*	*	*	*	6
Hasanov (2019)	*		*		*	*	*		5
Guaraldi (2020)	*	*	*		*	*	*	*	7

Table 3
Quality assessment of selected cohort study design using NOS

Study (year)	Selection		Comparability		Outcome			Total	
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assesment of outcome	Was follow-up long enough for outcomes to occur		Adequacy of follow-up of cohorts
Jang (2016)	*	*	*	*	*	*	*	*	8
Raverot (2017)	*	*	*	*	*	*	*		7

Discussion

The meta-analysis revealed a significant difference in the aggressiveness of the adenoma size ≥ 10 mm. The results of the meta-analysis support this by comparing the mean size of the adenoma and giant adenoma, both of which showed significant aggressiveness, with mean differences of 5.61 (3.29-7.92) and OR 2.21 (1.17-4.18), respectively (figure L2 and L3). The findings of Liang Lv et al.²⁰ study, which compared adenomas' diameter and volume, are also intriguing. The findings were surprising because, despite a significant mean difference in diameter, there was no clinical difference (3.42 ± 1.08 cm and 2.80 ± 0.84 cm, $p < 0.0001$). When measured by volume, however, there is a clinically significant difference ($12.1 (0.06-76.20)$ cm³ and $6.00 (0.05-50.60)$ cm³, $p < 0.0001$). This finding could help to reduce the risk of bias or error when measuring adenoma diameter.

The corticotroph type was more aggressive than the other types, while the somatotroph type was less aggressive. Figure L7 depicts the results of other types of meta-analysis. There are currently no guidelines that could determine which type of pituitary adenoma is more aggressive than the other. However, two of the five high-risk subtypes highlighted by WHO, namely crook's cell adenoma and silent corticotroph adenoma, are found to be part of the corticotroph type.¹⁹ The small number of studies evaluating this subtype could be due to the WHO's relatively recent recommendation in 2017 or certain difficulties in the examination, which is quite detailed and costly. However, as recommended by WHO, this should still be considered when evaluating patients with pituitary adenoma.^{19,21}

In the case-control meta-analysis, the invasive trait variable showed a significant difference in aggressiveness. The significance of invasiveness could be seen through the assessment of grade 2a, which showed significant differences in aggressiveness compared to grade 1a in the Jang et al.²⁹ study and similarly in the Raverot et al.¹⁷ study. Pituitary adenomas and other neoplastic diseases have long been assessed using this invasive technique. Based on Hardy and Knosp, pituitary adenoma is divided into two categories based on the level of invasion.^{32,33} In general, a higher level of invasion makes it more difficult for the surgeon to remove the mass completely, increasing the risk of the adenoma becoming aggressive.¹¹ In 2004, WHO recommended the classification of atypical pituitary adenomas where it prioritizes proliferative properties over invasiveness in predicting pituitary adenomas'

aggressiveness.¹⁸ Experts at the time were outraged, and this drew much criticism. The WHO abolished the atypical classification in 2017 after it was proven that many patients do not have proliferative traits but have an aggressive outcome.^{19,21}

On the aggressiveness, the proliferative trait variable showed significance in the meta-analysis result. Because it requires a combination of two positives from three IHC tests (Ki-67, p53, and mitosis), each of these components is predicted to have a prognostic value for the aggressiveness of pituitary adenoma, this proliferative property has a fairly strong prognostic value.

The variable Ki-67 showed a significant meta-analysis result on the aggressiveness. This is also supported by the meta-analysis results of the mean aggressiveness difference, which shows a significant difference of 1.05 (0.87-1.22)% (Figure L4). No meta-analysis could be performed in the cohort study group; however, Jang et al.²⁷ found that aggressiveness was associated with higher Ki-67 values. This procedure has long been used to diagnose endocrine tumors, particularly pituitary adenomas. Guadagno E et al.³¹ conducted a fairly large study on the significance of Ki-67 in pituitary adenomas, with mixed results. Ki-67 is one component in assessing the proliferative nature of pituitary adenoma, according to WHO guidelines, so it must be combined with other markers to provide a better prognostic value.^{18,19,21}

In one of the three studies that looked at it, the variable of mitosis rate showed a significant difference in aggressiveness. Three studies with significant results on the aggressiveness were meta-analyzed.

In one of the four studies that looked at it, the p53 variable showed a significant difference in aggressiveness. A positive p53 was found to significantly impact the aggressiveness in the meta-analysis.

The variable of adenoma's grade showed significant aggressiveness at grade 2b. The findings of a meta-analysis comparing grades 2b and 1a with significant differences in aggressiveness back this up (figure L5). Although no meta-analysis could be performed in a cohort study, Raverot et al.¹⁷ found aggressive aggression at grade 2b versus grade 1a. Trouillas et al.¹⁵ proposed this grade in their study evaluating prognostic factors for pituitary adenoma postoperative outcome. This grade is based on pituitary adenomas' invasive and proliferative nature, both of which have long been used to predict its' prognosis. The higher the grade, the more positive prognostic factors there are, so this assessment becomes objective and means that the postoperative outcome is quite good.

Because it has been extensively studied in the selected literature, the postoperative residue is an additional component that is quite important in assessing the aggressiveness of postoperative pituitary adenomas. In studies that looked at the tendency to occur in adenomas with postoperative residues, this component showed significant differences in aggressiveness. This component is commonly used to assess postoperative outcomes in other organ malignancies. On patients where gross total resection cannot be performed, the unclear removal of the mass tissue will result in future recurrence. The meta-analysis found that aggressiveness was significantly increased in the presence of postoperative residues, with an OR of 2.86 (1.32-6.19). (Fig. L6).

The limitations include:

1. Wide range of study designs
2. The number of independent variables studied and research subjects.
3. The study's quality
4. Differences in definitions and variable data types resulted in a separated meta-analysis of each variable between studies with case-control and cohort designs.
5. The limited number of studies.

According to an assessment of case-control study quality, four studies had poor quality, and five studies had an unclear definition of control, indicating a selection bias possibility from the included studies. Meanwhile, the cohort study's quality assessment revealed a high dropout rate for no apparent reason, indicating the possibility of study outcome bias. The proliferative trait variable is one of the components of adenoma grade, where an anatomical pathology examination relies on the subjective assessment of anatomical pathologists—only one anatomical pathologist is examining in the studies, so the chance of assessment bias is there. Because pituitary adenoma has a low incidence, there may be unpublished studies. This publication bias could also be due to limited access to large databases like Embase.

Conclusion

The aggressiveness of postoperative pituitary adenomas is influenced by clinicopathological factors such as adenoma size, adenoma type/subtype, invasiveness, proliferative nature (Ki-67, mitotic rate, and p53), and adenoma grade.

Recommendations

To compare high-risk and low-risk adenoma subtypes to postoperative pituitary adenoma aggressiveness and develop a scoring system to predict postoperative pituitary adenoma aggressiveness.

Abbreviations

PitNET: pituitary neuroendocrine tumor; IHC: immunohistochemical; ESE: European Society of Endocrinology; WHO: World Health Organization; PICO: Patients/Problem, Intervention, Comparison, and Outcome; NOS: Newcastle Ottawa Scale.

Declarations

Consent Form

Not applicable.

Ethical and consent

Not applicable.

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Authors' contribution

Idea, study design: TJET, HAA, JK; Data collection and analysis: TJET, HAA, JK; Writing draft for publication: TJET, HAA

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Competing Interest

The authors have no conflict of interest to disclose in this meta-analysis.

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Figures

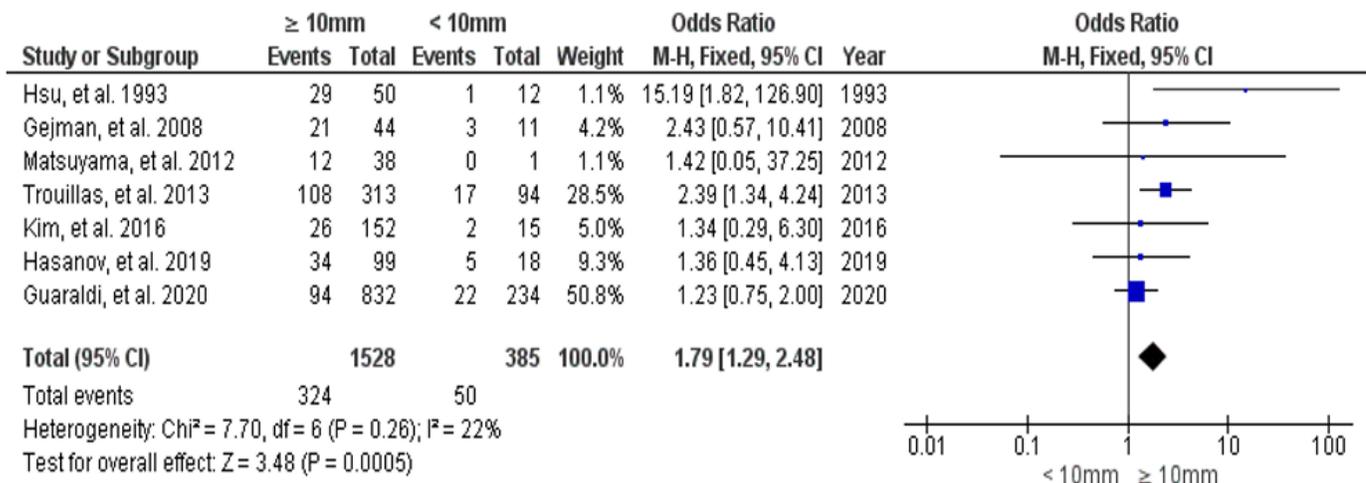


Figure 1

Forest plot of adenoma size ≥10mm with adenoma size <10mm on aggressiveness (case-control study)

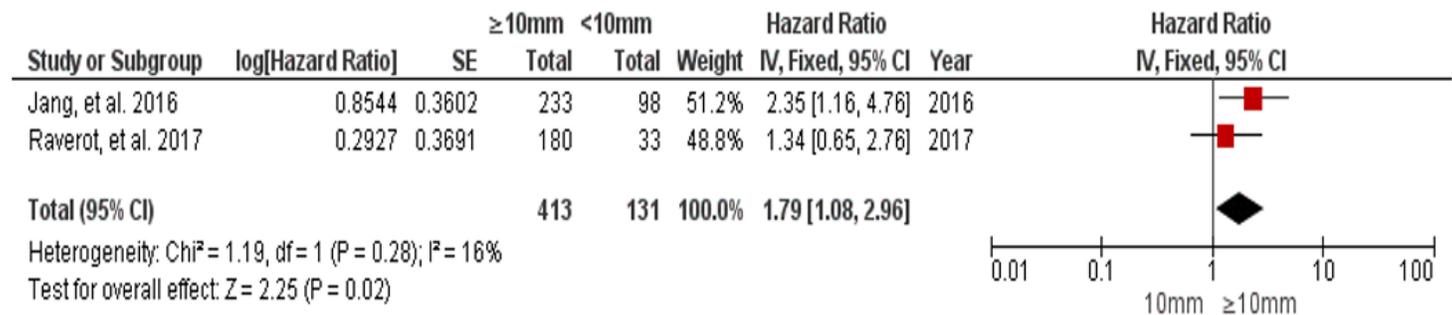


Figure 2

Forest plot of adenoma size ≥10mm with adenoma size <10mm on aggressiveness (cohort study)

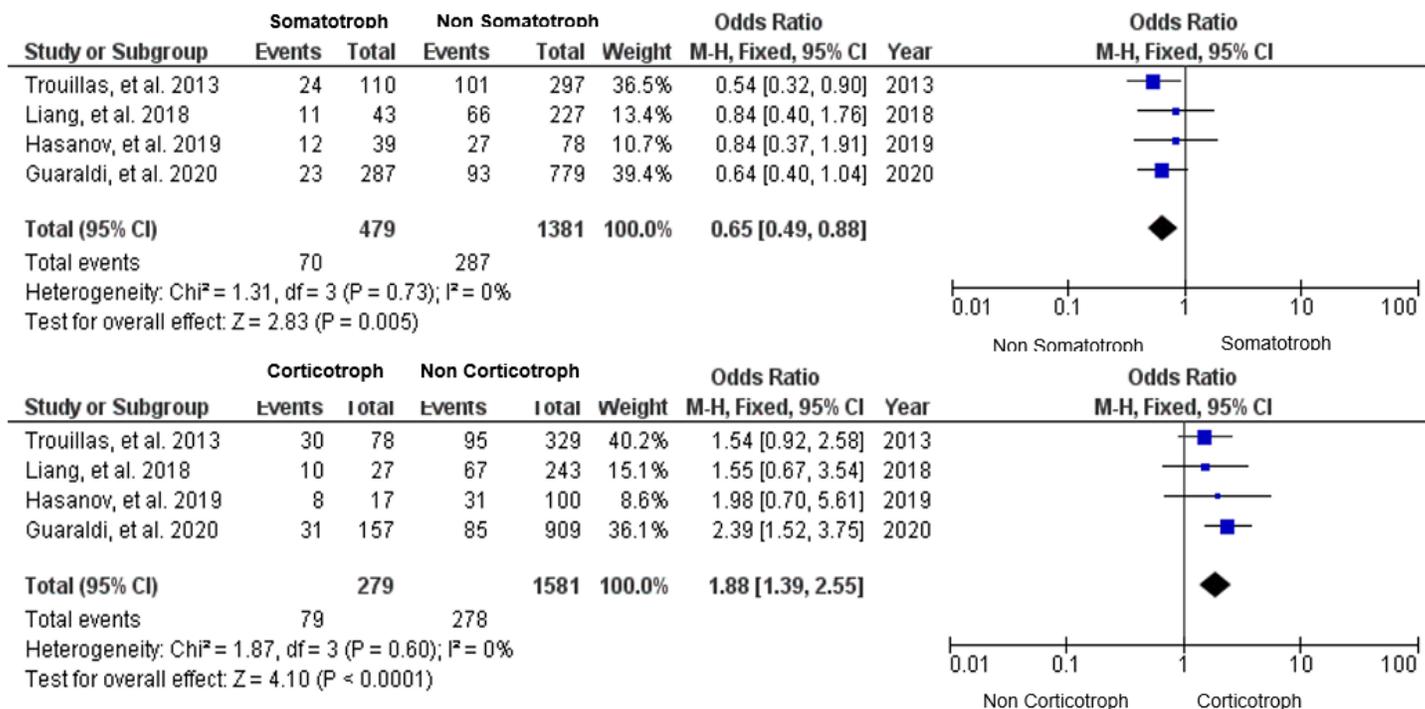


Figure 3

A forest plot of aggressiveness based on adenoma type (somatotroph and corticotroph)

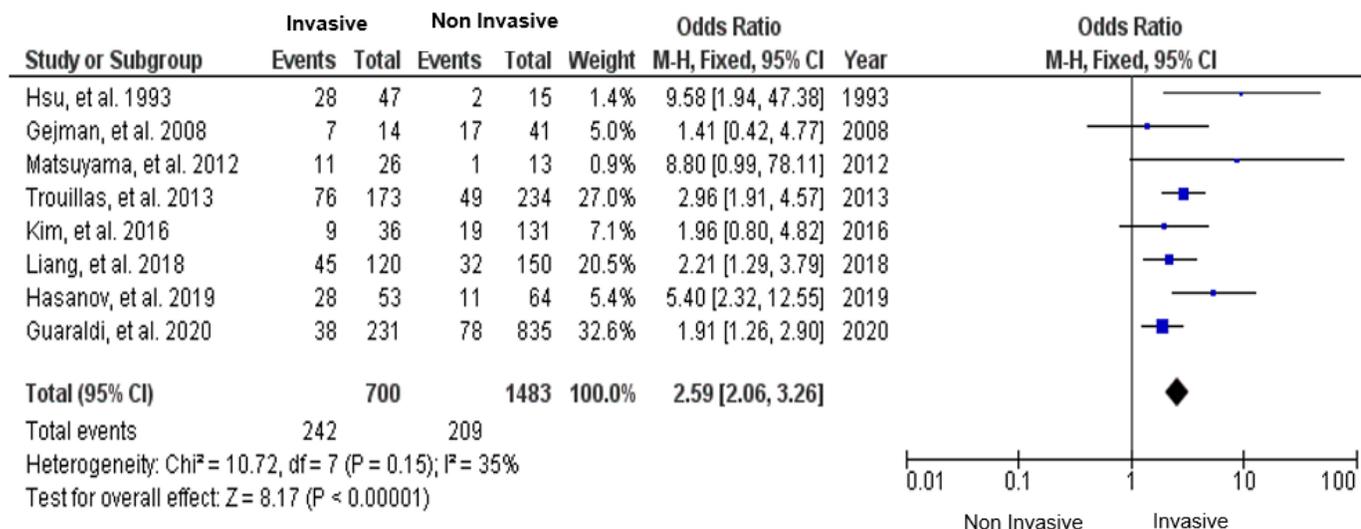


Figure 4

A forest plot of invasive and non-invasive properties on aggressiveness

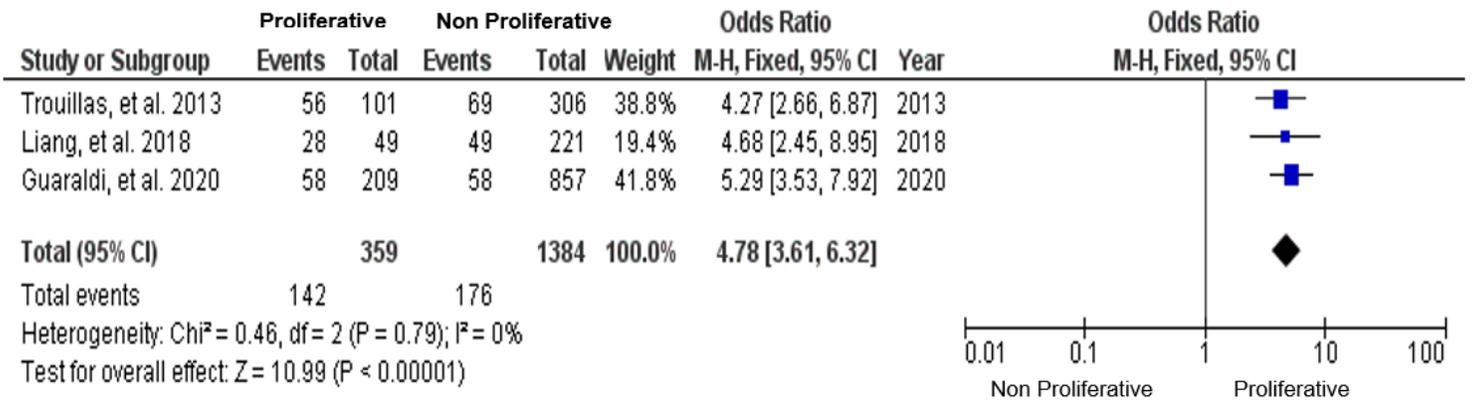


Figure 5

Forest plot of proliferative and non-proliferative traits on aggressiveness

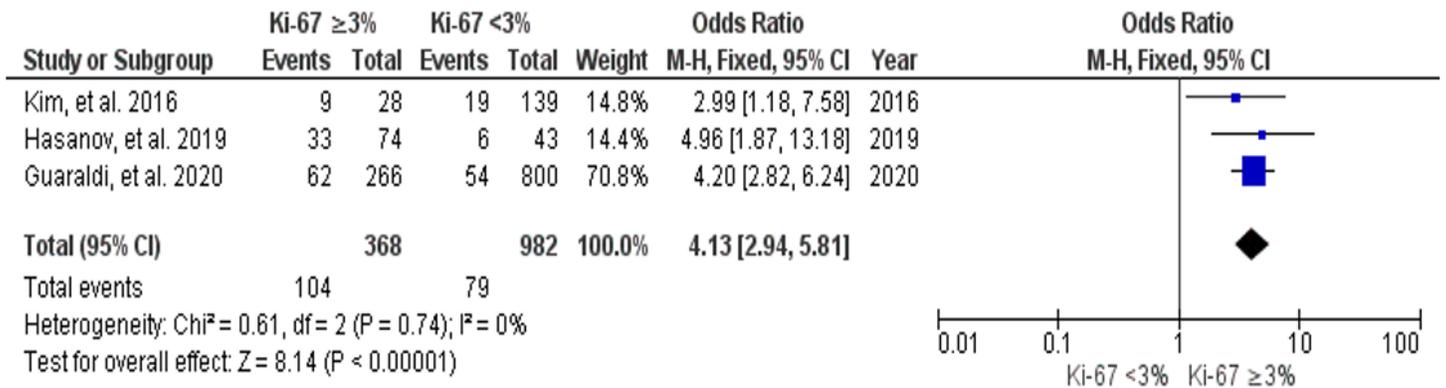


Figure 6

Forest plot of Ki-67 ≥3 with Ki-67 <3 on aggressiveness

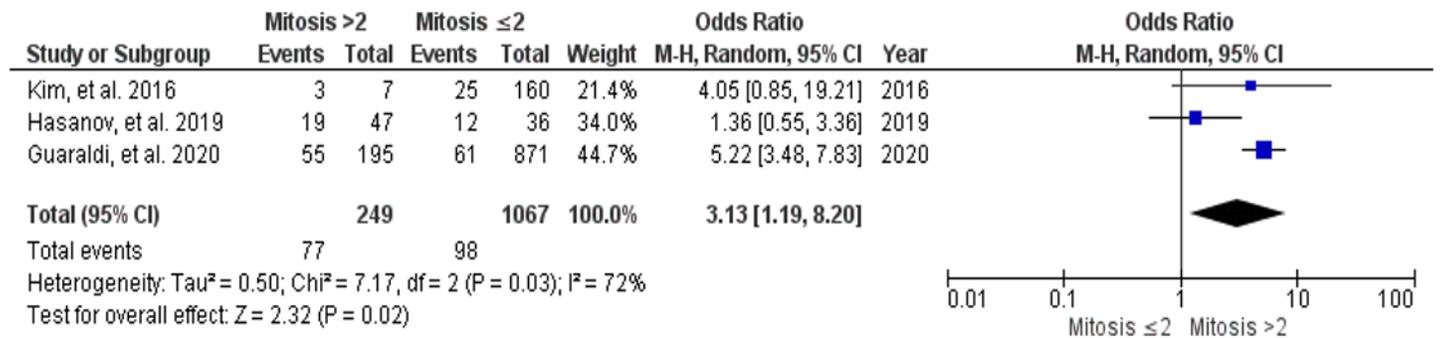


Figure 7

Forest plot of mitotic rate >2 with mitotic rate ≤2 on aggressiveness

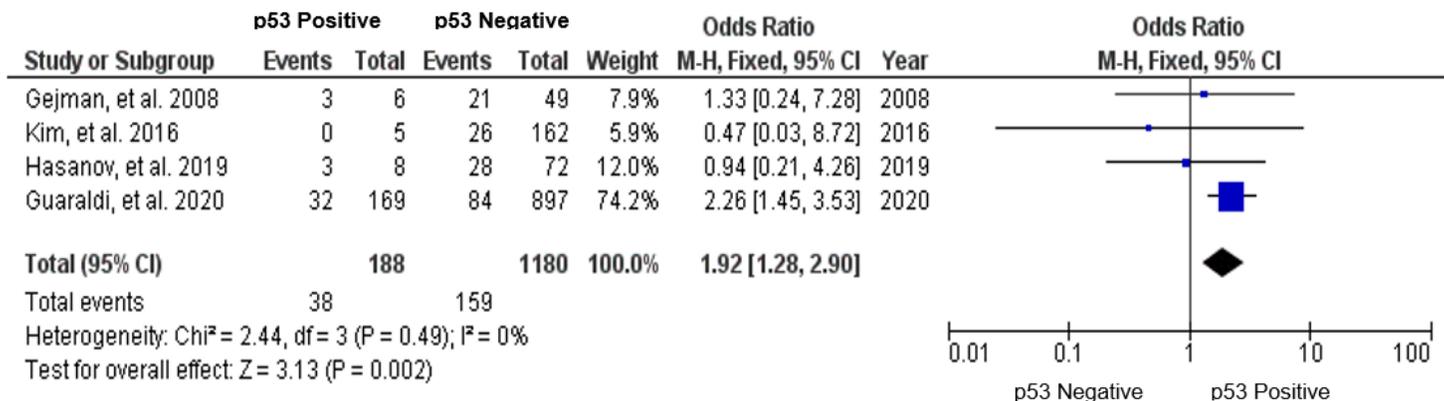


Figure 8

Forest plot of p53 positive with p53 negative on aggressiveness

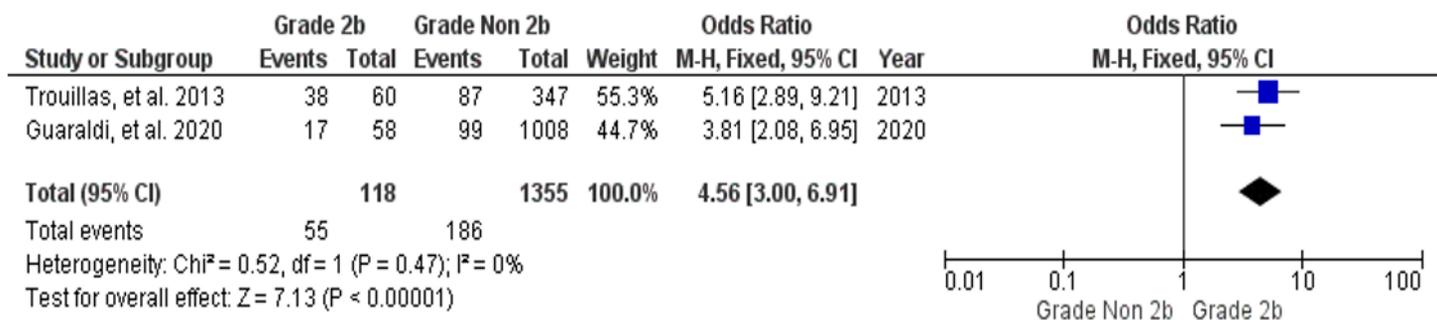


Figure 9

Forest plot of grade 2b (invasive and proliferative) with grade non 2b on aggressiveness

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Attachment.docx](#)