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p53, p16 and ki67 as immunohistochemical prognostic markers in uterine smooth muscle tumors of uncertain malignant potential (STUMP)

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ABSTRACT

The risk stratification in gynecologic smooth muscle tumors of uncertain malignant potential (STUMP) is a crucial issue, but at present there are no validated prognostic markers. We aimed to assess p53, p16 and ki67 as immunohistochemical prognostic markers in STUMP through a systematic review and meta-analysis. Electronic databases were searched from their inception to July 2020. All studies assessing p53, p16 and/or ki67 immunohistochemistry in gynecologic STUMP series were included. Immunohistochemical patterns were categorized as "abnormal" vs "wild-type" for p53, "diffuse" vs "focal/negative" for p16, ≥ 10% vs 10% for ki67. The prognostic value for recurrence was assessed through Cox regression analysis; a p-value 0.05 was considered significant. Markers that resulted significant were assessed for prognostic accuracy with calculation of area under the curve (AUC) and post-test probability of recurrence. Seven studies with 171 patients were included. Significant association with disease-free survival was found for p53 (p 0.0001) and p16 (p 0.0001), but not for ki67 (p = 0.911). p53 showed sensitivity= 83%, specificity= 86%, AUC= 0.89, and post-test recurrence probabilities of 54% and 7% in the case of abnormal and wild-type expression, respectively. p16 showed sensitivity= 84%, specificity= 88%, AUC= 0.91 and post-test recurrence probabilities of 56% and 7% in the case of diffuse and focal/negative expression, respectively. In conclusion, p53 and p16 might be useful in the risk assessment of STUMP, despite not being suitable as stand-alone prognostic markers.

1. Introduction

Uterine smooth-muscle tumors are the most common gynecologic neoplasms, affecting more than three fourths of women [1–4]. In most cases, histomorphologic features are sufficient to categorize them as leiomyomas (benign) or leiomyosarcomas (malignant) [5]. However, in a minority of cases a definite diagnosis of benignity or malignity cannot be made; these cases are termed "smooth muscle tumor of uncertain malignant potential" (STUMP) [5,6]. The biological behavior of STUMPs is highly variable [6]. In most cases they have a benign behavior; however, about 11–13% of cases show local or distant recurrence; finally, STUMP may recur as overt leiomyosarcoma [5]. On the account of such variability, the management of STUMP is not standardized. In young women who wish to get pregnant, the excision of the lesion with close follow-up can be an option; otherwise, hysterectomy with long-term follow-up is recommended. In recurrent cases, systemic therapy can be adopted [7].

Unfortunately, to date there are no validated prognostic markers to predict the behavior of STUMP [5]. Recently, Croce et al. proposed a prognostic stratification system of STUMP based on genome profiling

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[8]. However, a genomic-based approach appears not widely available in the common practice, due to the costs and complexity of genomic analyses [9].

With regard to immunohistochemistry, the most studied prognostic markers have been p53, p16 and ki67 [10–17]. However, their accuracy has never been systematically assessed for validation purpose. Such assessment may be difficult on large series of patients, given the rarity of STUMP.

The aim of this study is to assess the prognostic value of p53, p16 and ki67 in STUMP through a systematic review and meta-analysis of the literature.

2. Materials and methods

2.1. Study protocol

Methods of this review were designed before the beginning of the study, according to our previous studies [18,19]. All review stages (electronic search, study selection, data extraction, risk of bias within studies assessment and data analysis) were independently performed by three authors (AT, AR, AG). After each review stage, disagreements were solved by consensus among all authors. This review was reported following the PRISMA statement [20].

2.2. Search strategy and study selection

Four electronic databases (Scopus, MEDLINE, Google Scholar and Web of Sciences) were searched from their inception to July 2020 for all studies assessing p53, p16 or ki67 immunohistochemistry in case series of gynecologic STUMPs. The following combination of text words was adopted: (uterine OR uterus OR gynecologic) AND (STUMP OR smooth muscle tumor of uncertain malignant potential). Reference lists were also searched for further relevant studies.

Exclusion criteria were: sample size < 5; follow-up duration not reported; data not extractable; reviews; inappropriate criteria for interpreting p53 immunohistochemistry (i.e. not reflecting *TP53* mutation).

2.3. Risk of bias within studies assessment

In each study, the QUADAS-2 [21] were used as a basis to assess the risk of bias in four crucial domains: 1) Patient selection (i.e. if patient selection criteria and period of recruitment were reported, if histological slides were reviewed and if morphological features of STUMPs were reported); 2) Index test (i.e. if immunohistochemical methods were clearly reported); 3) Reference standard (i.e. if the time from diagnosis to recurrence and the site of recurrence were reported); 4) Flow (i.e. if no more than one patient was lost to follow-up or not assessed by immunohistochemistry). The risk of bias was categorized as "low", "unclear" or "high" as previously described [22].

2.4. Data extraction

Data from primary studies were extracted according to the PICO [20]:

"P" (population) was constituted by patients with uterine STUMPs;.

"I" (intervention or risk factor) was the presence of an altered pattern of the immunohistochemical marker assessed; the altered patterns were defined as "abnormal" (strong diffuse or completely negative) expression for p53, diffuse positivity for p16, and labeling index (LI) $\geq 10\%$ for ki67;.

"C" (comparator) was a normal pattern of the immunohistochemical marker assessed (wild-type p53 pattern, negativity or focal positivity for p16 and LI $<10\%$ for ki6);.

"O" (outcome): recurrence of STUMP.

For the survival analysis, the follow up time from surgical removal to local/distant recurrence or to the last check was extracted. If the follow-up duration was not specified, the minimal follow-up reported by the study was considered for the non-recurrent cases and the mean follow-up for the recurrent cases.

For the prognostic accuracy analysis, immunohistochemistry was considered as the index test, which was positive in the case of altered expression and negative in the case of normal expression for each marker; patient status at follow-up was considered as the reference standard, which was positive in the case of recurrence and negative in the case of no recurrence.

2.5. Data analysis

For each immunohistochemical marker assessed, a Cox regression analysis with calculation of hazard ratio (HR) with 95% confidence interval (CI) was performed for the risk of recurrence in patients with STUMP, according to the expression pattern of the marker (altered or normal); a p-value< 0.05 was considered significant.

In the case of significant HR, the immunohistochemical marker was further assessed for prognostic accuracy: sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-), diagnostic odds ratio (DOR) and area under the curve (AUC) on summary receiver operating characteristics curves (SROC) were calculated; data were pooled according to the random effect model of DerSimonian-Laird. The prognostic accuracy was quantified as previously described [18,23]. Post-test probability of recurrence with 95% CI was calculated by using Fagan's nomogram, as previously described [23].

Data analysis was performed by using Statistical Package for Social Science (SPSS) 18.0 package (SPSS Inc., Chicago, IL, USA) and MetaDiSc version 1.4 (Clinical Biostatistics Unit, Ramon y Cajal Hospital, Madrid, Spain).

3. Results

3.1. Study selection and characteristics

Seven studies with a total sample size of 171 patients were included [10–16]. The process of study selection is shown in Supplementary Figure 1. Characteristics of the included studies are shown in Table 1.

3.2. Risk of bias assessment

For the "Patient selection" domain, one study was considered at unclear risk of bias (period of enrollment not reported) [13], while the other studies were considered at low risk. For the "Index test" domain, one study was considered at high risk, since it did not clarified criteria to define p16 and p53 positivity for all patients, although data for ki67 were clearly reported [16]; three studies were considered at unclear risk (unclear threshold to define p53 accumulation) [12,15], while the other studies were considered at low risk of bias. For the "reference standard" domain, one study was considered at unclear risk (unclear time from diagnosis to recurrence) [10] and the other studies at low risk. For the "flow" domain, two studies were considered at unclear risk (not all patients were assessed by immunohistochemistry) [13,15] and the other studies at low risk. Risk of bias results are presented graphically in Supplementary Figure 2.

3.3. Survival analysis

Significantly increased risk of recurrence was associated with abnormal p53 expression (HR=7.35; 95% CI, 2.78–19.43; $p < 0.0001$) (Fig. 1) and diffuse p16 expression (HR=8.75, 95% CI 3.13–24.47; $p < 0.0001$) (Fig. 2), but not with ki67 $\geq$ 10% (HR=1.127, 95% CI 0.138–9.207; $p = 0.911$) (Fig. 3).

Table 1
Characteristics of the included studies.

STUDY	COUNTRY	PERIOD OF ENROLLMENT	SAMPLE SIZE	MYOMECTOMY/ HYSTERECTOMY	RECURRENCE (abdominopelvic/distant metastases)	FOLLOW-UP DURATION (mean)	IMMUNOHISTOCHEMICAL MARKERS ASSESSED
Atkins 2008	USA	1987–2006	8	0/8	3 (0/3)	(80 m)	p16
Ip 2009	Canada, USA, Hong Kong	1992–2006	16	1/15	2 (2/0)	21–192 m (80.8)	p53, p16, ki67
Danska-Bidzinska 2012	Poland	2008–2011	10	3/7	0	4–29 m (16)	p53, ki67
Slatter 2015	New Zealand, Hong Kong	unclear	18	1/17	6 (unclear)	1–140 m (58)	p53, p16
Karatasli 2019	Turkey	2003–2018	28	7/21	1 (1/1)	5–180 m (45.4)	p53, p16, ki67
Zheng 2020	China	2010–2018	26	6/20	6 (6/0)	13–96 m (65.9)	p53, p16, ki67
Huo 2020	China	2005–2019	67	38/29	10 (10/0)	2.6–170.2 m (48.4)	p53, p16, ki67

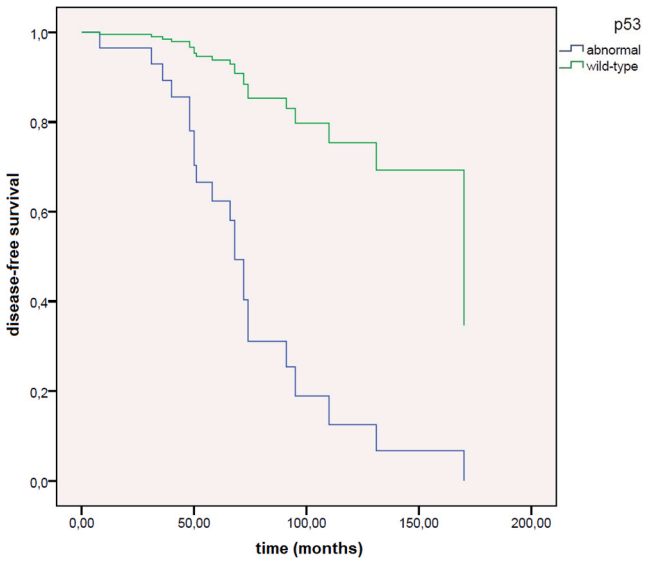

Fig. 1. Disease-free survival curves of STUMP cases according to p53 immunohistochemistry.

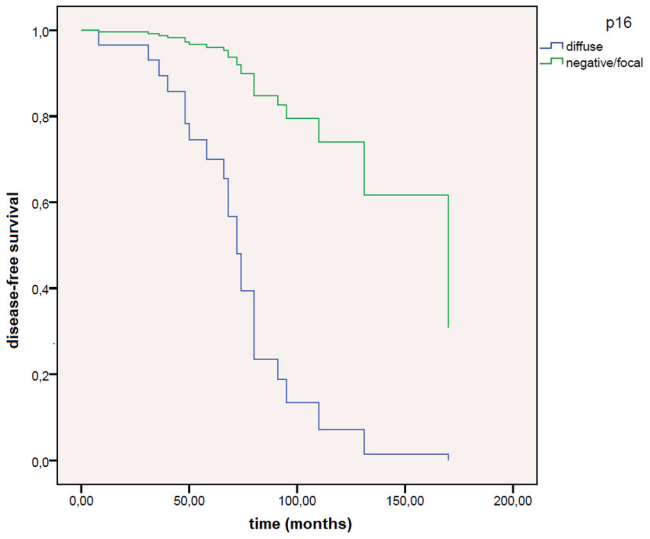

Fig. 2. Disease-free survival curves of STUMP cases according to p16 immunohistochemistry.

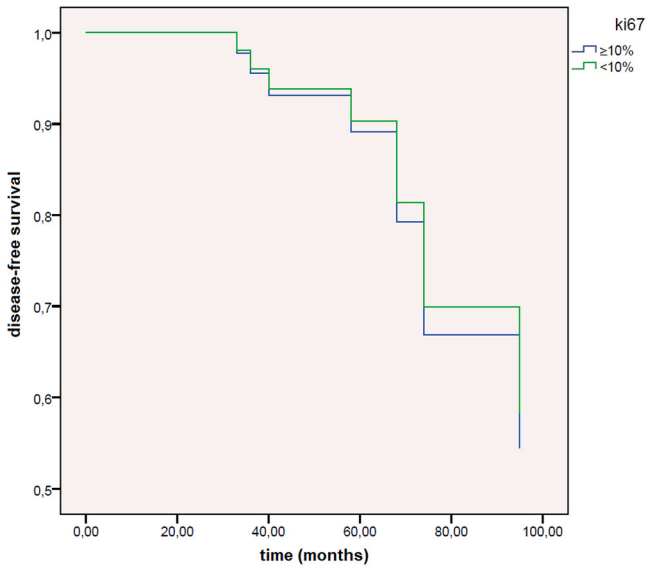

Fig. 3. Disease-free survival curves of STUMP cases according to ki67 immunohistochemistry.

3.4. Prognostic accuracy analysis

Sensitivity and specificity of p53 abnormal expression in predicting STUMP recurrence were 0.83 (95% CI 0.59–0.96) and 0.86 (95% CI 0.75–0.93) respectively, with a LR+ and LR- of 4.69 (95% CI 2.54–8.66) and 0.30 (95% CI 0.13–0.69) respectively, a DOR of 19.54 (95% CI 4.99–76.52) and an AUC of 0.89 (Fig. 4). In the case of abnormal p53 expression (positive test), the probability of recurrence was 54% (95% CI 39–68%); In the case of normal p53 expression (negative test), the probability of recurrence was 7% (95% CI 3–15%) (Supplementary Figure 3).

Sensitivity and specificity of p16 diffuse positivity in predicting STUMP recurrence were 0.84 (95% CI 0.6–0.97) and 0.88 (95% CI 0.78–0.95) respectively, with a LR+ and LR- of 5.09 (95% CI 2.2–11.8) and 0.31 (95% CI 0.15–0.64) respectively, a DOR of 31.69 (95% CI 7.49–134.13) and an AUC of 0.91 (Fig. 5). In the case of diffuse p16 expression (positive test), the probability of recurrence was 56% (95% CI 40–71%); in the case of focal/negative p16 expression, the probability of recurrence was 7% (95% CI 3–15%) (Supplementary Figure 4).

Prognostic accuracy results are summarized in Table 2.

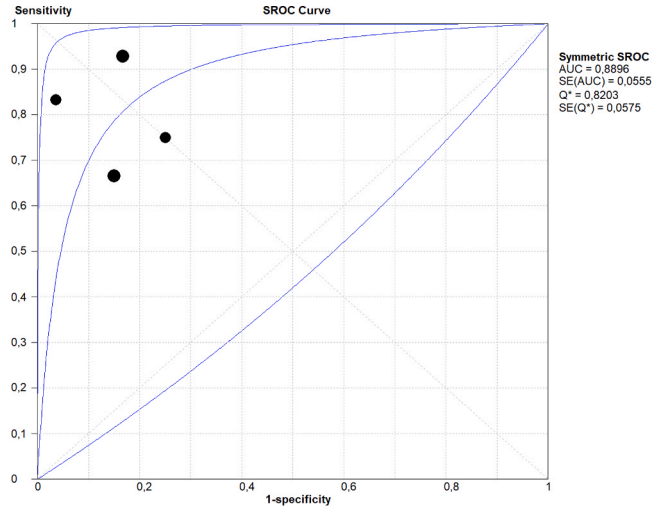

Fig. 4. Area under the curve (AUC) on summary receiver operating characteristics curves (SROC) for p53 immunohistochemistry in predicting recurrence of STUMP.

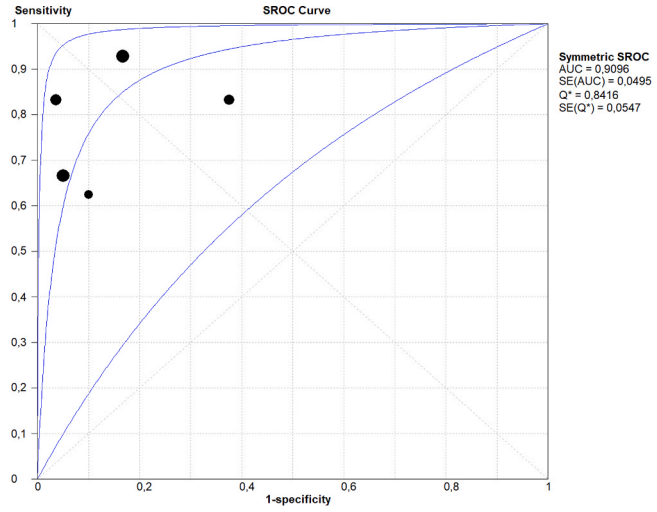

Fig. 5. Area under the curve (AUC) on summary receiver operating characteristics curves (SROC) for p16 immunohistochemistry in predicting recurrence of STUMP.

4. Discussion

4.1. Main findings and interpretation

This study showed that altered expression of p53 and/or p16 was significantly associated with recurrence in STUMP. Both p53 and p16 showed moderate accuracy as immunohistochemical prognostic markers in STUMP, with a probability or recurrence > 50% in the case of altered patterns (positive test) and < 10% in the case of normal patterns (negative test). On the other hand, a prognostic value could not be demonstrated for ki67.

The prognostic stratification of uterine smooth muscle tumors is a long-standing issue. In fact, they may considerably vary with regard to cellularity, cellular morphology, nuclear atypia, mitotic index, growth pattern and necrosis [5,24]. According to the "Stanford criteria" based on the study by Bell et al., a diagnosis a leiomyosarcoma requires at least two of three crucial histomorphologic parameters: mitotic figures > 10/10 high-power fields, moderate-to-severe nuclear atypia, and coagulative tumor cell necrosis [24]. However, the interobserver variability in the assessment of these parameters (which are not always straightforward) and the presence of the other above-mentioned morphologic features make the diagnosis difficult [5]. Regarding immunohistochemistry, several markers have been studied for distinguishing between benign and malignant lesions, including estrogen and progesterone receptors, ki67, p53, p16, Bcl2 [17,25]. Unfortunately, most studies did not correlate immunohistochemical data with prognosis [25].

Given the rarity of STUMP, only few studies that correlated immunohistochemical markers with prognosis are present in the literature. The main immunohistochemical markers assessed in STUMP were p53, p16 and ki67 [10–17].

We found that an abnormal p53 expression and a diffuse p16 expression were significantly associated with the risk of recurrence of STUMP. The value of p53 lies in its association with the status of the *TP53* gene [26–28]. In fact, *TP53* is one of the most important suppressor genes and its mutation is involved in the development of many human malignant neoplasms [29]. When *TP53* is wild-type, p53 is expressed in a variable percentage of cell nuclei, with variable intensity. On the other hand, *TP53* mutations lead to an abnormal expression of p53, with strong positivity in the nuclei of almost all tumor cells. Rarely, *TP53* mutations may lead to a complete absence of p53 expression, or to its accumulation in the cytoplasm [30]. In uterine smooth muscle tumors, p53 abnormal expression has been described as a marker of malignancy [31]. However, an abnormal pattern of p53 has been described in a variable percentage of uterine leiomyosarcomas (30–60%), in about 20% of STUMPs and in almost 10% of leiomyoma variants, although the immunohistochemical criteria adopted were inconsistent [25]. Therefore, in spite of the association between p53 pattern and STUMP behavior, its prognostic accuracy is not foregone.

Similarly, p16 is a tumor suppressor protein encoded by the *CDKN2A* gene. Acting as a cyclin-dependent kinase inhibitor, p16 has a crucial role in regulating the cell cycle [32]. A defect in p16 function can be responsible for many type of cancers and can result in an accumulation of the protein in the nucleus and cytoplasm of tumor cells; this may be observed at immunohistochemistry as a strong and diffuse positivity for p16 [32,33]. Similarly to p53, p16 has long since been studied as a marker of malignancy in uterine smooth muscle tumors [31]. Diffuse p16 expression has been described in a highly variable percentage of uterine leiomyosarcomas (20–90%), in about 25% of STUMPs and in over 30% of leiomyoma variants [25].

Given the variability in their expression, it appeared necessary to quantify the accuracy of p53 and p16 immunohistochemistry, in order to define their usefulness in the common practice.

For both p53 and p16, we found an overall moderate prognostic

Table 2
Prognostic accuracy results.

MARKER	SENSITIVITY	SPECIFICITY	LIKELIHOOD RATIO		DIAGNOSTIC ODDS RATIO	POST-TEST PROBABILITY		AREA UNDER THE CURVE
			POSITIVE	NEGATIVE		POSITIVE TEST	NEGATIVE TEST	
p53	0.83 (0.59–0.96)	0.86 (0.75–0.93)	4.69 (2.54–8.66)	0.30 (0.13–0.69)	19.54 (4.99–76.52)	0.54 (0.39–0.68)	0.07 (0.03–0.14)	0.89
p16	0.84 (0.6–0.97)	0.88 (0.78–0.95)	5.09 (2.2–11.8)	0.31 (0.15–0.64)	31.69 (7.49–134.13)	0.56 (0.4–0.71)	0.07 (0.03–0.15)	0.91

accuracy in predicting the risk of recurrence in STUMP. This implies that a diagnosis of benignity and malignity, as well as the choice of treatment, cannot be determined by these markers as stand-alone. However, for both p53 and p16, the post-test probability of recurrence in the case of positive test was > 50%. This implies that STUMPs with altered pattern of p53 and/or p16 are more likely to recur than not to recur. Such information could be helpful in directing the management and the follow-up of the patients with STUMP. For instance, the presence of abnormal p53 expression and/or diffuse p16 expression may suggest a longer and closer follow-up. It should be remarked that immunohistochemical data should always be interpreted in the light of histomorphological parameters. Aberrant expression of immunohistochemical markers may be observed in usual leiomyomas with infarct-type necrosis [34], as well as in leiomyoma variants, as discussed above. Therefore, the correct recognition of the type of necrosis (i.e. infarct-type necrosis vs coagulative tumor cell necrosis [24]), the distinction between true mitoses and degenerative nuclei [35], and the identification of a significant cytological atypia [24] remain as crucial points in the diagnosis of uterine smooth muscle tumors.

Interestingly, the study by Slatter et al. also included two vaginal STUMPs (which were not included in our analysis) [13]. These two cases showed an aggressive behavior, and both showed normal expression of p53 and p16. It would be interesting to assess whether p53 and p16 are more relevant in tumors originating from the myometrial cells than in smooth muscle tumors of the lower genital tract.

Regarding ki67, it is a proliferation marker which is positive in the nuclei of proliferating cells. Therefore, immunohistochemistry for ki67 provides an estimate of the growth fraction of the tumor [36]. Although a high ki67 LI has been proposed as a diagnostic markers of malignancy in uterine smooth muscle tumors, a wide overlap exists between benign and malignant lesions; in fact, a ki67 LI ≥ 10% is reportedly found in about 65–70% of uterine leiomyosarcomas, 10% of STUMPs and 20% of leiomyoma variants [25]. There is also evidence suggesting that a high ki67 LI is associated with adverse outcomes in leiomyosarcoma [17]. In the series we assessed, ki67 did not show a significant association with prognosis in STUMP. In fact, only one case with high ki67 LI recurred [16], while 8 recurrences were observed in cases with low expression. Remarkably, in uterine smooth muscle tumors, a high mitotic index in the absence of atypia and necrosis is usually associate with a benign behavior [24]. Since proliferation index and mitotic index are in part related [36], it is not implausible to hypothesize that a high ki67 LI might not affect prognosis in the absence of other unfavorable prognostic features. In fact, in the primary studies, ki67 LI tended to be higher in cases with high mitotic index [11,14].

Considering the well-accepted prognostic value of histomorphologic parameters [6,24], an integration between immunohistochemical and histomorphologic factors appear advisable in the diagnostic approach to STUMP. Several other markers, such as bcl2 and PCNA, appear worthy to be assessed in STUMP, since they have shown some evidence of prognostic value in uterine smooth muscle tumors. On this account, large multicentric studies with centralized pathologic review and long-term follow-up are encouraged, in order to achieve a better risk stratification and a more tailored management of patients with STUMP.

4.2. Strengths and limitations

To our knowledge, this is the first meta-analysis assessing the prognostic value of p53, p16 and ki67 in STUMP. Regarding p16, a previous meta-analysis assessed its association with malignancy and risk of recurrence, but neither survival analysis, nor accuracy analysis were performed [33]. Our meta-analysis aimed to define the accuracy and the clinical usefulness of these immunohistochemical markers, rather than only assessing their generic association with recurrence.

The main limitation of our study lies in the overall small sample size, which might limit the statistical power. Furthermore, the interpretation of immunohistochemistry may be subject to inter- and intra-observer variability. In particular, the correct interpretation of p53 immunostaining has been shown to require an optimized immunohistochemical procedure, strict interpretation criteria and expertise in identifying artifacts [30]. However, given the small number of studies in this field and the difficulty in achieving a large sample size, our meta-analysis may increase the level of evidence, providing a stronger basis for further investigation.

5. Conclusion

Despite being insufficient as stand-alone prognostic test, immunohistochemistry for p53 and p16 might be helpful in the prognostic stratification of STUMP. In particular, the presence of an altered expression of p53 and/or p16 suggests a risk of recurrence > 50%, while a normal expression of both proteins is associated with a risk of recurrence < 10%. On the other hand, a prognostic value could not be demonstrated for ki67. Large multicenter studies in this field should be encouraged in order to assess and validate immunohistochemical prognostic markers and promote their integration with clinicopathological data for a more tailored management of STUMP.

Ethics approval and consent to participate

Not applicable.

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Informed Consent

Not applicable.

CRediT authorship contribution statement

Antonio Travaglino: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Antonio Raffone:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Annarita Gencarelli:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing - original draft. **Daniele Neola:** Data curation, Formal analysis, Resources, Software, Validation, Writing - original draft. **Domenico Alessandro Oliviero:** Data curation, Formal analysis, Investigation, Methodology, Writing - original draft. **Rosa Alfano:** Investigation, Methodology, Validation, Writing - original draft. **Maria Raffaela Campanino:** Data curation, Resources, Visualization, Writing - original draft. **Federica Cariati:** Investigation, Methodology, Resources, Writing - original draft. **Fulvio Zullo:** Conceptualization, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Antonio Mollo:** Conceptualization, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Luigi Insabato:** Conceptualization, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of Competing Interest

The authors report no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prp.2021.153592.

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