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Factors predictive of progression in lesions categorised as well-differentiated papillary mesothelial tumour of the pleura, tunica vaginalis and peritoneum: a scoping review

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ABSTRACT

Purpose: This scoping review examines the literature on factors predictive of progression of well-differentiated papillary mesothelial tumours (WDPMT) to identify features relevant to their prognosis.
Methods: A comprehensive search was conducted across six databases to identify English-language case reports and case series published between 2000 and 2024 that described progression of WDPMT to diffuse mesothelioma. Ten studies met inclusion criteria. Data were extracted and synthesised using thematic analysis, and critical appraisal was undertaken using the JBI checklists to assess reporting quality.
Results: Quality appraisal rendered the 10 studies satisfactory for inclusion. Multifocality, and BAP1 loss on immunohistochemistry were consistently associated with progression of WDPMT to diffuse mesothelioma.
Discussion: This scoping review provides insights into the current understanding of WDPMTs and highlights the paucity of published literature on disease progression, with only 10 relevant articles identified over a two-decade period. WDMPT and papillary mesothelioma in situ (MIS) morphologically are indistinguishable but biologically distinct entities. BAP1 loss on immunohistochemistry (IHC), and multifocality are factors associated with risk of progression to diffuse mesothelioma. Testing for BAP1 and MTAP is mandatory for diagnosis. We suggest that WDPMT-like lesions with BAP1 and/or MTAP loss should be classified as papillary MIS.

1. Introduction

Well-differentiated papillary mesothelial tumour (WDPMT) is a distinctive tumour of mesothelial origin composed of non-invasive thin to broad-based papillae lined by a single layer of bland mesothelial cells [1–3]. WDPMT is the contemporary name for what was previously called well-differentiated papillary mesothelioma (WDPM). This change in terminology follows the current WHO classification of tumours where all mesotheliomas are defined as malignant and highlights the purported indolent nature of WDPMT [1–3]. Current WHO guidelines reserve the diagnosis of WDPMT for tumours that lack stromal invasion, but in the past cases with superficial invasion were included in some case series [4–7]. Typically, WDPMT have BAP1 retained on IHC although the WHO definition does not mandate this [1,2]. The inconsistent application of diagnostic criteria complicates our understanding of these lesions and maybe the reason for variable clinical outcomes. We here review the available literature using current diagnostic criteria to identify salient prognostic factors.

Most WDPMT measure between 0.1 to 2 cm in size though lesions up to 5 cm have been reported [5,7–9]. Most WDPMT are peritoneal, located in the omentum or attached to the ovary, uterus or other pelvic structures including the tunica vaginalis. Fewer WDPMT are located in

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the pleura [1,2] or the pericardium [10,11].

WDPMT are often found incidentally during investigations or treatments for other causes [7,9], and this was noted in early diagnostic criteria [12]. More recently, peritoneal WDPMT are described as presenting with abdominal pain, ascites or symptoms related to pelvic inflammatory disease or infertility [9,13–16]. Testicular WDPMT can present with a hydrocoele or rarely a mass in the scrotum [17,18]. Peritoneal WDPMT are more often reported in women of reproductive age whereas pleural WDPMT are commonly reported in men aged between 70–80 years [4,6,9,19] although Sun et al. found approximately equal gender distribution of WDPMT of the pleura [20]. Pleural WDPMT can present with dyspnoea [6].

Treatment for WDPMT ranges from observation when asymptomatic, to cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for recurrence or microinvasion, depending on clinical considerations, including preservation of fertility [21].

Unlike diffuse mesothelioma, WDPMT typically has an indolent course [6,7]. However, reports of progression to diffuse mesothelioma suggest that the prognosis may be variable [4]. Factors predicting behaviour are not well understood. Sampling error or disease progression have been implicated [9,22]. Long term follow up and adequate sampling is thus recommended [7,18,23–25].

Mesothelioma in situ (MIS) is defined as a preinvasive stage of diffuse mesothelioma characterised by BAP1 or MTAP loss on IHC that is also seen in approximately 60 % of invasive mesothelioma [26]. Patients with MIS may present with recurrent pleural effusions in the absence of radiologic or clinical evidence of disease [2]. MIS may evolve to invasive mesothelioma over a period of 1 to 5 years or longer [27]. Microscopically MIS appears as flat or raised mesothelial proliferations [28,29]. Papillary architecture has been reported in MIS [27]. The frequency and significance of BAP1 and MTAP loss have not been systematically evaluated in lesions resembling WDPMT. Conceptually, and based on our molecular understanding, loss of BAP1 and MTAP in mesothelial lesions denotes malignancy at the molecular level and would support designation of these lesions as MIS. WDPMT by molecular profiling shows mutations in EHD1, ATM, FBXO10, SH2D2A, CDH5, MAGED1, TP73 [30] and also in TRAF7 and CDC42 [31]. In contrast, mesothelioma-associated mutations namely BAP1, NF2, SETD2 and CDKN2A were not found in these studies. The findings in some studies are difficult to interpret due to inclusion of cases that do not meet current diagnostic criteria of WDPMT [32].

Since retained BAP1 on IHC is currently not essential for a diagnosis of WDPMT [2], WDPMT and MIS may be indistinguishable [33] but need to be separated. We suggest that BAP1 loss in WDPMT-like lesions indicates progression. This and other factors predicting progression have not been systematically investigated. We here performed a scoping review to evaluate best evidence regarding factors determining progression in WDPMT.

2. Methods

2.1. Search strategy

A comprehensive search strategy was developed and implemented across six databases: MEDLINE, ProQuest, Web of Science, Scopus, CINAHL, and Google Scholar. The search was conducted on 15 August 2024 and utilised a combination of keywords, Boolean operators, MeSH terms, and truncations. The aim was to identify case reports and case series describing the progression of well-differentiated papillary mesothelial tumours (WDPMT) to diffuse mesothelioma from the year 2000 onward. This date range was selected to align with the use of contemporary histopathological definitions. Full details of the search strategy are provided in Supplementary Table 1.

2.2. Eligibility criteria

We included peer-reviewed case reports and case series written in English that documented well-differentiated papillary mesothelial tumours of the pleura, tunica vaginalis, or peritoneum with progression to diffuse mesothelioma. Articles were excluded if they (i) were not in English, (ii) did not document progression, or (iii) did not meet updated WHO diagnostic criteria for WDPMT.

2.3. Study selection

All articles were screened using Covidence software. Titles and abstracts were independently reviewed by two authors. Full texts were retrieved for studies that met inclusion criteria or required further evaluation. Disagreements were resolved through discussion and consensus. A total of 10 studies were ultimately included in the review.

2.4. Critical appraisal

Although critical appraisal is not a standard requirement for scoping reviews, we conducted it to enhance the transparency and quality of our findings. The JBI critical appraisal tools for case reports and case series were used [34]. Two reviewers appraised the articles independently, with consensus confirmed by a senior mesothelioma expert.

2.5. Review framework

This scoping review was conducted in accordance with the methodological framework established by Arksey and O'Malley (2005), which was further refined by the Joanna Briggs Institute (JBI) guidelines for scoping reviews. This approach was selected to systematically map the available literature on progression in well-differentiated papillary mesothelial tumours (WDPMT), particularly given the rarity of the condition and the evolving diagnostic terminology. The framework encompasses the identification of a research question, systematic identification of relevant studies, selection of studies based on eligibility criteria, data charting, and collation and synthesis of results. This methodology supports a broad exploration of emerging evidence and thematic trends without requiring assessment of the strength of evidence or meta-analysis, which are not typically appropriate in rare and heterogeneously reported entities.

2.6. Data extraction and synthesis

Data extraction was performed using a structured template to capture relevant variables such as patient demographics, tumour site, BAP1 and MTAP status, asbestos exposure, multifocality, treatments, and time to progression. Thematic analysis was conducted using Braun and Clarke's six-phase framework [35]. This process enabled the identification and organisation of patterns and themes relevant to factors associated with progression in WDPMT.

3. Results

3.1. Characteristics of included studies

The comprehensive database search initially yielded 764 articles (Fig. 1). After deduplication, the remaining articles ($n = 303$) underwent rigorous title and abstract screening to determine their suitability for inclusion. Of these, 284 studies failed to meet the inclusion criteria and were subsequently excluded. The remaining studies ($n = 19$) were subjected to full-text analysis, excluding 9 articles due to inclusion criteria non-conformity. Ultimately, 10 articles were deemed eligible for inclusion. (Table 1)

The included studies were conducted across a diverse array of locations, encompassing the United States ($n = 4$), Italy ($n = 1$), United

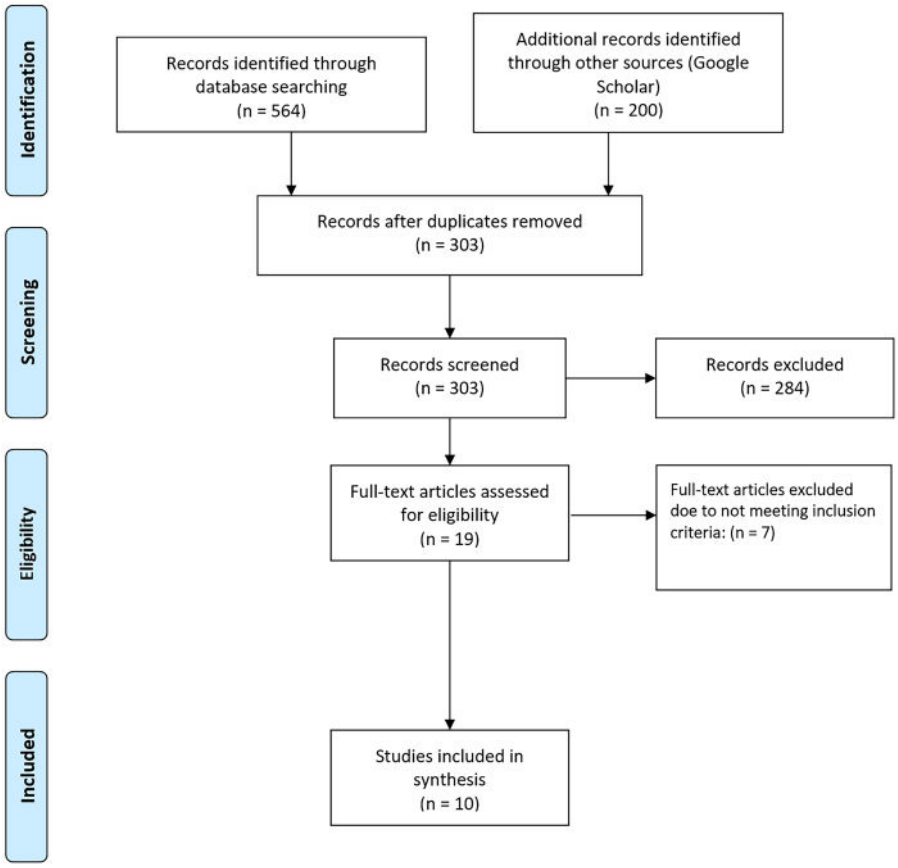

Fig. 1. Flow chart of selection of articles.

Kingdom ($n = 1$), Australia ($n = 1$), Japan ($n = 1$), China ($n = 1$) and France ($n = 1$). Study designs and formats utilised included case reports (3) and case series (7) (Table 1).

There were a toral of 148 cases of WDPMT reported across all studies, 14 of which progressed. Of 10 studies, 7 included more than one WDPMT and 3 described single cases of WDPMT. Overall, 14 of 148 WDPMT reported in the 10 articles progressed to diffuse mesothelioma (Fig. 2). Of 14, six were peritoneal WDPMT, 4 pleural, 2 testicular, 1 of unknown origin and 1 had both pleural and peritoneal origins. (Supplementary Table 3)

Progression ranged from 1.1 to 15 years (13 months to 180 months), with 8 of 14 cases progressing after >5 years. Three of 6 peritoneal and both testicular WDPMT progressed within 5 years of diagnosis, and the majority of pleural WDPMT (3 of 4), WDPMT of dual origin (pleural and peritoneal) as well one WDPMT of unknown origin progressed after 5 years. (Supplementary Table 3)

3.2. Methodological quality

The 10 studies selected were included as they fulfilled the current definitions of WDPMT. These studies had high scores on the critical appraisal checklists and demonstrated sound research design, rigorous methodology, effective recruitment strategies, and appropriate data collection methods aligned with the stated aims and research issues. Furthermore, data analysis exhibited rigorousness, and findings were clearly presented, culminating in perceived research value. Of the 10 studies, 5 were considered as case reports and 5 as case series. Three studies among 5 case series received a score of 9/10 and 2 received a score of 8/10. Of 5 case reports, 3 received a score of 7/8 and 2 received a score of 5/8. (Supplementary Table 2) Overall, minimal methodological deficiencies were identified across the 10 studies. The shortcomings included a lack of documentation on clarity of case description including treatments and adverse events.

3.3. Study findings

A total of 148 WDPMT were reported in the 10 studies. Progression to diffuse mesothelioma was described in 14 (9 %). Of these 14, the median age for all pleural cases at diagnosis was 75.7 years (range 72–79), 58.5 years (range 38–72) for peritoneal, 40.5 years (range 32–29) for testicular WDPMT and 58.8 years (range 32–79) for all cases that progressed. Two of four pleural WDPMT were older at 72 and 79 years and the 2 WDPMT of the tunica vaginalis were younger, aged 32 and 49 years. (Supplementary Table 3) Asbestos exposure was reported in 28 of 70 cases of WDPMT where data was available. Of the WDPMT that progressed to diffuse mesothelioma, 6 (43 %) had a history of asbestos exposure, 3 had no exposure and exposure history in the remaining 5 was unavailable. Of the WDPMT that progressed, 7 were symptomatic (6 peritoneal, 1 pleural) at diagnosis, 2 were incidentally found and data was unavailable in another 5, whereas symptoms were present across 43 of 124 of all cases where data was available. The median ages of patients with WDPM who progressed at each site were consistent with the median ages at presentation reported in the WHO guidelines for each respective site. Nearly 36 % of cases that progressed had missing data on history of asbestos exposure and mode of presentation. Since these data have the potential to skew results that do or do not favour progression or influence progression of WDPMT, we are unable to confirm that they are factors that predict prognosis of WDPMT. (Supplementary Table 3)

3.4. Themes of study findings

Across the included articles, three themes were identified, directly addressing the review's objective.

Table 1
Data extraction table of selected articles.

Authors	Year, Country	Sample Size	Site of WDPMT	Asbestos exposure	BAP1 IHC results	WDPMT Histology	Progression to Mesothelioma	Timeframe for Progression	Treatment	Outcome
Butnor et al.	2019, USA	2 WDPMT	Tunica vaginalis testis	Asbestos exposure in 2 WDPMT	Not specifically reported for WDPMT in this article	Single layer of cytologically bland cuboidal mesothelial cells lining fibrovascular to myxoid-appearing cores, lack of stromal invasion.1 had focal psammomatous calcifications	Yes, in one patient	2 years for the noted progression case	Specific treatment details not provided; general mention of need for long-term follow-up.	Progressed to invasive peritoneal mesothelioma after 2 years
Costanzo et al.	2014, Italy	1 WDPMT	Pleura	Asbestos exposure history present	Not performed	Fibrovascular papillary formations lined by epithelioid cells, lack of stromal invasion, cytological atypia and mitoses	Yes	13 years	Chemotherapy, radiotherapy, talc pleurodesis	Progression to mesothelioma in mediastinal lymph nodes
Hejmadi et al.	2003, UK	1 WDPMT	Peritoneum	Not specified	Not performed	Papillary fronds covered by a single layer of benign-appearing mesothelial cells	Yes	9 years	Peritoneal shunt for ascites & laparotomy	Progression to epithelioid mesothelioma, died after 1 week of surgery
Kelly Butnor et al.	2001, USA	14 WDPMT	7 Pleura, 6 Peritoneum, 1 Tunica vaginalis	12 had a known source of asbestos exposure	Not performed	Thin fibrovascular cores covered by single layer of uniform cuboidal mesothelial cells with, mild atypia, 2 had focal stromal invasion	Yes, in one patient with peritoneal WDPMT	3 years	4 had no adjuvant therapy, 3 had chemotherapy postoperatively	Mixed outcomes, 1 progressed to mesothelioma despite chemotherapy
Lee et al.	2018, USA	8 WDPMT	1 Pleura, 5 Peritoneum, 1 both site, 1 Tunica vaginalis	WDPMT with no asbestos exposure	1 with BAP1 loss	WDPMT features with mild stratification of cells lining papillae	Yes, in 1 patient with peritoneal WDPMT	9 years	One with progression had chemotherapy	Alive at 138 months
Hassan et al.	2024, Australia	21 WDPMT	20 Peritoneum, 1 Pleura	6 had known asbestos exposure	BAP1 loss in 9 cases	Papillary structures, no stromal invasion	Yes, in 4 patients (3 peritoneal, 1 pleural)	2–6 years	Various, including debulking, HIPEC, immunotherapy	4 with BAP1 IHC loss progressed to mesothelioma
Galateau-Sallé et al.	2004, France	24 WDPMT	Pleura	11 had asbestos exposure	Not performed	Papillary structures with myxoid cores, no deep invasion; bland, epithelioid cells	Yes, in 2 patients	10 years	Various, including chemotherapy, immunotherapy, pleurodesis &surgery	2 progressed to invasive mesothelioma and died
Sun et al.	2019, China	74 WDPMT	70 abdomen & Peritoneum, 3 Pleura, 1 tunica vaginalis	1 had asbestos exposure	Not specified	Papillary structures with single layer of bland mesothelial cells; 6 cases with microinvasion	Yes, in 1 patient	15 years	Only surgery mentioned	One case progressed to mesothelioma; others had no progression
Toriyama et al.	2021, Japan	1 WDPMT	Pleura, & Peritoneum	No asbestos exposure	Not specified	Initial ovarian specimen showed papillary structure with mesothelial markers	Yes	8 years	Only surgery mentioned	Progression to mesothelioma

(*continued on next page*)

Table 1 (*continued*)

Authors	Year, Country	Sample Size	Site of WDPMT	Asbestos exposure	BAP1 IHC results	WDPMT Histology	Progression to Mesothelioma	Timeframe for Progression	Treatment	Outcome
Zafar et al.	2022, USA	2 WDPMT	Paratesticular	Not specified	BAP1 IHC retained	Papillary structures with broad branching; no invasion in WDPMT	Yes, in 1 of 2 patients	2 years	Radical orchiectomy	One WDPMT progressed to biphasic mesothelioma, alive at 66 months

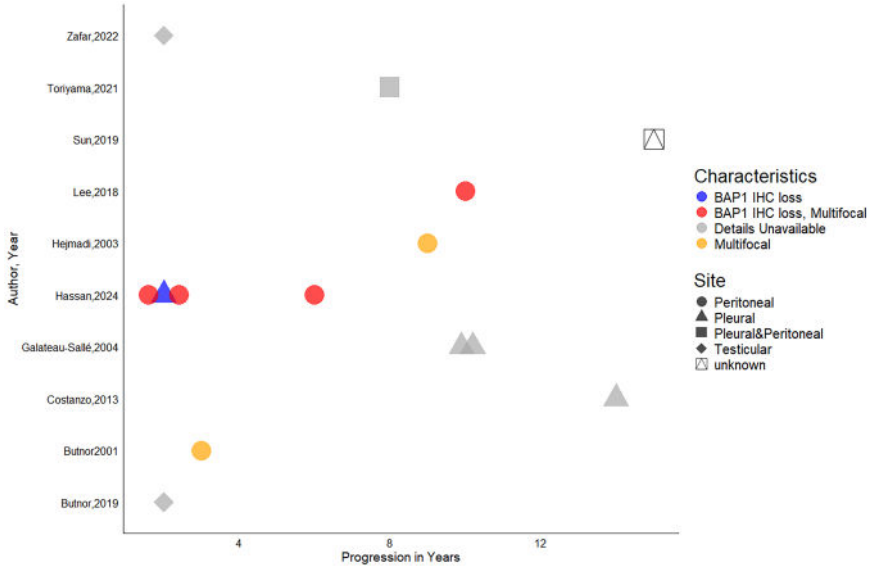

Fig. 2. WDPMT with progression.

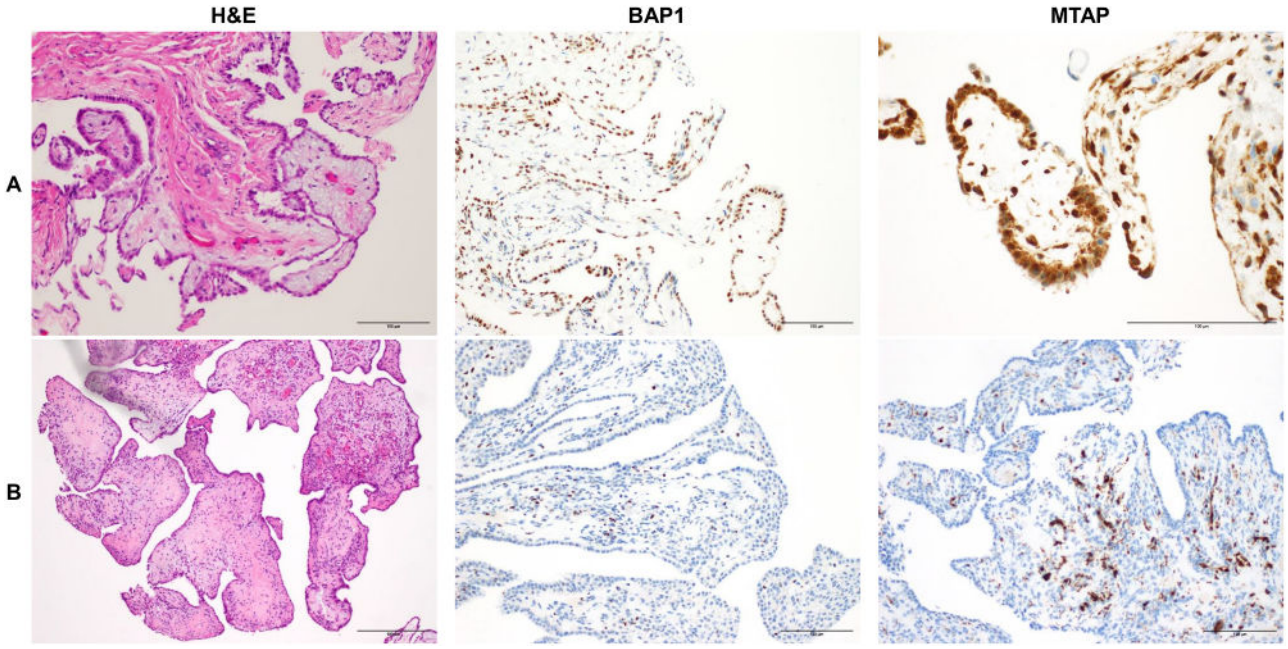

Fig. 3. Examples of papillary mesothelial lesions highlighting the diagnostic problem. 3A. Well-differentiated papillary mesothelial tumour (WDPMT) of the peritoneum. This lesion was an incidental finding during surgery performed for other reasons. The image shows a papillary mesothelial proliferation consisting of thin to broad-based papillae lined by a single layer of flattened to cuboidal mesothelial cells with bland nuclei and no stromal invasion on H&E stain. BAP1 and MTAP are retained on IHC (brown staining). H&E and BAP1 at 20x magnification, MTAP at 40x magnification. Scale bars, 50 μm. 3B This lesion was the only finding during laparoscopy in a symptomatic patient. It represents papillary mesothelioma in situ of the peritoneum. The image shows broad papillary fronds lined by a single layer of relatively bland and attenuated mesothelial cells on H&E stain, indistinguishable by morphology in isolation from WDPMT. BAP1 and MTAP are lost on IHC (loss of brown nuclear and cytoplasmic labelling in lesional cells). Scale bars, 50 μm.

3.4.1. BAP1 loss

BAP1 IHC was performed in 31 of 148 WDPMT among the 10 studies that reported on WDPMT that progressed to diffuse mesothelioma. Of the 14 WDPMT that progressed, BAP1 IHC studies were performed in 7 with BAP1 loss on IHC noted in 5 of these 7 lesions. (Supplementary Table 3 and Fig. 2). Four of the 5 were in female individuals with peritoneal WDPMT, 3 of whom also had a history of asbestos exposure (Supplementary Table 3) [36], none of the cases with intact BAP1 expression progressed [37]. BAP1 immunohistochemical analysis was not conducted before 2015. Hence data is not uniformly available in the studies. Examples of WDPMT and papillary mesothelioma in situ that are not distinguishable by morphology alone are shown in Fig. 3.

3.4.2. Multifocality

Details of focality of lesions were available in 6 studies of the 10 we analysed [4,6,20,36–38] (Supplementary Table 3). Multifocality was reported in 48 of 117 WDPMT reported in studies analysed in this scoping review where data was available. Six of eight peritoneal WDPMT among the 14 WDPMT that progressed were multifocal, representing 75 % of all peritoneal WDPMT that progressed. All 6 multifocal peritoneal WDPMT were female with a median age of 58.5 years at diagnosis.

4. Discussion

In this review, we focussed on identifying criteria that may be clinically useful to predict progression of WDPMT to mesothelioma, based on published cases. Loss of BAP1 on IHC, and multifocality were common in WDPMT that progressed. From this scoping review, the role of BAP1 loss in tumour evolution suggest it plays an important role in WDPMT progression to mesothelioma.

The peritoneal WDPMT described by Butnor et al. was a multifocal tumour and the patient died of progressive disease after 3 years [4]. Additionally, of 4 WDPMT that progressed to mesothelioma, Hassan et al. reported on 3 that were multifocal tumours [36]. Although the exact role of multifocality in WDPMT is currently not known, presence of this feature in WDPMT that have shown progression (particularly in the peritoneum) is concerning and suggests the need for regular follow-up.

Failure to surgically remove all visible disease may be one of the causes of progression to mesothelioma. Details on cytoreduction and residual disease were mentioned for 2 cases among the 19 analysed in this scoping review. Malignant transformation in one peritoneal WDPMT case each were described by Baratti et al. and Deraco et al. [39,40] Incomplete cytoreduction reportedly resulted in infiltrative disease 67 months and 13 months from diagnosis respectively. Incomplete cytoreduction can result from a high tumour burden within the peritoneal cavity and is measured by the peritoneal cancer index (PCI) [41]. Also, WDPMT can sometimes have highly invasive biological behaviour which can contribute to incomplete cytoreduction [39]. In a study by Gilani et al., 11 WDPMT and 28 multicystic peritoneal mesothelioma were labelled low-grade peritoneal mesothelioma. Four out of five of these tumours with incomplete cytoreduction died due to disease progression though the exact number of WDPMT among them is not mentioned in the manuscript. Individuals with complete cytoreduction however were alive at their next follow up [42]. Although information on completeness of surgery and residual disease is only infrequently mentioned in studies of WDPMT, incomplete cytoreduction may indicate a higher likelihood of WDPMT progressing to diffuse mesothelioma.

Since WDPMT is rare, and diagnostic criteria have changed, data on WDPMT that meet current diagnostic standards is very limited. Our scoping review has only included those publications that included WDPMT that progressed to diffuse mesothelioma. Incorporating case series and case reports into scoping reviews is essential for compiling evidence on outcomes in rare diseases, investigating potential risk factors, and capturing data on uncommon clinical events [43]. Case reports can foster clinical discussion, enhancing knowledge on rare tumours that could be applied in making treatment decisions. Narrative summaries of themes related to these reports consolidate the understanding of rare tumour behaviour [44]. Limitations imposed on case reports and case series due to the paucity of relevant studies and their retrospective nature may be offset by the potential for generating new knowledge on a topic where no prospective data is available [45].

Our scoping review examines the best available evidence on this complex area in a systematic fashion and provides rational guidance on management of contemporarily defined WDPMT [2] Our findings emphasise that WDPMT must be differentiated from diffuse mesothelioma. WDPMT with invasive foci previously included in case series tend to relapse (at least in the peritoneum) and in line with current diagnostic criteria should be classified as (early) diffuse mesothelioma [19]. Therefore, from the study by Lee et al., we included only case number 6 and omitted cases 7 and 8 (that had minute foci of invasion) [37].

The role of asbestos exposure as a cause of WDPMT or factor associated with BAP1 loss for progression is unclear. Asbestos exposure is reported in patients diagnosed with WDPMT [4,6,9,19,20,22,36,46,47], with one specifically mentioning retention of BAP1 on IHC [46]. In one study, 6 of 21 WDPMT had a history of asbestos exposure, 5 of these had BAP1 loss on IHC, and 3 progressed to mesothelioma [36]. Further studies may clarify the role of asbestos exposure, and molecular signatures may be useful in this context.

WDPMT and mesothelioma show significant molecular differences. More work is needed to tightly define them as some previous studies included ill-defined cases [48,49]. Progression of MIS defined by loss of BAP1 and/or MTAP on IHC or CDKN2A deletion by FISH has shown a median time to progression of 60 months (range 12–92 months) [27]. In this scoping review, cases of WDPMT that progressed to mesothelioma reveal a median of 84 months (range 19–180 months) that aligns with time to progression in MIS. MIS that morphologically resembles WDPMT is strongly linked to development of invasive mesothelioma [33] and this review provides the rationale to classify WDPMT with BAP1 loss as MIS with papillary features. Therefore, WDPMT cases progressing to diffuse mesothelioma reported prior to availability of BAP1 and MTAP IHC may represent papillary MIS [4,6,20] . Molecular studies may consolidate a molecular profile and elucidate the relationship between genetic and environmental factors and predict clinical behaviour. Given the rarity of these lesions, multinational registries and dedicated biobanks may be needed. Such studies will inform treatment options and avoid unnecessary aggressive treatment [19].

5. Conclusion

This scoping review has reviewed the best available evidence for factors that predict progression of WDPMT to diffuse mesothelioma and provided rationale for classification of WDPMT with BAP1 and MTAP loss as MIS. We suggest that BAP1 and MTAP IHC is mandatory for WDPMT diagnosis.

Ethics approval

This work was approved by the Central Local Health Network Clinical Human Research Ethics Committee (approval number R20190415).

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SK prepares medicolegal reports on diagnosis of asbestos-related conditions. All other authors declare there are no other conflicts of interest to disclose. This work was supported by the Professor Douglas Henderson AO bequest fund administered by Flinders University.

CRediT authorship contribution statement

Sarita Prabhakaran: Writing – original draft, Methodology,

Investigation, Formal analysis, Data curation. **Harry James Gaffney:** Methodology, Formal analysis, Data curation. **Yazad Irani:** Writing – review & editing, Methodology. **Ashleigh J. Hocking:** Writing – review & editing, Data curation. **David Roder:** Writing – review & editing, Supervision. **Sonja Klebe:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

Professor Sonja Klebe reports a relationship with Medicolegal reports to the courts in Australia that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2026.101137.

Data availability

Access to identifiable data is subject to ethics approval.

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