

Review

## The Significance of Peritoneal Washing as a Prognostic Indicator for Ovarian Cancer Patients

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**Abstract.** *Background/Aim:* During ovarian cancer (OC) debulking surgery, the surgeon can examine the peritoneal cavity for malignant cancer cells with peritoneal washing (PW) cytology. The goal of this study was to examine the significance of peritoneal washing as a prognostic indicator for ovarian cancer patients. *Patients and Methods:* Information considering the prognostic factors of OC and their impact in PW's result was collected, compared, and combined. *Results:* Omental metastasis, tumor type, tumor invasion, tumor size, tumor grade/ stage, tumor's cytoreduction, and recurrence affect both the peritoneal washing result and the patient's

*prognosis. The correlation that most of the above factors have with a positive PW and dismal prognosis, led us to the assumption that PW has a significance as a prognostic indicator. Conclusion:* The significance of PW as a prognostic indicator remains an assumption.

Ovarian cancer (OC) is considered one of the most common tumor malignancies, affecting approximately 200,000 women each year (1-4). As less than 50% of the patients appear to reach a 5-year survival, it is considered as the eighth most frequent cause of death among cancer patients and the leading cause of death among gynecological cancers (2-3, 5-8).

Actually, due to the absence of primary symptoms and the lack of proper and efficient screening procedures, ovarian cancer is usually diagnosed in advance stages (III-IV), contributing to cancer fatality (9-12). The most common histological type is serous carcinoma, which appears in approximately 1/3 of the cases (1, 13).

The standard treatment for advanced ovarian cancer patients is primary debulking surgery (PDS), followed by platinum – based chemotherapy (9, 10, 14, 15). If an optimal cytoreduction is not feasible with this procedure, neo-adjuvant chemotherapy, followed by interval debulking surgery (IDS) is preferred (9-10, 14, 16-18). The latter may provoke less surgical complications, but both are considered similarly effective regarding survival (19-23).

Peritoneal washing (PW) has been included in gynecological cancer surgical procedures, as an easy, simple,

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cheap, and safe technique (24-26). This technique consists of the installation of fluid in the peritoneal cavity, followed by its extraction and cytological examination (27). The aim is to detect malignant cells found in the peritoneum indicating a possible metastasis of an ovarian tumor and/or an incomplete cytoreduction (1-2, 5, 27-30). Thus, PW can provide valuable information and is considered to have a prognostic value (1, 25-26, 31). When PW appears positive, it can upstage a T1a/T1b and a T2a/T2b cancer to a T1c and T2c, respectively (25).

Therefore, it is included in the FIGO staging and the TNM system, in cases of early-stage ovarian neoplasms (25, 30, 32).

## Patients and Methods

The main goal of our review was to study and analyze PW's utility in the gynecologic cancer surgeries and consider its prognostic impact on patient survival. We collected information about the main factors that influence the technique's results and the principal parameters that affect patient outcome.

For preparing this review, we collected information from published articles in the PubMed platform. Our main purpose was to prioritize studies published during the last decade to reassure their credibility. However, studies from former decades were not excluded from our study to expand the information evaluated.

## Results

**Omental metastasis.** Positive peritoneal cytology strongly relates with omental metastasis. Usually, positive results indicate the peritoneal spread of the tumor. In Naz's *et al.* study, out of the 35 positive PW cases, 31 represented omental metastasis and out of the 25 negative cases, only 2 revealed neoplastic histology. They concluded that the correlation between peritoneal washing and peritoneal metastasis was statistically significant, suggesting the sensitivity and specificity of peritoneal washing cytology (PWC) (1). As Nour Sneige *et al.* stated, PW appears to be an effective indicator of omental metastasis even in tumors with low malignant potential, with a sensitivity of 69% (29). In a different study, 99.7% of patients with positive PW showed a malignancy or neoplasm (30).

Likewise, in Zuna's study, 86.6% of positive PW was correspondent with peritoneal histology (33). In the same study, 6.8% of the negative cytological results were histologically positive, whereas 1.1% of the positive ones were histologically negative. OC directly spreads in the peritoneal cavity and assisted by the peritoneal circulation results in tumor implantation (34). Peritoneal metastasis is correlated with a worse prognosis, since it increases the possibility of tumor recurrence and mortality (33, 34).

Sehouli *et al.* claimed that patients with metastasis in the upper abdomen had a shorter median survival (56 months) than those with metastasis in the lower abdomen (61 months).

Furthermore, upper abdominal metastasis was significantly related with a higher possibility of lymph node involvement, which in turn indicates a shorter survival (26, 35).

**Tumor type.** The histological type of the ovarian tumor corresponds with PW findings and affects the sensitivity of the method (1, 36). As mentioned before, the serous subtype is the most common, thus it is logically expected to be found more frequently than other types in PW cytology (1, 13).

Hou *et al.* provided additional evidence in support of this hypothesis. In their study, 47.3% of positive PW was associated with high grade serous carcinomas, 27.3% with ovarian serous borderline tumors, 8% with clear cell carcinomas, 4% with low grade serous carcinomas and 3.3% with endometrioid cancers (30). Similarly, other studies have found that 29%-38% of the positive PW results were associated with serous neoplasms (29, 33, 37, 38). Additionally, the histological subtype of OC may correlate with the detection rate in PW cytology (Table I). In Naz's *et al.* study, 100% of clear cell carcinomas, 76.9% of serous carcinomas, 66% of Mullerian tumors, 50% of germ cell tumors, 44% of endometrioid and 25% of mucinous carcinomas presented a positive PW result (1). Similar results were also presented by Iura *et al.* who noticed that all clear cell carcinomas appeared with a positive result (28).

However, Giordano *et al.*, mentioned that 95.4% serous and 25% clear cell cancers showed neoplastic elements on PW (27). Therefore, no certain conclusion can be reached regarding the detection rate. Simultaneously, one of the main prognostic factors for OC development is the histological type of the tumor (2, 29, 39). It is actually described as an independent indicator of overall survival (OS) (28).

In Iura's *et al.* study, among patients with positive PW, the median OS of those with serous carcinomas was longer (36.5 months) compared to the non-serous types (19.3 months). The serous tumors were correlated with a significantly better prognosis compared to the clear cell carcinomas (28). All clear cell carcinomas presented a positive PW and showed a dismal prognosis. The poor prognosis of clear cell tumors was confirmed in other studies (40-42).

**Capsular invasion.** Besides the relation between positive PW and omental metastasis, many studies have also showed a significantly positive correlation between positive PW and capsular invasion (1, 43). Giordano *et al.*, noticed that the majority of the serous neoplasms with positive elements on PW revealed histological involvement of the ovarian surface. They also drew attention to one case, which did not seem to have any capsular invasion initially, but a positive PW was found. After the reexamination, an invasive cancer diagnosed. This diagnosis was due to PW, underlining its importance. Additionally, the same study stated that negative

Table I. Correlation between ovarian cancer prognostic factors and positive peritoneal washing cytology (PW).

Prognostic factors	Positive PW	Dismal prognosis	Possible significance of PW as a prognostic indicator
Omental metastasis	Related	Related	Related
Tumor invasion	Related	Related	Related
High tumor grade/stage	Related	Related	Related
Incomplete cytoreduction	Related	Related	Related
Tumor recurrence	Related	Related	Related

Tumor type and tumor size were not included in the table since their relationship with PW and prognosis was not clear.

PW results implied no involvement of the ovarian surface by the tumor (27).

Conclusively, the correspondence of PW with tumor invasion indicates its usefulness in the management of ovarian cancers (1). The differentiation of the ovarian cancer into invasive and non-invasive tumors seems to be of great prognostic significance (39). Invasive primary tumors tend to provoke a poorer prognosis compared to the non-invasive ones (44).

Sneige *et al.* declared that patients with invasive tumors had a significantly higher risk of disease recurrence and mortality. In their study, all disease relapses derived from invasive cancers (29).

Another study showed that not only stage I borderline tumors presented with a high 5-year survival rate (95%-97%), but also stage II and III, which appeared with a survival rate of 65%-87%, proving the great outcome of non-invasive tumors. Similarly, another study highlighted that most borderline tumors reveal great survival outcomes (45). Jeffrey *et al.* also stated that non-invasive tumors have a more benign character. Among patients with advanced stage tumors, non-invasive cancers were correlated with 95.3% survival rate, whereas invasive carcinomas with 66% (39).

**Tumor size.** Many publications claim the relationship between PW findings and tumor size. Naz *et al.*, showed that tumors of smaller sizes appear significantly more frequent with positive peritoneal specimens. More precisely, the majority (84%) of positive PW results derived from a tumor sizing below 10 cm. Oppositely, most tumors above 20 cm revealed negative PW and no peritoneal metastasis and no capsular invasion. For example, the mucinous carcinomas who develop in large sizes and respect ovarian boundaries, result in negative PW (1).

**Tumor grade – Tumor stage.** A different parameter, possibly affecting PW, is the tumor grade. Naz *et al.* reported that the higher the grade of tumors were, the more frequent they appeared with a positive PW result (1). However, this correlation was not statistically significant. In the contrary, Ozkara showed the above relation as significant (36). While

Zuna *et al.*, revealed that 29.4% of stage I patients, 66.7% of stage II patients, 89.6% of stage III patients and 92% of stage IV patients had positive PW (33). Thus, we can hypothesize that the higher the stage of the disease is, the higher the possibility of detecting malignant peritoneal elements is.

Tumor stage is also proved to be a significantly important prognostic factor influencing patient survival (2, 40). Sehouli *et al.* showed that 72% of patients with FIGO stage I and II had a 5-year survival, whereas only 33% of patients with stage III and IV had the same survival rate (35).

A different study revealed that 17%-36% of patients with advanced ovarian cancer had a 5-year survival, confirming the previous results (46). Furthermore, Wang *et al.* showed that stage IIIc patients had a significantly prolonged OS (43.8 months), compared to stage IV patients (23.5 months) (14). However, Iura *et al.* noticed a non-significant difference in median OS between stage III (16.5 months) and stage IV (21 months) patients (28).

**Complete cytoreduction/recurrence.** An additional factor, related to positive PWC, refers to the residual cancer cells after debulking surgery. Many studies claim that a positive cytological result indicates an incomplete cytoreduction (5, 9). Nagasaka *et al.*, revealed that 82% of patients with negative PWC accomplished complete cytoreduction, in contrast to the 41% of the positive ones. Thus, they showed a significant correlation between PWC and residual disease. Even where the complete removal of the tumor was awaited, a positive cytological result suggested that microscopically tumor cells had remained in the peritoneum (9). Another research underlined that positive PW results were associated with a residual disease of over 2 cm (28). Incomplete cytoreduction has an undeniable negative impact on patient prognosis (2, 40). However, the achievement of an optimal cytoreduction has been associated with a better survival (14, 43). A metanalysis, studying 6885 patients with advanced ovarian cancer who were treated with chemotherapy after debulking surgery, observed that median overall survival was extended by 5.5% for every 10% increase in the removable tumor (47).

Sehouli *et al.* mentioned that among their patients with no residual tumor, 59% had a 5-year survival, whereas the same

survival rate was achieved in 25% of patients with a residual disease of less than 2 cm and in 9% of those with a residual tumor larger than 2 cm (35). Similarly, another study indicated that patients with a residual tumor <2 cm had a worse 5-year survival rate than those without residual disease (RD) (21). In addition, Nagasaka *et al.* suggested that patients with a complete tumor removal appeared to have a significantly better overall survival (OS) and progression-free survival (PFS), compared to those with an incomplete cytoreduction (9). However, the same study mentioned no significant correlation between OS, PFS and the amount of the residual disease. However, Wang *et al.* noticed that patients with RD=0, 0<RD<1 cm and RD≥1 cm revealed a significant difference in both OS and PFS (14).

Iura *et al.* revealed that patients with a residual disease of less than 1 cm, compared to those with a residual disease of over 1 cm, had an OS of 28.5 and 17 months respectively, proving that a debulking surgery with a RD <1.0 cm is statistically significantly related to an improved OS. However, no significant difference was observed when comparing patients with no residual disease with those with a remaining tumor of less than 1 cm (OS=27 months for RD=0 patients, OS=20 months for RD<1 cm patients), proving that patients with a small residual disease had a similar outcome with those with complete cytoreduction (28). In addition, PW is also correlated with tumor recurrence. As Germana *et al.*, Sneige *et al.* and Douligieris *et al.* have mentioned that positive PWC is related to a higher risk of relapse (2, 29, 48). In Kojima's study, 59.09% of the patients had positive PWC and 63.9% of the patients showed a relapse, confirming the above conclusion. In addition, another study highlighted that even in stage I patients without omental metastasis, a positive cytology result was associated with an increased possibility of recurrence (1). Similarly, Nagasaka *et al.* presented that in cases with complete cytoreduction, a positive PW cytology was linked to a disease relapse (9).

*OS/PFS.* Finally, it is worth mentioning that PW tends to have a direct association with OS and PFS. Nagasaka *et al.* showed a significant correlation between both OS and PFS with positive and negative PW, respectively. To be more specific, negative cases, even those with T3c disease, had generally good prognosis (9). Likewise, Douligieris *et al.* cited that OS and PFS were double in the negative cases. However, they could not prove this relationship as statistically significant for OS (2).

In Kojima's study, the median OS and PFS for PWC positive patients was 32 and 18 months, respectively, whereas for the negative cases was 31 and 29 months, respectively. Therefore, they noticed a significant relation only between PFS and PW (5). In Iura's study, the median OS and PFS in PW positive cases was 18 and 13, while in negative PW cases was 47 and 17, respectively. Both OS and

PFS were significantly correlated with PW (28). Additionally, Binesh *et al.* showed that negative PW was associated with prolonged OS in patients (with no statistically significant evidence), as 19.3% of the negative and only 9.01% of the positive cases reached a 5-year survival (24). Further studies have also suggested that positive cytology may relate to poorer OS, while others showcased a significant correlation between PW and PFS (9, 28, 49). Last but not least, Karsten *et al.* presented that 65% and 9.2% of patients with negative and positive cytology, respectively, had a 5-year survival.

## Discussion

Positive PW usually reflects omental metastasis. However, Hou *et al.* reported that approximately 23%-52% of patients with biopsy proven peritoneal metastasis appear with false negative cytology results, whereas false positive results reach up to 4.5% (30). Due to inadequate sampling during PW, errors at the preparation or the procedure of PW and sometimes even the similarity between benign and malignant lesions, peritoneal involvement may be unnoticed at PW. Additionally, reactive mesothelial cells, endometriosis, endosalpingiosis and psammoma bodies may create false positive results in PW (50, 51). Therefore, we acknowledged that false positive PW results remain the minority of PW cases. We assume that positive PW strongly correlates with omental metastasis, which indicates a poorer prognosis. Thus, we can suggest that positive PW, omental metastasis, and survival rate are linked. However, since the possibility of a negative PW result is not negligible, we should always take into consideration that a negative PW result does not necessarily exclude metastasis. Therefore, the procedure of PW should be properly organized and carefully accomplished, while additional examination for peritoneum metastasis would be beneficial.

As stated above, tumor type may relate with both PW and prognosis. Clear cell carcinomas usually present as large lesions, localized in the ovary and compressing the surrounding organs (52). Thus, clear cell carcinomas may delay spreading in the peritoneum and provide a positive PW, explaining why some studies have found clear cell tumors with a low detection rate (27).

However, since approximately 70-75% of OC cases are discovered in advanced stages (11-12, 39, 53), we assume there is a higher possibility for omental metastasis occurrence. This, combined with clear cell tumor's resistance to chemotherapy that may be responsible for a residual disease, provide positive PW results in the favorable detection rate of 100% and indicate the aggressiveness of clear cell carcinomas. Contrastingly, serous carcinomas metastasize earlier, resulting in an increased possibility of a positive PW result, but still have a prognosis better than the other tumor types (1, 28, 52, 54). Therefore, the relation between histological tumor type,



PW and cancer prognosis is not clear and additional studies are needed to prove PW's significance.

Invasive carcinomas are correlated with worse prognosis than non-invasive ones. This is most probably due to the more aggressive character that invasive tumors are expected to have. Therefore, they metastasize more frequently and thus, have a higher tendency to appear positive in PWC. Additionally, non-invasive cancers are more likely to be discovered in an earlier stage. A study revealed that 75% of borderline tumors presented with FIGO stage I at diagnosis, whereas only 20% of invasive cancers were at the same stage. Most of the invasive tumors (60%) had reached stage III at the time of diagnosis (55).

The advanced stage during the diagnosis of invasive cancers, enhances their correlation with a positive PW and dismal prognosis. We assumed there is a relation connecting invasive tumors, with positive PW and hence a poorer prognosis.

According to the information given above, tumor stage is considered to be related with the cancer's forecast. It is also worth mentioning that more advanced stages appear with a higher detection rate in PW, as they give noticeable metastasis more frequently. Thus, tumor stage may be associated with PW and prognosis. However, PW appears to have a more powerful significance in prognosis than tumor staging. As Iura *et al.* declared, a positive, over a negative, PW result indicated a poorer prognosis, despite the stage of the tumor (28).

In agreement with this study, Zuna *et al.* noticed that among patients with stage I tumors, 82% of those with negative PW reached a 5-year survival, in contrast to the 20% of those with positive PW (33). We can thus suggest that even though stage can influence tumor prognosis, PW may constitute a stronger indicator.

As mentioned, residual disease indicates that microscopic cancer cells have remained in the peritoneum. This may be due to their chemo-resistant character. As a result, they have a higher chance of progressing and developing into a recurrent tumor (33, 56, 57). Thus, residual tumor is associated with a tumor recurrence and a poorer prognosis. Therefore, it is more preferable to aim for a complete cytoreduction, which should be the ultimate purpose (19, 35). Residual tumors and the possibility of a tumor recurrence are usually associated with a positive PW result, which indicates a poorer prognosis. Kojima *et al.* claimed that a positive PW, especially after chemotherapy treatment, means that part of the tumor had remained in the peritoneum, provoking recurrence, and affecting negatively patient outcome (5). Thus, we can assume that a positive PW reflects a residual disease and therefore increases the chance of recurrence and a dismal prognosis. However, despite an incomplete cytoreduction, a negative PW can increase the chances of survival (33). Therefore, a negative PW outcome is inferred to be a more determinant factor than complete cytoreduction, as it is more strongly correlated with a better prognosis.

We can assume PW's prognostic significance through its correlation with the factors mentioned above. Since most of these parameters seem to relate with a positive PW result and a more dismal prognosis, we suggest PW to be used as a prognostic factor. PW appears to have a direct relation to patient's survival. According to the results presented, a positive PW result is usually associated with reduced patient OS and PFS. This proves PW's significance as an independent prognostic factor. We hypothesize that the dismal prognosis of positive PW is most probably due to the existence of at least one of the above factors, which provoke a positive result and thus cause a negative outcome.

However, it is worth mentioning that when studying each parameter individually, their prognostic significance may be minor compared to that of PW. As described above, a positive PW result associates with a dismal prognosis, despite the existence of an early grade tumor or a complete cytoreduction. We suppose this may be possibly due to a different prognostic factor intervening with patient outcome. Therefore, PW is presented to be a stronger indicator of prognosis, than each of the above parameters independently.

## Conclusion

The outcome of patients with OC is determined by several factors that provoke a positive result in PW. i) Omental metastasis usually appears positive in PW and has a dismal outcome; ii) Serous carcinomas, as the most common ovarian tumor, appear more frequently in positive peritoneal results, than other histological tumor types. However, they usually have a good prognosis, in contrast to clear cell tumors, which usually have a bad outcome; iii) Invasive carcinomas tend to provoke a positive PW result and poorer prognosis; iv) Smaller tumors of less than 10 cm usually metastasize easier compared to the larger ones, and thus result in a positive PW; v) Higher grade and higher stage tumors, as more aggressive, tend to spread in the peritoneal cavity, resulting in positive PW and worse outcomes; vi) Incomplete cytoreduction, frequently appears positive in PW and increases the chance of tumor recurrence and diminished survival.

Through this correlation we concluded that PW can be used as an independent prognostic tool when examining and treating patients with OC. When comparing the prognostic value of PW to each parameter independently, PW appears to be a more determinant indicator. No absolute result can be conducted from this review and additional research is needed to prove the significance of PW.

## Conflicts of Interest

The Authors declare that there are no conflicts of interest in relation to this study.

## Authors' Contributions

K.A, F.Z, T.N, C.C and K.SE; Contributed to conception and design. K.NE; Were responsible for overall supervision. V.A, P.V, D.G and P.A; Drafted the manuscript, which was revised by K.K, S.S, C.C, A.S, A.C, D.G and K.NE. All Authors read and approved the final manuscript.

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