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Role of Post-Intraoperative Radiation Therapy Wound Fluids in Interaction with White Blood Cells on Cancer Cell Growth

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ABSTRACT

Background: Intraoperative radiation therapy (IORT), is a promising method which has been widely applied in breast cancer lumpectomy. Although its effect on destructing remaining cancer cells was approved, maintaining or draining post intraoperative radiation therapy wound fluids (PIWF) is challenging. Moreover, the roles of immune cells in interaction with PIWFs have not been studied before which is the main investigation of this paper.

Methods: Surgical wound fluids were collected from 24 IDC patients one day after lumpectomy. The patients were divided into control and IORT groups. The collected wound fluids were centrifuged for 20 minutes at 2000 rpm. The concentration of tumor-associated cytokines and inflammasomes were recorded using the immunoassays.

Results: PIWFs stimulate the residue of cancer cells in cavity sides causing disease progression. Here we have focused on the effect of PIWFs on the proactivation or deactivation of WBCs in the tumor bed environment. By sequential imaging in time-transient intervals from the interaction between WBCs and cancer cells, PIWFs have no additive proactivating effect on immune cells.

Conclusion: PIWFs have significant roles in proliferation of cancer cells but did not show an observable role in pro-activating immune cells against cancer cells. The functions of immune cells did not show any independent proactivation in the presence of PIWFs with respect to their activation in the presence of blood serum. It seems that draining the PIWFs may be required. In future research, we will use tumor samples of the patients instead of cell lines to better investigate the personalized immune-tumor interactions of patients.

INTRODUCTION

While Breast- lumpectomy followed by Intra-operative radiation therapy (IORT) has attracted much interest during the past decade[1], whether the post-IORT wound fluids (PIWFs) affect the growth of non-destructed residual tumor cells in the resection location raises some doubts, which requires much more in-depth investigation.

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Hence, the IORT secretion influences on lumpectomy location are a challenging subject. Many attempts have revealed that the post-surgical drainage would stimulate residual cancer cell growth.[2] Although many reports have confirmed the destructive effects of radiotherapy on malignant residues, modifying effects of IORT on the environment of cancerous mass and the probable development of the tumor is still unknown.[3] Moreover, some reports have indicated the post IORT radiation-induced bystander effect (RIBE) on neighboring non-exposed cells.[4,5] All of these reports have presented the release of some cytokines and chemokines, which play a role against[6,7] or in favor of tumorigenesis.[8] Some reports have discussed the effect of wound fluid released after lumpectomy followed by targeted IORT on non-cancerous and cancerous cells.[2] One crucial distinction between these studies is the time of WF collection. For example, it is revealed that PIWFs collection seven days after surgery showed smaller stimulating effects on cancer stem cells compared to non-IORT WFs collected after similar days.[9] On the other hand, PIWFs collected one day after the surgery induced invasive and proliferative effects on live tumor cells as derived from the same patients.[8]

A significant point not considered in those investigations is the role of immune cells released in the tumor bed, which interact with PIWFs. The effects of WF, serum, and PIWFs may stimulate or degrade the activities of immune cells of tumor bed ambient in favor or against tumor cells.

Previous reports have revealed the tumorigenic properties of fluids released from lumpectomied cavity which had undergone IORT.[8] We suggested that this effect might be caused by bystander secretion effect of the tumor bed cells.

Due to this evidence, in this study, we aimed to check the effect of PIWFs, WFs and serum of breast cancer patients undergoing BCS (in one group) and BCS + IORT (in another group) on the activity of their WBCs in interaction with MDA-MB-231 breast cancer cells. To the best of our knowledge, no previous study has focused on the independent role of immune cells in tumor bed ambient, after being interacted with PIWFs, in the destruction or growth of cancer cells.

METHODS

Sampling and collecting the fluid released from lumpectomy cavity

In this study, all patients underwent intraoperative radiation therapy (IORT) for the treatment of invasive ductal carcinoma. The classical criteria for IORT were observed in all patients, which included[10]:

- Age of 50 years or older
- Evidence of invasive ductal carcinoma
- Tumor size of 3.5cm or smaller
- No more than focal lymphovascular space invasion
- Positive for both estrogen receptor (ER) and progesterone receptor (PR)
- No evidence of multicentric disease
- No clinical or radiologic evidence of axillary nodal involvement
- No history of systemic neoadjuvant therapy
- No history of previous ipsilateral breast cancer or radiation
- No known BRCA or other high-risk mutation.

Additionally, in all cases, the margins were negative first in frozen and then in permanent sections. A drain was placed in the tumor bed during the operation, and the patient-specific whole-breast irradiation (PWIF) was extracted from the drain.

Surgical wound fluids were collected from the patients 24 hours after lumpectomy at the Khatam-al-Anbya Hospital in Tehran, Iran. The patients were divided into control and IORT groups. The IORT group patients were subjected to an IORT boost while the control group patients did not receive radiotherapy. The collected wound fluids were centrifuged for 20 minutes at 2000 rpm. The centrifuged wound fluids were sterile filtered and used for further analysis on monitoring the interactions of white blood cells and MDA-MB-231 cell lines.

PBMC and serum isolation

PBMCs were enriched from fresh heparinized blood tube stored for 15 minutes at 37°C. PBS dilution was done first, followed by layering over ficoll. (Cat number: F4375, Merck, Germany) (4:3) in a centrifuge tube. Centrifuging at 2000rpm for 20 minutes was then carried out. By this method, we achieved individual layers including diluted blood plasma, and PBMCs. This layer was gently removed and mixed with PBS (1:3) for another two rounds of centrifugation for 10 minutes at 2000 and 1500 rpm in order to remove any remaining platelets. Then, the PBMCs were diluted in 1cc of PBS and counted using Trypan blue staining in the Neubauer chamber.

In case of blood serum isolation, freshly drawn blood stored in gel tubes was centrifuged for 20 minutes at 2000 rpm. The serum was derived from the upper part of the gel tube after centrifugation.

Cytokine measurement by ELISA

We measured the levels of IL-6 (Cat number: D6050, R&D Systems, United States), TGF-β (Cat number: RK00055, R&D Systems, United States),

IFN-γ (Cat number: DIF50, using ELISA kit R&D Systems, United Stat). Also, VEGF (Cat number: RK00023, R&D Systems, United States) was measured using an enzyme-linked immunosorbent assay. The known concentrations of recombinant human IL-6, TGF-β, IFN-γ, and VEGF along with the experimental samples were co-cultured in polystyrene microtiter plates coated with an antibody against the appointed cytokine, and incubated with an enzyme-linked polyclonal antibody directed to the cytokine. Then, we added an enzyme reactive substrate solution which stopped the color development due to the addition of 2N H2SO4. The absorbed peaks were recorded using a microplate spectrophotometer. The expression amount (by the unit of picogram per CC) of IL-6, TGF-β, IFN-γ, and VEGF in each sample was measured through a standard curve generated in each assay. The reproducibility of all measurements was within 10% in our laboratory.

Cell culture

Triple negative breast cancer cell line MDA-MB-231 was purchased from the National Cell Bank of Pasteur Institute of Iran. MDA-MB-231 were incubated in Dulbecco's Modified Eagle's Medium (DMEM, Sigma) containing 10% fetal bovine serum (FBS, Gibco) and 1% penicillin/streptomycin (Pen Strep, Gibco). Cell lines were held in a conventional cell incubator (37°C, 5% CO2), and the medium was refreshed every two days. As for the interaction of WBCs and cancer cell lines, separated samples of WBCs were firstly interacted with three individual fluid ambients: (1) PIWFs, defined (wound fluids collected from the same patients after BCS plus IORT treatment), (2) WF, (wound fluids collected from the same patients after lumpectomy alone), and (3) blood serum collected from the same patients' peripheral blood after surgery. Overall, l5 patients were included in this experiment. After 6 hrs of interaction, the WBCs and their fluid ambient were interacted with cultured MDA-MB231 cells for 6 hrs. Their interaction was recorded by time laps imaging under the microscopy.

Ethics statement

The study was approved by the Research Ethics Committee of Cancer Research Center of Shahid Beheshti University of Medical Sciences, study number IR.SBMU.CRC.REC.1400.049.

Statistical methods and data analysis

The recorded results were analyzed by GraphPad Prism software version 8.3.0 (GraphPad Software, Inc. La Jolla, CA, USA), in which each data point is a representative of the mean value of three independent recordings.

RESULTS

Cancer cell behavior after incubation with PIWFs and WFs

This investigation was designed to analyze the effect of post-IORT WF collected from human samples on the activity of WBCs. As we recently found that PIWFs would activate the invasion of cancer cells that might be alive in tumor bed (due to many effects such as bystander)[8], it is important to know if the cancer-killing abilities of WBCs would be increased or decreased after interaction with PIWFs.

For better evaluation, we first analyzed the changes in the invasive activities of patients' WBCs (their invasion to MDA-MB-231 cancer cells) after incubation with three individual cohorts of fluids: (1) PIWFs, defined as wound fluids collected from the patients after BCS plus IORT treatment, (2) WF, defined as wound fluids collected from the patients after lumpectomy alone, and (3) blood serum collected from the patients' peripheral blood after surgery. Each cohort consisted of samples from 5 patients. Recently, it was reported that surgical PIWFs and WFs obtained one day after the surgery stimulated the wild behavior of cancer tumors in all assayed patients. A higher stimulation of the cancerous phenotype was observed after interactions with PIWFs compared to fluids harvested after BCS.[8]

Due to the mentioned achievements, here, we aim to investigate if WF collected one day after lumpectomy (early WF) would trigger the cancer-killing effects of WBCs. For the experiments, TN breast cancer (BC) cell lines with known histopathological evaluation named MDA-MB-231 were studied. After incubation of WBCs with the mentioned fluids (for about 6 hours), the WBCs and postoperative fluids were added to the cultured MDA-MB-231 cells, and the possible invasion of WBCs to cancer cells (such as inducing membrane blebbing and destroying cancer cells) in different groups of the medium associated with each patient was evaluated.

Induction of hyperactivated proliferation/invasion was observed in MDA-MB-231 cell lines after being incubated by the PIWFs of all patients recruited in this research. Also, the blood serum of the patients stimulated the cancer cell lines but not as severe as the stimulation by PIWFs (Figure 1-A and -C). The effect of WF in non-IORT patients was weaker than that of the blood serum in stimulating MDA-MB-231 cells (Figure 1-B and -D).

Considerable differences were observed among non-IORT treated WF groups, with various parameters associated with stimulatory effects on the

MDA-MB-231 cell lines, but it is worth noting that the stimulatory effect of PIWFs was significantly higher than that of WF on the cancer cells (29.7% ± 6.7). Moreover, with respect to control media (DMEM), PIWF showed stronger stimulating activities on the cells (Figure 1-C).

We profiled the four important tumor-associated cytokines in PIWFs, WFs, and blood serum of the lumpectomy cases who had been treated either by IORT or surgery without IORT. These cytokines are IL-6, TNF-α, TGF-β, and VEGF. The results showed increases in TGF-β and VEGF cytokines in both blood serum (Figure 1-E) and wound fluid (Figure 1-F) of IORT-treated patients compared to non-IORT-treated cases.

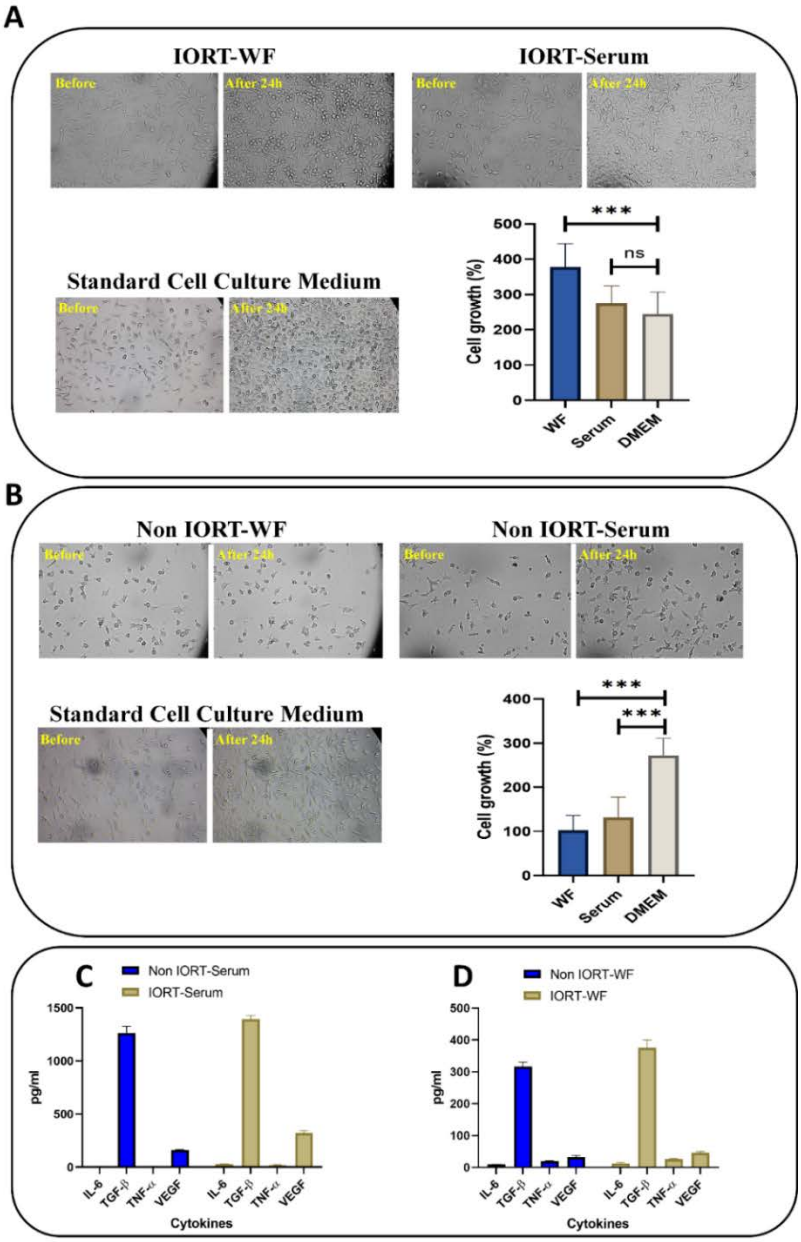

Figure 1. Analyzing the effect of post IORT wound fluid (PIWF) collected from patients on the activity of WBCs. A) IORT patients: PIWF induces hyperactivated proliferation and invasion in MDA-MB-231 cell lines being incubated. Hyperactivation was less severe for cells incubated by blood serum compared to cells incubated by PIW (MDA-MB-231 cell lines were incubated by standard cell culture medium as control cohort). B) Non-IORT patients: The proliferation rate of MDA-MB-231 cell lines showed that the effect of WF in non-IORT patients was weaker than that of the blood serum. C & D) four important tumor-associated cytokines (IL-6, TNF-α, TGF-β, and VEGF) in PIWFs, WFs, and blood serum of the lumpectomy cases who had been treated either by IORT or surgery without IORT. The results showed increases in TGF beta and VEGF cytokines in both (C) blood serum and (D) wound fluid of IORT-treated patients with respect to non-IORT-treated cases (ns $P > 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$).

WBCs activities against cancer cells after incubation with PIWFs and WFs

To clarify the effect of incubation with PIWFs and WFs on supporting or suppressing activities of WBCs, we incubated the WBCs derived from two cohorts of patients; first those who had undergone lumpectomy and second those who had undergone lumpectomy + IORT. WBCs of each patient were divided into separated groups. The first group interacted by DMEM for 6 hours, the second group by tumor bed secretion (PIWFs in the IORT cohort and WFs in the non-IORT cohort), and the third group by blood serum of the same cohorts. In the next step, we interacted each group of WBCs containing the same media with MDA-MB-231 cells and monitored the invasive behavior of WBCs against cancer cells by time-lapse imaging under microscopy. In this regard, six types of interactions had to be investigated, as shown below (Table 1).

Table 1. Six cohorts to investigate the effect of PIWF and WF on supporting or suppressing the activities of WBCs consisting of two groups of patients (lumpectomy & lumpectomy + IORT) in three different mediums (wound fluid, serum, and standard cell culture)

	Patients	
Medium	Lumpectomy	Lumpectomy + IORT
Wound Fluid (WF)	Cohort 1	Cohort 4
Serum	Cohort 2	Cohort 5
Standard Cell Culture	Cohort 3	Cohort 6

The results showed no meaningful independent pro-activation of WBCs which had been incubated in PIWFs in comparison with those incubated in blood serum and DMEM against cancer cells. Invasion of a WBC to a cancer cell (Figure 2-A) means the entrance of the immune cell's invadopodia to the cancer cells and transferring perforin and granzyme from WBC to these cells resulting in cancer cell apoptosis.[11]

In patients whose WBCs attacked MDA-MB-231 cells after they had been incubated in DMEM solution, their WBCs also attacked cancer cells in serum and PIWFs environment (Figure 2-B Top panel). On the other hand, WBCs that did not attack cancer cells in DMEM solution showed no attack on those cells in PIWFs (Figure 2-B bottom Panel). Hence, the attack pattern of WBCs on cancer cells in IORT treated patients is independent of the media in which the WBCs were incubated (Figure 3-A). A similar behavior was observed on WBCs extracted from the patients who did not undergo IORT (between DMEM, Serum, and WFs media) (Figure 3-B). Hence, the invasion of immune cells to cancer cells would not significantly be activated in PIWFs media. These results were recorded while the number of immune cells in blood samples (which we did investigation) was much more than that of immune cells in the tumor bed.

DISCUSSION

IORT is a new interesting method that is very helpful in increasing the survival rate of breast cancer. One recent concern raised about this method is maintaining or draining Post IORT wound fluids. Recent reports have revealed the tumorigenic properties of fluid drainages from the lumpectomy site of the patients who had undergone IORT. [8]

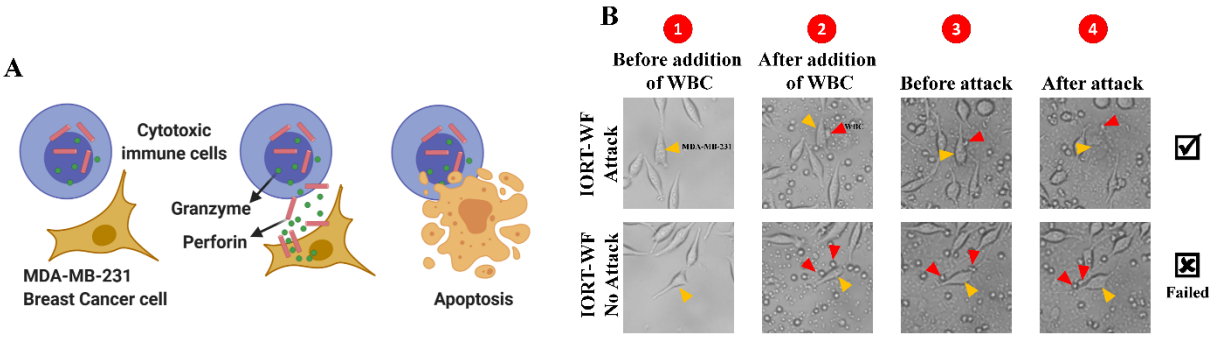

Figure 2.A) The invasion of a WBC to a cancer cell is considered as the entrance of the immune cell's invadopodia to cancer cells and transferring perforin and granzyme from WBC to the cancer cell, which would result in cancer cell apoptosis B) In patients whose WBCs attacked MDA-MB-231 cells after they had been incubated in DMEM solution, their WBCs showed the same attack in serum and PIWFs environment (Fig 2B Top panel). On the other hand, WBCs which did not show any attack on cancer cells in DMEM solution showed no attack on those cells in PIWFs (Fig 2B bottom Panel). As a result, the attack pattern of WBCs on cancer cells in IORT treated patients is independent of the media in which the WBCs were incubated

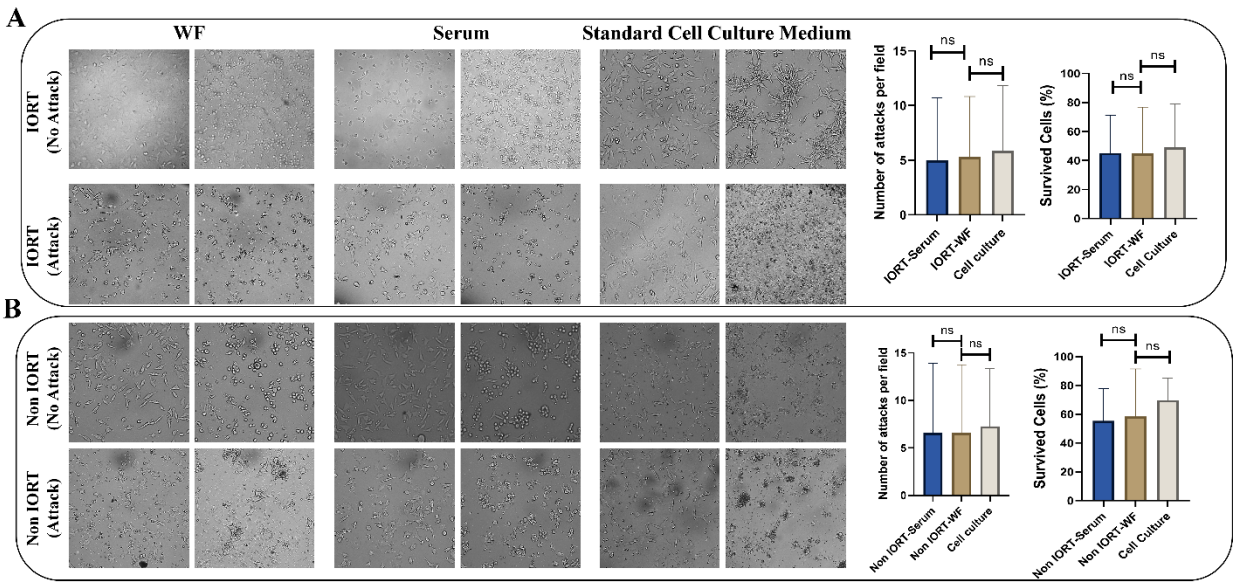

Figure 3. The effect of PIWF and WF on supporting or suppressing the activities of WBCs was investigated in six cohorts consisting of two groups of patients (lumpectomy & lumpectomy + IORT) in three different mediums (wound fluid, serum, and standard cell culture). A) The invasion pattern of WBCs to cancer cells in IORT treated patients is independent of the media in which the WBCs were incubated. B) A similar behavior was observed on WBCs extracted from non-IORT patients. Consequently, the invasion of immune cells to cancer cells would not significantly be activated in PIWFs media. (ns $P > 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq 0.0001$).

We suggested that this effect might be caused by bystander secretion effect of the tumor bed cells. To better characterize whether the role of PIWFs is tumor-supportive or suppressive, the effect of this fluid on WBC activities of the IORT cohort patients was analyzed by time-lapse imaging analysis. Moreover, the effect of WFs on WBCs of non-IORT cohort patients was also investigated. Independent roles of PIWFs and WFs on MDA-MB-231 cell lines (as host cells for WBC attack) were also studied. The profile of important cytokines (IL-6, TNF-α, TGF-β) in blood serum, PIWFs of IORT and WFs of non-IORT patients were measured. In our opinion, these results would better clarify the effect of PIWFs on tumor bed by considering the role of immune cells and probably live tumor residues. This will help us decide whether to drain PIWFs from the tumor bed or not. It seems that the adverse effect of PIWFs for the patients is categorizable in two pathways; first, it stimulates the remained cancer cells in the margins by its cytokinea and chemokines. Second, it cannot severely pro activate the environmental immune cells against cancer cells. Hence, not only the cancer cells become PIWFs induced aggressive but also they can suppress the PIWFs induced immune cells similar to bare immunocells. Although the released results are considerable, second cytokine measurements from the ambient of interacted WBCs with WF/PIWF/DMEM and MDA-MB231cell lines would be so helpful for better illustration of the effects, which is our future focus.

It is worth noting that we did not have access to normal cell lines. However, as the worst-case scenario, we used TNBCs (MDA-MB231) which have the greatest capability in invasion to other cells. All patients with even TPBCs have some triple negative cells because the pathological score is not high (e.g. ER 60%, PR:50%, HER2neu:35%; therefore, some cells without the expression of ER, PR and HER2neu are presented among the cancer cells in tumor). From this point of view, using the most aggressive features, TNBC cell lines, may better reflect the effect of post IORT wound fluids on cancer cells in BC patients with heterogeneous histology even if the pathological report is triple positive.

CONCLUSION

We conclude that PIWFs have significant roles in favor of proliferation and mitosis of cancer cells but did not show an observable role in pro-activating immune cells against cancer cells. Cytokine profiles extracted from PIWFs, Serum, and WFs did not show any evidence against our result. The functions of immune cells did not show any independent proactivation in the presence of PIWFs with respect to their activation in the presence of blood serum. By considering all of these data, it seems that draining the PIWFs may be required. In future research, we must use tumor samples of the patients instead of cell lines to better investigate the personalized immune-tumor interactions of patients.

ETHICAL CONSIDERATIONS

All procedures performed in studies involving human participants followed the Ethics Committee of Shahid Beheshti University of Medical Sciences (Code of Ethics: IR.SBMU.CRC.REC.1400.049)

CONFLICT OF INTEREST

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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