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REVIEW

Neutrophils, a candidate biomarker and target for radiation therapy?

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ABSTRACT

Background: Neutrophils are the most abundant blood-circulating white blood cells, continuously generated in the bone marrow. Growing evidence suggests they regulate the innate and adaptive immune system during tumor evolution. This review will first summarize the recent findings on neutrophils as a key player in cancer evolution, then as a potential biomarker, and finally as therapeutic targets, with respective focuses on the interplay with radiation therapy.

A complex interplay: Neutrophils have been associated with tumor progression through multiple pathways. Ionizing radiation has cytotoxic effects on cancer cells, but the sensitivity to radiation therapy *in vivo* differ from isolated cancer cells *in vitro*, partially due to the tumor microenvironment. Different microenvironmental states, whether baseline or induced, can modulate or even attenuate the effects of radiation, with consequences for therapeutic efficacy.

Inflammatory biomarkers: Inflammation-based scores have been widely studied as prognostic biomarkers in cancer patients. We have performed a large retrospective cohort of patients undergoing radiation therapy (1233 patients), with robust relationship between baseline blood neutrophil count and 3-year's patient's overall survival in patients with different cancer histologies. (Pearson's correlation test: $p = .001$, $r = -.93$).

Therapeutic approaches: Neutrophil-targeting agents are being developed for the treatment of inflammatory and autoimmune diseases. Neutrophils either can exert antitumoral (N1 phenotype) or protumoral (N2 phenotype) activity, depending on the Tumor Micro Environment. Tumor associated N2 neutrophils are characterized by high expression of CXCR4, VEGF, and gelatinase B/MMP9. TGF-β within the tumor microenvironment induces a population of TAN with a protumor N2 phenotype. TGF-β blockade slows tumor growth through activation of CD8 + T cells, macrophages, and tumor associated neutrophils with an antitumor N1 phenotype.

Conclusions: This supports the need for prospective neutrophils evaluation in clinical trials, making neutrophils a predictive biomarker with potential specific therapies.

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Background

Tumor associated inflammation

Cancer is a chronic disease that relies on the crosstalk of tumor cells with their environment, with the inflammatory response being an essential factor for cancer initiation and development [1,2]. Inflammation can result in immunosuppression, thereby providing a preferred environment for tumor development [3,4]. Key mediators of tumor-associated inflammation include Nuclear Factor kappa B (NF-κB), signal transducer and activator of transcription 3 (STAT3) pathways, reactive oxygen and nitrogen species (ROS), inflammatory cytokines, estrogens, prostaglandins, and specific microRNAs among others [5, p. 53]. Their collective activity is responsible for either a pro-tumorigenic or anti-tumorigenic inflammatory response through changes in cell proliferation, cell death, cellular senescence, DNA mutation rates, DNA methylation, and angiogenesis [3,4].

Tumor micro-environment (TME)

Tumor evolution is similarly modified by an extensive TME, made of diverse and abundant host cells, including immune cells [6]. Influence of tumor associated macrophages and lymphocytes is relatively well characterized, but the role of neutrophils, as part of the TME and as circulating cells, has yet to be fully characterized [7].

Neutrophils: effector cells of the immune system

Neutrophils were firstly described by Ehrlich in 1879 [8]. They are the most abundant blood-circulating white blood cells, continuously generated in the bone marrow from precursors because of their <24 h lifespan. They have been considered the 'kamikaze' cells, sacrificing themselves while killing the invading pathogens with a variety of mechanisms: phagocytosis, secretion of reactive oxygen species (ROS), hyperchlorous

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acid, and antimicrobial proteins (defensin, lysozyme, and proteases such as elastase and cathepsin), or active extrusion of DNA to generate Neutrophils Extracellular Traps (NETs) [9].

Growing evidence is challenging this vision, suggesting that neutrophils may regulate the innate and adaptive immune system during tumor evolution. The exponential research in the field of anticancer immunotherapies has generated an increasing amount involving neutrophils [2,10].

Radiation therapy

Effects of radiation therapy are dependent of intrinsic radioresistance of cancer cells and extrinsic influence of the TME [11]. Numerous tumor-associated non-malignant cell populations are implicated in promoting tumor recurrence after radiation therapy [11]. After radiation therapy, tumor cells recruit inflammatory cells from the bone-marrow, including CD11b + myeloid cells and macrophages [12,13]. Recruited cells can recognize components of dying cells, which include Toll Like Receptor (TLR) agonists [11,14,15]. Studies suggested that myeloid cells could stimulate restoration of tumor blood vessel after radiation therapy [11,16]. However, the biology underlying tumor resistance after radiotherapy is to define.

A complex interplay

Neutrophils promote cancer evolution

A complex and interdependent relationship between neutrophils and cancer cells support cancer progression and metastasis process [17]. Cancer cells and stromal cells within the tumor microenvironment educate the generation and release of neutrophils from the bone marrow early in their evolution [10]. They generate neutrophils phenotypic and functional polarization states able to enhance tumor growth, locally as well as systemically in distant organs [10]. Neutrophils and cancer cells produce regulating enzymes, e.g., matrix metalloproteinases (MMPs), lysyl oxidase (LOX), urokinase (uPA), that alter the tumor extracellular matrix [18]. In turn, the tumor extracellular matrix mediates function of the myeloid and cancer cells [18]. Moreover, through the secretion of various MMPs, neutrophils suppress natural killer cell activity and enhance the extravasation of tumor cells [19]. Such protection from attack by innate and adaptive immune system offers a clear advantage to tumor cells in transit [20]. Consequently, tumor-associated neutrophils have recently been presented as a cornerstone of tumor initiation, angiogenesis, growth, and metastasis [10,17].

Neutrophils have been associated with tumor progression through multiple pathways. In breast cancer, estradiol promotes breast cancer cell migration via recruitment and activation of neutrophils [21]. Estrogen has been associated with decreased mobility inflammatory activity of neutrophils, and progesterone with increased neutrophils chemotaxis [9]. Both hormones seems to have an anti-apoptotic effect on neutrophils [9,21]. Neutrophil NETosis, the formation of NETs, is a unique form of cell death mechanism characterized by the release of networks of extracellular fibers, primarily composed of DNA from neutrophils, which entangle pathogens [20,22]. Such entangled circulating tumor cells may be more apt to survive intraluminally, adhere to endothelial cells, and extravasate [20]. Emerging evidence that NETs produced by infection or induced by cancer cells in the absence of infection can promote cancer metastasis [23].

Neutrophils' double-deal

Neutrophils either can exert antitumoral (N1 phenotype) or protumoral (N2 phenotype) activity, depending on the TME [24]. Tumor-associated neutrophils (TANs) are polarized from an N2 to an N1 phenotype in the absence of transforming growth factor β (TGF-β) [24]. Reversely, N1 TANs are not induced in the absence of IFN-β [25]. Antitumor-N1 neutrophils induce cytotoxicity through ROS production, reduces tumorigenesis through MMP-8 secretion, induce tumor cells apoptosis through Fas-ligand and antibody dependent cell-mediated cytotoxicity (ADCC), and stimulates leukocytes recruitment and immune activation by producing various chemokines and cytokines [26]. On the other hand, protumor-N2 neutrophils enhance carcinogenesis and decreases tumor cells apoptosis through MMP-9 production, promote tumor cells extravasation via collagenase and AKT activation via neutrophil elastase, stimulates angiogenesis through MMPs and chemokines recruitment, and generate leukocytes recruitment and immune suppression through chemokines and arginase production [26].

There is similarly an complex interplay between TANs and Tumor-Infiltrating Lymphocytes (TILs) [24,26]. Myeloid-derived suppressor cells (MDSCs) expand during cancer and inflammation, and suppresses T-cell responses [27]. Increased levels $CD8^+$ TILs have been previously associated with better outcome various cancer histologies [28,29, p. 8]. Accordingly, studies negatively correlated tumor-associated neutrophils with $CD8^+$ TILs content [30,31]. Contradictory, *in vitro* studies related $CD66b^+$ neutrophils with increased $CD8^+$ TILs, suggesting that they might effectively promote antitumor immunity [30,32]. The interplay between neutrophils and TILs additionally illustrates neutrophils' Janus-faced behavior.

Radiation therapy, immune response

The traditional view of radiation therapy as immunosuppressive has been challenged by the findings on its potential synergy with immunotherapy [33]. Radiation therapy amplifies tumor adaptive and innate immune response by inducing tumor the release of proinflammatory cytokines, promoting the recruitment of effector T cells to tumors, immune cell extravasation, and cytotoxic T lymphocyte-mediated immunogenic cell death [34]. Toll-like receptor 9 (TLR9) ligands released by tumors were described as crucial components in driving myeloid-cells inflammation and initiating tumor regrowth after local radiation therapy [11]. The tumorigenic effects of TLR9 depended on MyD88/NF-κB-mediated upregulation of interleukin (IL)-6 expression which in turn resulted in downstream activation of Jak/STAT3 signaling in myeloid cells [11].

Clinical studies revealed that radiation therapy can initiate responses outside the radiation field, called the 'abscopal

effect' by Mole et al. in 1953 [34–36]. Irradiated tumors induce an increase in MHC class I presentation, leading to tumor recognition. They also release danger signals, activating anti-tumor CD8 + T lymphocyte [34]. The underlying mechanisms are still poorly understood, and weakly therapeutically exploited [36].

Neutrophils and radiation therapy

Although probably major, to date our knowledge on the role of neutrophils in radiation therapy responses is limited and contradictory [10]. In preclinical studies, anti-Ly6G antibody-mediated neutrophil depletion improved the efficacy of radiation therapy, while Gr1 + antibody-mediated depletion does not alter radiation therapy responses [12,37]. Once more, the contradictory roles of neutrophils in anticancer therapy responses may reflect differences in tumor phenotypes [10].

Radiation therapy activates innate immunity through TLR-dependent mechanisms [33]. Neutrophils recognize TLRs agonists after localized radiation therapy [11,14,15]. Ligation of TLRs enhances the immune responses directed against tumor-associated antigens, increasing both the antitumor immunity and the immune-mediated targeting of tumor stroma, besides diminishing regulatory T cell activity [33]. STAT3 plays a key role in down-regulating immunostimulatory effects of TLRs in myeloid cells [38]. Ablating STAT3 in hematopoietic cells has been associated with activation of innate immunity by TLRs, with enhanced production of IFN-γ, TNF-α, IL-12, activation of neutrophils, and enlarged antitumor activity [38].

Irradiated tumors recruit large numbers of bone-marrow derived CD11b + myeloid cells expressing matrix metalloproteinase-9 (MMP-9), thereby restoring the vasculature and tumor growth [39]. This hypothesis has been supported by significant enhancement of radiation antitumor effect after systemic concomitant CD11b antibodies therapy, inhibiting bone marrow-derived cell adhesion and transmigration [12].

Key role for neutrophils in radiation-induced antitumor immune response has been recently reported during the early immunological effects of radiation therapy in the tumor microenvironment [40]. In this study, radiation therapy was associated with induction of sterile inflammation: CD11b + Gr1 + neutrophils infiltration into the tumors [40]. This sterile inflammation induced ROS production, tumor cells apoptosis, the activation of tumor-specific cytotoxic T cells, resulting in the tumor reduction [40].

TGF-β expression in the tumor microenvironment promotes metastasis and progression, and induces a population of TANs with a pro-tumor N2 phenotype [41]. TGFβ mediates the activation of the SMAD, PI3K-AKT, RHOA, and MAPK pathways [9]. Radiation therapy has also been demonstrated as inhibitor of the TGF-β pathway, thereby stimulating the anti-tumor-N1 neutrophil phenotype polarization [24,40].

Interactions between tumor cells, TME, peripheral neutrophils, as well as the interactions with radiation therapy and immune cells are summarized in Figures 1 and 2.

Inflammation biomarker

Inflammation-derived biomarkers

Inflammation-based scores have been widely studied as prognostic biomarkers in cancer patients. The combination of

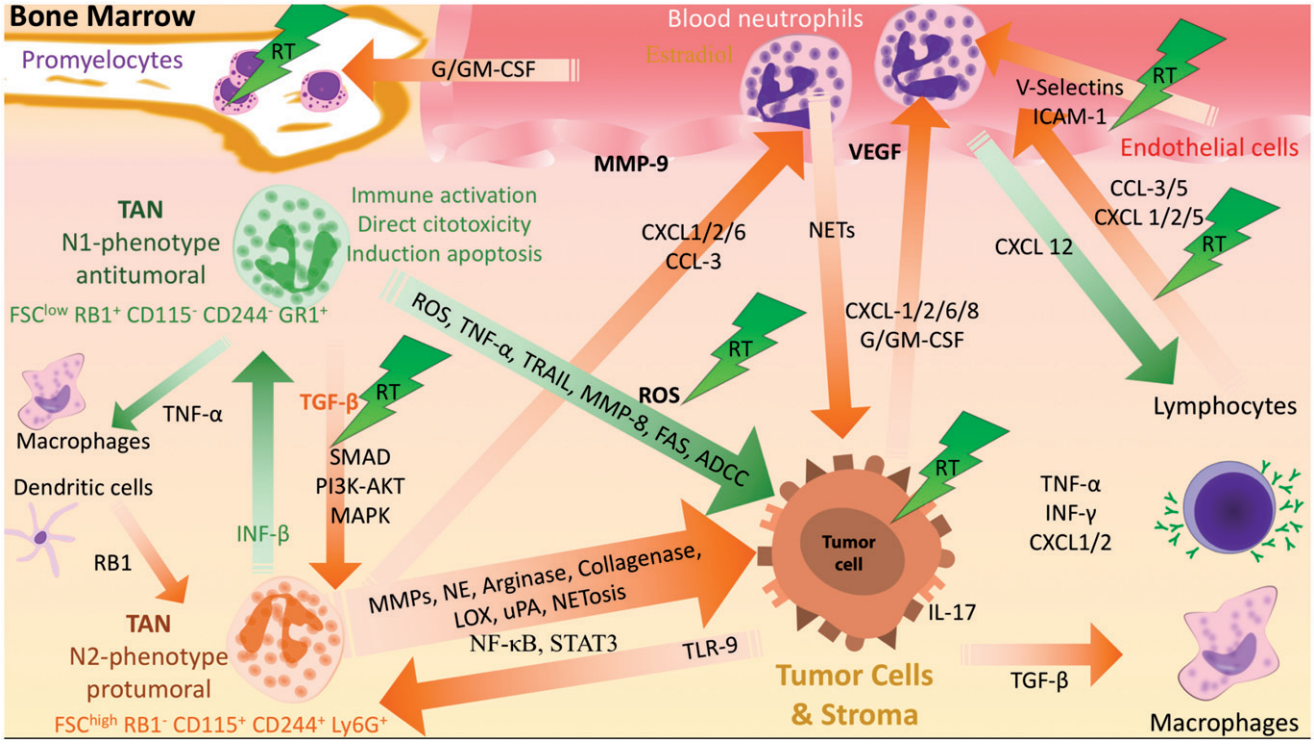

Figure 1. Neutrophils polarization and interactions with cancer. N1-phenotype: immune activation, direct cytotoxicity, induction apoptosis and N2-phenotype: immune suppression, tumor angiogenesis, tumor proliferation, prometastatic activity. TAN: tumor-associated neutrophils.

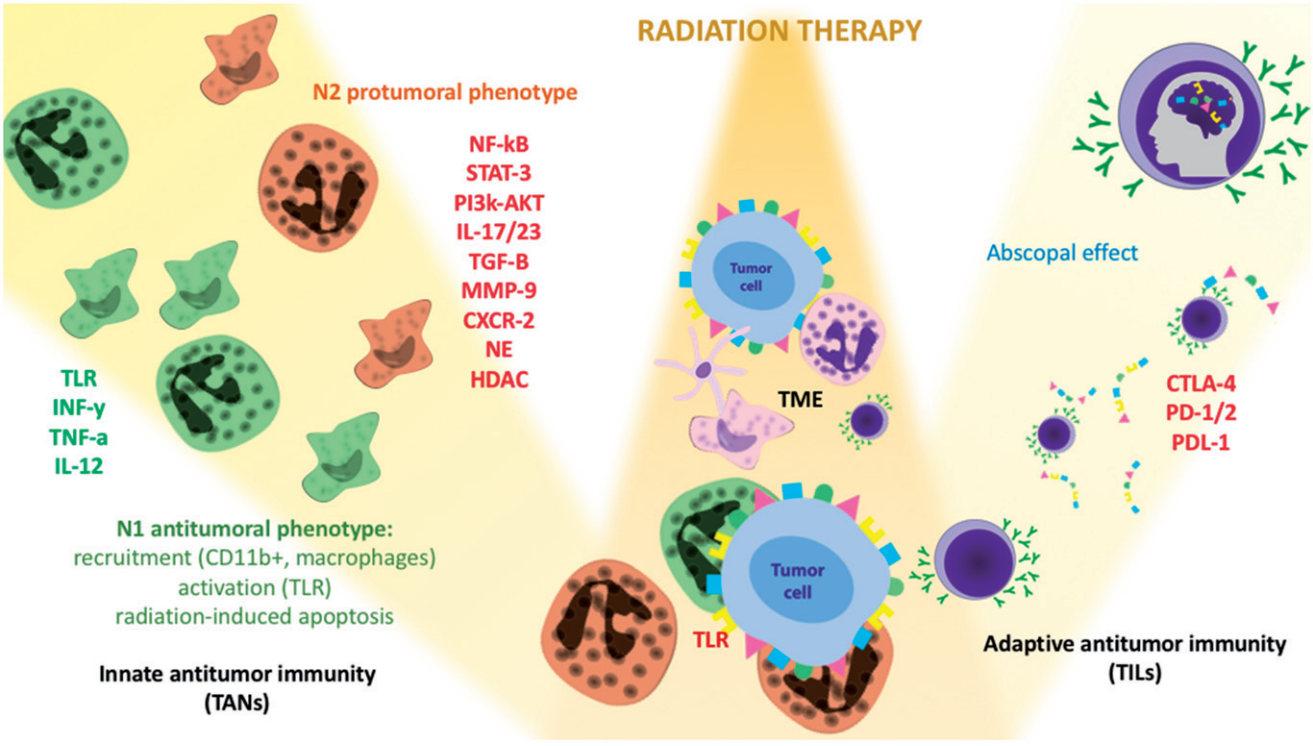

Figure 2. Radiation therapy interaction with antitumor immunity. TAN: tumor-associated neutrophils; TILs: tumor-infiltrating lymphocytes.

C-reactive protein (CRP) and albumin, i.e., the Glasgow Prognostic Score (GPS), is validated in a variety of cancer scenarios [42]. The neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) among others are also well established biomarkers [43,44]. Still, NLR illustrates (i) isolated increased neutrophil count, (ii) decreased lymphocyte count, or (iii) association of both [45]. These markers are effective because they highlight an inflammatory state, but are not specific markers with actionable targets.

Neutrophilia: prognostic biomarker

In the field of radiation therapy, as well as immunotherapy, there is a need for biomarker to predict and assess the immune response [34]. Neutrophils make up a significant portion of the inflammatory cell infiltrate in TME. They were even established as the most prevalent immune cell type in non-squamous cells lung cancer (NSCLC) microenvironment [26,46]. A negative association between high levels of TANs and unfavorable recurrence-free, cancer-specific, and overall survival has been described in various types of cancer [47].

Debate persists as to which suppressive properties of neutrophils are maintained by their tumor-infiltrating counterparts [48]. Inflammation has been associated with poor prognosis, sometimes assessed through the NLR [43]. Retrospective studies associated circulating neutrophil count >7 G/L, i.e., neutrophilia, with worse outcome in different tumor models, mostly squamous cell carcinomas, in patients undergoing radiation therapy [49–53]. In the EORTC 18951 trial, high pretreatment neutrophilia was an independent prognostic factor for shorter OS in patients with metastatic melanoma undergoing interleukin-2-based immunotherapy [54]. Extrinsic lung inflammation has also been associated with the recruitment of bone marrow-derived neutrophils through thrombospondin-1 (TSP-1) glycoprotein overexpression within tumor stroma, which promotes cancer metastasis [55, p. 1]. These findings could partially explain why ~80% of NSCLC patients initially fail immune checkpoint inhibitor therapy [46].

We have compiled recent retrospective data collections from Gustave Roussy Radiotherapy department (Villejuif, France) that included biological data. All included consecutive previously untreated patients that underwent radiation therapy between June 2001 and September 2016 in our institution. Pretreatment blood samples had to be taken in our institution in the week preceding the first radiation therapy course. Histologically confirmed tumors were stage III NSCLC (238 patients), gliomas (192 patients, including 164 high grade gliomas), head, and neck (339 patients: 193 that underwent curative intent radiation therapy for locally advanced tumors, and 146 T3-T4 tonsil or uvula tumor patients), and cervical (108 patients) anal (98 patients) esophageal (70 patients) squamous cell carcinomas. We added clinical records of consecutive patients undergoing definitive chemoradiation for histologically proven anal (133 patients) or esophageal (55 patients) squamous cell carcinomas, from two others French centers: (i) Paoli-Calmettes Institute (PCI, Marseille, France) between May 2000 and November 2014; (ii) Tenon Hospital (Paris, France) between October 2011 and June 2015. Patients who have received chemotherapy before blood count were excluded from the survival analysis, leading to 1233 analyzable patients. Stratifying on tumor histology, there was a relationship between neutrophilia, defined as baseline neutrophil count >7.0 G/L, and worse overall survival (log-rank test: $p = .001$, Figure 3). Moreover, considering each histology set as a single observation, there was a robust

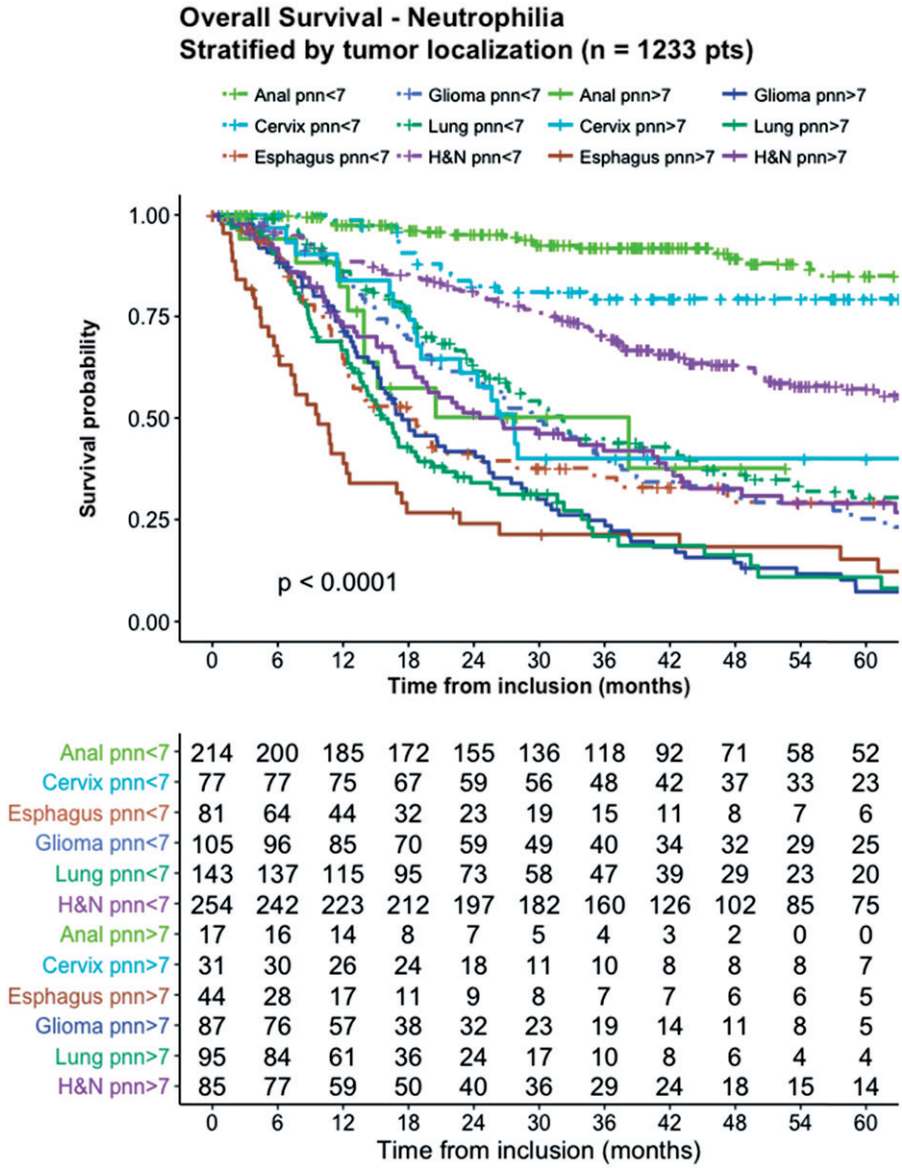

Figure 3. Kaplan–Meier's survival curves for estimated overall survival in patients with or without neutrophilia, stratified on tumor localizations (log rank test: $p < .001$). Neutrophilia: baseline neutrophil blood count >7 G/L (solid lines). H&N: head and neck; pnn: neutrophils.

correlation between proportion of patients that displayed baseline neutrophilia in each sets and 3-year overall survival (Pearson's correlation test: $p = .001$, $r = -.93$, Figure 4). Still, comparison with NLR was not achievable because lymphocyte count was not available.

Neutrophilia: predictive biomarker

Predictive association between neutrophilia and treatment resistance has been poorly studied, with most studies focusing on the association with patients' overall survival. A post hoc analysis from a randomized clinical trial in unresectable pancreatic carcinoma patients displayed a predictive association between neutrophilia and neutrophil count evolution with local response after chemoradiation versus chemotherapy [56]. This support the need for prospective neutrophils evaluation in clinical trials, making neutrophils a predictive biomarker with potential specific therapies.

Therapeutic approaches

Neutrophil-targeting therapies

Neutrophil-targeting agents are being developed for the treatment of inflammatory and autoimmune diseases [10]. In patients with chronic obstructive pulmonary disease, the use of CXCR2 antagonist decreases absolute neutrophil counts, reduces biological inflammation and disease symptoms [57]. Inhibition of CXCL8–CXCR1/2 signaling by CXCL8 antibodies, or small molecules targeting CXCR1 and/or CXCR2, also decreases tumor growth and progression in tumor mouse models [7]. CXCR2 inhibition has also been associated with enhanced response of both tumor and micrometastases to chemotherapy treatment [58]. Clinical trials evaluating reparixin, a CXCR1 and CXCR2 inhibitor, are ongoing in cancer patients [10]. In a comparable approach, inhibitors of Neutrophil-elastase (NE) displayed promise in lung cancer mouse models [59]. Another neutrophil-associated pathway

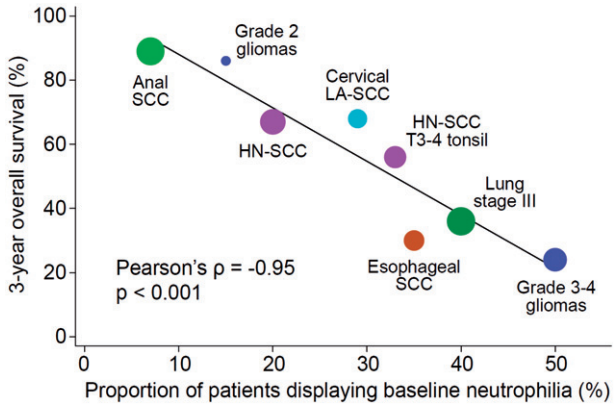

Figure 4. Estimated 3-year overall survival in each population, regarding percentage of patients displaying baseline neutrophilia (Pearson correlation test using weighted data: $p = .001$, $r = -.95$). LA: locally advanced; HN: Head and Neck; SCC: squamous-cell carcinoma.

under intense investigation is the IL-23–IL-17 axis [10]. The IL-17/neutrophil pathway has been correlated with increased distant metastatic progression [60]. Inhibition of the leukotriene-generating enzyme arachidonate 5-lipoxygenase (Alox5) abrogates neutrophil pro-metastatic activity have been reported to limit metastatic progression in preclinical models [61].

Nanoparticles (NPs) are an additional strategy [7]. The use of nanoparticles to target TANs has been described in a mouse model of inflammation to block neutrophil adhesion [62] Another approach through hijacking neutrophils *in vivo* using NPs to deliver therapeutics into tumor has reported nanoparticle tumor accumulation, mediated by neutrophils [63]. Also, treatment with NET-digesting DNase I coated nanoparticles reduced metastases in mice models [23]. Thus, NETs were reported as potential candidate pharmaceutical targets in cancer patients [22].

As neutrophils are critical for host defense against infection, their targeting can be associated with side effects [7]. Alternative approach could be to directly target the neutrophils in the TME and not the entire pool of circulating neutrophils, via reverse migration and polarization [7]. Moreover, neutrophil-targeting approaches in the clinic will require a critical assessment of optimal combination therapy strategies [10]. For example, neutrophilia has been associated with resistance to anti-VEGFA therapy, suggesting potentiate for anti-angiogenic and anti-neutrophils targeted therapies [10]. Indeed, therapeutic synergy has been observed when anti-VEGF-A therapy is combined with depletion of neutrophils [64].

Neutrophil-manipulating therapies

Not all neutrophils have protumor effects. Tumor associated N2 neutrophils are characterized by high expression of CXCR4, VEGF, and gelatinase B/MMP9 [7]. TGF-β within the tumor microenvironment induces a population of TAN with a protumor N2 phenotype [24]. TGF-β blockade slows tumor growth through activation of CD8 + T cells, macrophages, and tumor associated neutrophils with an antitumor N1 phenotype [24,41]. Studies showed an association between N1 neutrophils that expressed immunoactivating cytokines and/or chemokines, as well as low levels of arginase with an antitumoral competence induced by TGF-β blockade [7]. Understanding how neutrophils are polarized and if and how they can be reprogramed will be crucial to developing successful cancer therapies [7]. TGF-β inhibitors in oncology have therefore moved towards the use of combinatorial therapies with considerable promise for the clinic; clinical trials are ongoing [65,66]. With the same view, type 1 Interferons (IFN) seems to play the opposite role to TGF-β in neutrophil polarization, favoring an antitumoral 'N1' phenotype [9].

Epigenetic modification of neutrophils to modulate their polarization is not only limited to the field of research, since the approval of Histone deacetylase inhibitors (HDACi) for cancer therapy by the US Food and Drug Administration (FDA) [9]. HDAC impacts differentiation, proliferation and survival of distinct leukocyte populations [67]. HDACi both positively influence angiogenesis and the immune system in an antitumor perspective [67]. They also enhance the activity of anticancer drugs, including cisplatin and anti-Epidermal Growth Factor Receptor (anti-EGFR) [68].

Radiation therapy combined with neutrophil-targeting therapies

Pre-clinical models reported both anti-Ly6G antibody-mediated neutrophil depletion associated with improved radiation therapy efficacy, and antibody-mediated depletion of Gr1 + cells that were not associated with radiation therapy responses [10]. Contradictory, combining targeted radiation therapy with a neutrophil stimulant may enhance anti-tumor immunity, causing neutrophil-mediated tumor cell death [40]. Studies have demonstrated a shift from a chronic to an acute inflammatory environment and an anticancer effect via prolonged granulocyte colony-stimulating factor (G-CSF) treatment inducing neutrophilia [69]. The concurrent administration of G-CSF enhances radiation therapy mediated antitumor activity by activating neutrophils with N1-antitumoral phenotype [40]. Such an exciting development has been confirmed in an proof-of-principle clinical trial combining granulocyte-macrophage colony-stimulating factor (GM-CSF) and local radiation therapy to generate abscopal responses in patients with metastatic solid tumors [70,71]. Taken together, the diverse and sometimes opposing roles of neutrophils in radiation therapy responses may reflect differences functional differences in subtypes as well as the complexity of TME but also differences in tumor type, and radiation timing and fractionation [10,34].

HDACi were also reported as effective radiosensitizer in multiple histologies [72]. A promising triple combination strategy with HDAC inhibitors, irradiation and cisplatin could be of major interest in the treatment of NSCLC [73]. Following the finding that irradiated tumors recruit bone-marrow derived CD11b + myeloid cells expressing matrix metalloproteinase-9 (MMP-9), MMP-9 could also be a target to enhance the response of tumors to radiation therapy [39]. Similarly, radiation therapy could activate effectors of innate immunity stimulating the adaptive immune response to

cancer through TLR-dependent mechanisms, suggesting synergistic effects of radiation and TLR-targeted therapies [33].

Finally, from the identification of TLR9/STAT3-regulated genes involved in tumor-promoting inflammation and revascularization after local radiation therapy, combining localized tumor irradiation with myeloid cell-specific inhibition of STAT3 signaling are potential therapeutic targets to help eliminate radioresistant cancers [11].

Still, considering combinations of radiation therapy and immunotherapies, major issues remains unanswered: the total dose and fractionation, the optimal timing of radiation therapy and immunotherapies [34]. Combinations of neutrophil-targeting therapies with radiation therapy are encouraging, but a better understanding of the immunologic effects of radiation therapy is warranted to design the next generation trials [34,36].

Others combinations with neutrophil-targeting therapies

A promising therapeutic approach is the combination of T cell checkpoint inhibitor immunotherapy with neutrophil manipulation [10]. Experimental studies have shown that anti-programmed cell death protein 1 (PD1) and anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA4) synergizes with anti-CXCR2 or anti-Ly6G, respectively, to delay tumor growth [74,75].

Chemotherapy is another potentiate combination partner, although, many types of chemotherapy themselves negatively affect neutrophil production. Chemotherapy-induced neutropenia has been associated with improved survival [10]. Considering neutropenia as a biomarker marker of chemotherapy efficacy, lack may indicate insufficient dosing and inadequate efficiency. Alternatively, the patient survival benefit of chemotherapy-induced neutropenia may arise from reduction of the neutrophils that counteract the efficacy of chemotherapy [10]. Gemcitabine and 5-fluorouracil, directly reduce the viability and/or change the functionality of myeloid cells, which then influences the anticancer efficacy of these drugs [10].

Conclusions

The role of tumor derived factors on neutrophil chemotaxis and polarization, and the pathways that regulate their pro- or antitumoral action need to be defined. Few studies have focused on the interactions between neutrophils and radiation therapy; along with a better understanding of radiobiology, further research is warranted.

In patients undergoing radiation therapy, there is actually strong evidence for a prognostic association between neutrophilia and survival in multiple histologies. To translate neutrophilia into a personalized biomarker, prospective evaluation and longitudinal measurements in individual patients are mandatory. Besides, to date neutrophilia has not been shown to be a predictive marker of treatment effect. Another question is whether parallel scoring of patient serum levels of neutrophil-activating and polarizing soluble mediators (IL-1β, IL-17, G-CSF, GM-CSF, and/or TGFβ) increases the prognostic or predictive power of neutrophil measurement.

Finally, neutrophil-targeted therapies represent a promising therapeutic route, with multiple paths to investigate. Characterization of TANs infiltration and polarization in diverse organs, histologies, tumor stages, and hosts inflammatory states is required to fully apprehend their potential as therapeutic targets. Still, targeting such a major host innate defense against infection with acceptable adverse events will be challenging. Developments in association with radiation therapy are limited, but early results are encouraging. Comparable with development of concomitant uses of radiation therapy checkpoint inhibitors, the optimal radiation therapy scheme (fractionation, dose and timing) will have to be defined.

Disclosure statement

No potential conflict of interest was reported by the authors.

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