Prognostic benefit of TILs independent of clinicopathological and molecular factors

Brummel, Koen; Eerkens, Anneke L; de Bruyn, Marco; Nijman, Hans W

Published in:
British Journal of Cancer

DOI:
10.1038/s41416-023-02335-6

Publication date:
2023

British Journal of Cancer www.nature.com/bjc

CORRESPONDENCE

Prognostic benefit of TILs independent of clinicopathological and molecular factors

British Journal of Cancer (2023) 129:737–738; https://doi.org/10.1038/s41416-023-02335-6

TO THE EDITOR:

We would like to thank Almangush et al. [1] for their interest in our recent review in the British Journal of Cancer, "Tumour-infiltrating lymphocytes: from prognosis to treatment selection" [2] and we would like to share our thoughts regarding their letter.

We fully agree with the authors that there are many additional important aspects of Tumour-infiltrating lymphocytes (TILs) across different facets of clinical care, for example within the tumour-node-metastasis (TNM)-Immune classification. Regretfully we were not able to elaborate on all of these aspects within the confines of our original manuscript.

As mentioned in our recent review, TILs have a role as prognostic biomarker, next to a predictive value for immune therapy in cancer. However, this effect does not occur in isolation and should be interpreted within the context of other prognosticators, such as p16 status in Human papillomavirus (HPV)-related cancers and molecular subtype in endometrial cancer. Ward et al. [3] and Wakeman et al. [4] both found that the addition of p16 status to TIL scores improved the prediction of prognosis significantly in oropharynx and anal cancer, respectively. Among patients with p16 positive tumours, TIL levels stratified patients into those with good and poor prognosis in terms of Overall Survival (OS), Disease-Specific Survival (DSS), Disease-Free Survival (DFS) and/or Progression-Free Survival (PFS) [3, 4].

In non-HPV related solid tumours, tumours have been frequently sub-classified based on molecular profiling. Perhaps one of the most striking examples is endometrial cancer where the use of molecular classification has substantially impacted our understanding of prognosis and treatment selection [5, 6]. Herein, the prognostic effect of TILs can vary even between different molecular subtypes, and the overall immune profile of the infiltrate. For instance, TIL density has proven a prognostic benefit in patients with a TP53 mutant endometrial carcinoma [7]. However, and perhaps counterintuitively, this prognostic effect of TILs was weaker/absent in the mismatch repair deficient (MMRd) subgroup. By contrast, the presence of organized TIL infiltrate in the context of tertiary lymphoid structures (TLS) had a favourable prognostic impact mainly in the MMRd patients with endometrial cancer, but not within the other molecular subgroups [6]. In addition, a recent study by Lee et al. described the prognostic benefit of TILs was dependent of the expression of p53 in patients with triple negative breast cancer [8]. They found that in the low p53 expression group, the TIL level did not affect the OS and DFS, while in the high and no p53 expression groups, OS and DFS increases with a higher level of TILs. They hypothesize that a subgroup of patients with missense TP53 mutation, can benefit from immune checkpoint blockade (ICB) because of the presentation of neoantigens and a subsequent TIL response [8].

As the above-described effects are difficult to incorporate into a generalized TNM system, we remain wary of incorporation of TILs directly into this classification, but fully support efforts to work towards the inclusion of TILs as a prognostic and potentially predictive biomarker in addition to the classical TNM and molecular classification. Herein, we support the conclusions of Almangush et al. [1] that further validation of the potential use of TNM-Immune staging is desirable prior to its introduction in clinical practice.

Koen Brummel[1,2], Anneke L. Eerkens[1,2], Marco de Bruyn[1,3] and Hans W. Nijman[1,3]✉

[1]*Department of Obstetrics and Gynecology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.* [2]*These authors contributed equally: Koen Brummel, Anneke L. Eerkens.* [3]*These authors jointly supervised this work: Marco de Bruyn, Hans W. Nijman.* ✉*email: h.w.nijman@umcg.nl*

DATA AVAILABILITY

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

REFERENCES

1. Almangush A, Mäkitie AA, Leivo I. Can TILs supplement the TNM staging system (as TNM-Immune)?
2. Brummel K, Eerkens AL, de Bruyn M, Nijman HW. Tumour-infiltrating lymphocytes: from prognosis to treatment selection. Br J Cancer. 2023;188:451–8.
3. Ward MJ, Thirdborough SM, Mellows T, Riley C, Harris S, Suchak K, et al. Tumour-infiltrating lymphocytes predict for outcome in HPV-positive oropharyngeal cancer. Br J Cancer. 2014;110:489–500.
4. Wakeham K, Murray L, Muirhead R, Hawkins MA, Sebag-Montefiore D, Brown S, et al. Multicentre investigation of prognostic factors incorporating p16 and tumour infiltrating lymphocytes for anal cancer after chemoradiotherapy. Clin Oncol. 2021; 33:638–49.
5. Getz G, Gabriel SB, Cibulskis K, Lander E, Sivachenko A, Sougnez C, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497:67–73.
6. Horeweg N, Workel HH, Loiero D, Church DN, Vermij L, Léon-Castillo A, et al. Tertiary lymphoid structures critical for prognosis in endometrial cancer patients. Nat Commun. 2022;13:1373.
7. Horeweg N, de Bruyn M, Nout RA, Stelloo E, Kedzierska K, León-Castillo A, et al. Prognostic integrated image-based immune and molecular profiling in early-stage endometrial cancer. Cancer Immunol Res. 2020;8:1508–19.
8. Lee M, Park IA, Heo SH, Kim YA, Gong G, Lee HJ. Association between p53 expression and amount of tumor-infiltrating lymphocytes in triple-negative breast cancer. J Pathol Transl Med. 2019;53:180–7.

AUTHOR CONTRIBUTIONS

KB and ALE drafted and revised the manuscript. MB and HWN conceived the project, supervised writing, and revised the manuscript. All authors read and approved the final version.

Received: 2 May 2023 Revised: 15 May 2023 Accepted: 19 June 2023
Published online: 13 July 2023

FUNDING
Not applicable.

COMPETING INTERESTS
HWN and MdB hold a patent on antibodies targeting CD103 (no 62/704,258).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Not applicable.

CONSENT FOR PUBLICATION
All authors have approved to publish this manuscript.

ADDITIONAL INFORMATION
Correspondence and requests for materials should be addressed to Hans W. Nijman.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.