

evidence of the effect of postmastectomy radiotherapy on patient-reported outcomes and QOL.

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1 EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; **383**: 2127–35.

- 2 Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med* 2015; **373**: 2005–14.
- 3 Arvold ND, Taghian AG, Niemi A, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. *J Clin Oncol* 2011; **29**: 3885–91.
- 4 Velikova G, Williams LJ, Willis S, et al. Quality of life after postmastectomy radiotherapy in patients with intermediate-risk breast cancer (SUPREMO): 2-year follow-up results of a randomised controlled trial. *Lancet Oncol* 2018; published online Oct 15. [http://dx.doi.org/10.1016/S1470-2045\(18\)30515-1](http://dx.doi.org/10.1016/S1470-2045(18)30515-1).
- 5 Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014; **15**: 1303–10.
- 6 Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015; **373**: 317–27.
- 7 Haviland JS, Mannino M, Griffin C, et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: results from the UK START (Standardisation of Breast Radiotherapy) trials. *Radiother Oncol* 2018; **126**: 155–62.

Personalised approach in follicular lymphoma

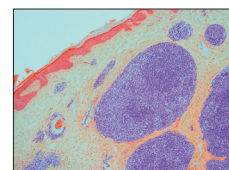
Follicular lymphoma is the most common subtype of indolent B-cell lymphoma, and patient outcomes are highly heterogeneous, with 20–30% of patients having aggressive (rather than indolent) disease.¹ These high-risk patients would benefit from a personalised approach to their care if validated and accurate prognostic tools were available to identify them as soon as possible after diagnosis. Although many prognostic tools and indices to predict survival in follicular lymphoma have been developed in the past 20 years, none of them have yet proven useful in therapeutic decision making.¹ The many reasons explaining the gap between prognostic and therapeutic research in follicular lymphoma include the relatively low accuracy of published scores, with high frequency of false positives and negatives, their poor ability to predict overall survival, the time lag before relevant prognostic information is available (eg, the use of disease progression within 24 months as a prognostic indicator), technical difficulties in the index calculation, and the stability of the prognostic score or index under the conditions of different treatment regimens (eg, R-CHOP [rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone], rituximab plus bendamustine, and R-CVP [rituximab plus cyclophosphamide, vincristine, and prednisone]) or maintenance therapy with anti-CD20 monoclonal antibodies.

In *The Lancet Oncology*, Judith Trotman and colleagues² describe the results of the largest study so far to investigate the prognostic role of metabolic response in more than 500 patients with

previously untreated, advanced-stage follicular lymphoma who were enrolled in the randomised phase 3 GALLIUM trial.³ These investigators should be congratulated for the prospective inclusion of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET among the required study procedures, and for the high quality of the central review process of metabolic response. Their findings showed that metabolic response to induction immunochemotherapy was prognostic for both progression-free and overall survival (eg, 2.5-year progression-free survival according to Lugano 2014 criteria was 87.4% [95% CI 83.7–90.2] in complete metabolic responders vs 54.9% [40.5–67.3] in non-complete metabolic responders; hazard ratio [HR] 0.2, 95% CI 0.1–0.3, $p < 0.0001$), and that Lugano response criteria were accurate and reproducible in follicular lymphoma. Furthermore, the investigators suggest that FDG-PET is the only diagnostic test required to assess response. More importantly, the results of the study show it is possible to generalise the prognostic role of metabolic response to nearly all patients with advanced-stage follicular lymphoma, including those receiving maintenance therapy and those treated with the new-generation anti-CD20 monoclonal antibody obinutuzumab. Lastly, although the study was not powered to analyse survival differences between different chemotherapy regimens, the stability of metabolic response with different treatments was strongly supported by the similar efficacy results with different treatment regimens. Therefore, because



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metabolic response in follicular lymphoma fulfils most of the required criteria of an accurate prognostic test, it seems to be the best candidate among prognostic features to develop risk-adapted therapies in this disease. Indeed, clinical trials are underway that investigate the efficacy of a response-adapted approach based on the use of FDG-PET (eg, NCT02063685 and EudraCT 2016-004010-10).

Nevertheless, some additional considerations are needed to better guide future steps towards a personalised approach to follicular lymphoma care. First, Trotman and colleagues suggest that with the most active immunochemotherapy available today, the prognostic impact of metabolic response is confirmed. Its impact in clinical practice, however, is only available at the end of induction therapy and diminishes to approximately one out of ten patients with the use of a more potent antibody (ie, metabolic response was 18% in a previous prospective study with R-CHOP).⁴ Of the two methods used in the Trotman and colleagues' study to analyse the prognostic role of metabolic response, the intention-to-treat analysis overestimated the actual proportion of patients with metabolic response because it also included patients without post-induction FDG-PET among non-responders. Thus, the 450 (89%) patients with metabolic response among the 508 who qualified for the landmark analysis better describes the actual proportion of patients who are suitable for a response-adapted approach. Second, the biological basis of a partial metabolic response is still not completely understood, and the major drivers of the increased risk of death in these high-risk patients remains unknown. Well-designed studies should try to clarify the association between absence of metabolic response and the risk of transformation or the presence of unfavourable pathological subtypes. Third, unlike in Hodgkin's lymphoma or aggressive lymphomas, the timing of response assessment in follicular lymphoma has never been questioned; the possibility of identifying

non-responders with response assessment at different timepoints thus remains unexplored. Finally, an urgent need remains for more active drugs in follicular lymphoma that could be moved from late to early treatment lines rapidly and safely and that could be incorporated into personalised, risk-adapted therapy to solve the problem of unfavourable outcomes in high-risk patients.

In conclusion, a plateau in the curability of follicular lymphoma has probably been achieved thanks to highly active available immunochemotherapy regimens, but a proportion of patients still have high-risk features. Trotman and colleagues' findings support metabolic response as one of the most important predictors of patient outcome, but its clinical significance is limited by the very low proportion of non-responding patients. The next generation of clinical trials in follicular lymphoma should be designed to test the efficacy of risk-adapted therapies in which metabolic response is integrated with robust clinical and biological prognostic factors to optimise the efficacy-to-safety ratio of therapy in the individual patient.

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- 1 Casulo C. Risk stratification in follicular lymphoma. *Best Pract Res Clin Haematol* 2018; **31**: 15–22.
- 2 Trotman J, Barrington SF, Belada D, et al. Prognostic value of end-of-induction PET response after first-line immunochemotherapy for follicular lymphoma (GALLIUM): secondary analysis of a randomised, phase 3 trial. *Lancet Oncol* 2018; published online Oct 8. [http://dx.doi.org/10.1016/S1470-2045\(18\)30618-1](http://dx.doi.org/10.1016/S1470-2045(18)30618-1).
- 3 Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med* 2017; **377**: 1331–44.
- 4 Dupuis J, Berriolo-Riedinger A, Julian A, et al. Impact of [(18)F] fluorodeoxyglucose positron emission tomography response evaluation in patients with high-tumor burden follicular lymphoma treated with immunochemotherapy: a prospective study from the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. *J Clin Oncol* 2012; **30**: 4317–22.