Hodgkin lymphoma

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Hodgkin lymphoma: is there really a need for interim and end-of-treatment FDG-PET evaluations?

Recently, an article entitled '*Hodgkin lymphoma: a negative interim-PET cannot circumvent the need for end-of-treatment-PET evaluation*' was published in the Journal (Mesguich *et al*, 2016). Their study included 76 patients with early- or advanced-stage Hodgkin lymphoma treated with adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) who underwent fluorodeoxyglucose positron emission tomography (FDG-PET) at baseline, after 2-4 cycles of ABVD (interim FDG-PET) and after treatment (end-of-treatment FDG-PET), and aimed to determine the prognostic value of these scans in predicting treatment failure. Interim FDG-PET scans were interpreted by using the liver (Deauville score ≥4) or the mediastinal blood pool activity (Deauville score ≥3) as thresholds to define positivity, whereas end-of-treatment FDG-PET scans were only considered positive if FDG uptake exceeded mediastinal blood pool activity (Deauville score ≥3). During a median follow-up period of 58·9 months, 15 patients developed refractory or relapsed disease. Using a Deauville score ≥4 as the threshold, interim FDG-PET achieved sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 46·7% (7/15), 85·2% (52/61), 43·8% (7/16), and 86·7% (52/60), respectively. Deauville score ≥3 was considered inappropriate as cut-off value due to a strikingly low PPV of only 22·6% (12/53). Predictive value end-of-treatment FDG-PET was better with sensitivity, specificity, PPV and NPV of 80·0% (12/15), 93·4% (57/61), 75·0% (12/16) and 95·0% (57/60), respectively (Mesguich *et al*, 2016). The authors concluded that a negative interim FDG-PET study cannot obviate the need for end-PET examination, and that the latter has a high accuracy in predicting treatment failure.

However, we believe Mesguich *et al* (2016) did not sufficiently discuss the drawbacks of both interim and end-of-treatment FDG-PET. First, they did not address how their unsatisfactory results on the interim FDG-PET evaluation should be interpreted for routine clinical management. The very low sensitivity (46·7%) and PPV (43·8%) indicate that more than half of patients who developed ABVD-resistant disease had a negative interim FDG-PET scan, and more than half of patients with interim FDG-PET positive results remained disease-free following continuation of standard ABVD therapy. This seriously questions whether interim FDG-PET results should be used for prognostication in this disease, and undermines the feasibility of FDG-PET adapted trials (given that the majority of patients who require treatment intensification beyond ABVD have negative interim FDG-PET scans, and patients with positive interim FDG-PET scans achieve cure in the majority of cases without treatment intensification). Second, Mesguich *et al* (2016) did not sufficiently describe how their results on the end-of-treatment FDG-PET evaluation relate to those of other studies. Although their study reported a sensitivity of end-of-treatment FDG-PET of 80·0%, these results were much less favourable in comparable studies (Table I), whose results were not reported by Mesguich *et al* (2016). It is unclear why the sensitivity of FDG-PET was higher at end of treatment than at interim, because the metabolically active tumour volume is generally lower in the former than in the latter situation (Adams & Kwee, 2016a). Due to the limited spatial resolution of current PET systems, a negative scan cannot exclude residual disease and this theoretically applies even more to the end-of-treatment rather than the interim FDG-PET evaluation. Of note, all previous studies on this topic used the (older) International Harmonization Project criteria which uses a Deauville score ≥3 (Table I), as the threshold to define positivity, which is lower than the contemporary Lugano guidelines (Deauville score ≥4). When applying the new Lugano guidelines, the sensitivity may have been even lower. The fact that Hodgkin lymphoma is a highly curable disease with a low relapse rate, in combination

Table I. Results of studies on the sensitivity of end-of-treatment FDG-PET for the detection of residual disease in Hodgkin lymphoma.

Study reference	Criteria for positivity	Sensitivity of end-of treatment FDG-PET (actual numbers)
Mesguich *et al* (2016)	Deauville score ≥3	80·0% (12/15)
Jalali *et al* (2016)	Deauville score ≥3	36·4% (12/33)
Filippi *et al* (2013)	Deauville score ≥3	0·0% (0/1)
Markova *et al* (2012)	Deauville score ≥3	33·3% (1/3)
Barnes *et al* (2011)	Deauville score ≥3	27·3% (3/11)
Lopci *et al* (2011)	Deauville score ≥3	63·6% (7/11)
Straus *et al* (2011)	Deauville score ≥3	55·0% (11/20)
Cerci *et al* (2010)	Deauville score ≥3	50·0% (11/22)

FDG-PET, fluorodeoxyglucose positron emission tomography.

with the low sensitivity of end-of-treatment FDG-PET, underlines that the number needed to scan (i.e., number of end-of-treatment FDG-PET scans required to detect one case with residual disease) is very high. Furthermore, FDG-PET scans are expensive, use ionizing radiation, provide patient discomfort, are not available in all institutions and generate false-positive findings (Adams & Kwee, 2016b; Mesguich *et al*, 2016). The latter can have serious consequences, such as unjustified changes in therapy management and prognostication (if histological confirmation of residual FDG-avid lesions is not performed), result in a high number of unnecessary biopsies, and cause patient anxiety. Finally, it has not considerably been proven that early (imaging-based) detection of residual disease before the onset of symptoms results in an improved patient outcome.

In conclusion, the currently available evidence shows that both interim and end-of-treatment FDG-PET have low sensitivity for the detection of residual disease, and routinely performing these tests has not been proven to benefit patient outcome. Therefore, there may be no need for interim and end-of-treatment FDG-PET evaluations.

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Conflicts of interest

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Author contributions

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