the performance of human beings assisted by machine. Such measurements must ultimately take place in clinical trials, recording false-negative identifications and undertreatment as well as overtreatment. Indeed, there is a case that the most pressing decision-support need in thyroid cancer is not in diagnosis but in making the decision to treat.

Thus, excellence in algorithmic performance is essential in our quest for automation, but ultimately we are interested in what a human being decides when using automation in the messy reality of health care. Until our machines are fully embedded in that reality, and see it better than us, our role as clinicians is to be the bridge between machine and decision. At least for now, algorithms do not treat patients, health systems do.

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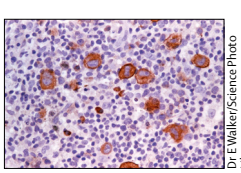
Optimisation of adaptive therapy for advanced Hodgkin lymphoma

Management of advanced-stage Hodgkin lymphoma balances tumour control with therapy toxicity. Multiple studies have established the importance of increased-dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone ($BEACOPP_{escalated}$) in providing long-term tumour control for patients with this disease, but this treatment is associated with extended haematological toxicity in normal tissue, including myelodysplasia and secondary malignancies. Some physicians are cautious about giving $BEACOPP_{escalated}$ to patients partly because of concerns that toxicity subtracts from the potential advantage of upfront tumour control. Conventional treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with the option of dose escalation in patients who respond minimally to upfront therapy is often preferred. Other physicians, however, argue that more aggressive upfront therapy with the option for de-escalation could lead to optimum outcomes for patients.[1–4]

Metabolic imaging with PET has been incorporated into multiple clinical trials of Hodgkin lymphoma with patients of all stages and risk factors. PET with fluorodeoxyglucose has been used to provide uniform thresholds for staging of disease and assessment of response to treatment. The Children's Oncology Group (COG) AHOD0031 trial[4] showed that imaging, including metabolic imaging, could be assessed by central review in real time to make treatment decisions based on response to induction therapy with ABVD. If PET after two cycles of ABVD did not show complete response, chemotherapy was intensified with dexamethasone, etoposide, cytarabine, and cisplatin. Although the COG AHOD0031 study showed that therapeutic titration was advantageous for patients with good responses, patients who needed dose intensification after two cycles of chemotherapy did not achieve the optimum outcome of disease-free survival, which suggests that a more intense therapy at the start of treatment could have been beneficial.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The COG AHOD0031 and other trials registered at the National Clinical Trials Network, coupled with work from multiple European study groups, have established the importance of metabolic imaging in clinical trials of response-adapted chemotherapy. With the availability of digital transfer tools and the enterprise data archiving function for anatomical and metabolic imaging, central review of imaging for real-time protocol management is feasible and functional.

In *The Lancet Oncology* René-Olivier Casasnovas and colleagues[5] report an important, non-inferiority trial of PET-adapted treatment that fills a knowledge gap in the management of patients with advanced stage Hodgkin lymphoma. The trial design combines the strength of upfront intense induction therapy with $BEACOPP_{escalated}$ with centrally reviewed PET-driven therapeutic titration after two cycles of induction chemotherapy (PET2). In the PET-driven treatment group, patients with positive PET scans continued on $BEACOPP_{escalated}$ (n=346) for two more induction cycles whereas those with negative scans responses were assigned ABVD (n=51) to ameliorate risks of toxicity. This strategy was compared with standard treatment (six cycles of $BEACOPP_{escalated}$ irrespective of PET2 results) in 413 patients. 5-year progression-free survival by intention to treat was 86·2% (95% CI 81·6–89·8) in the standard treatment group compared with 85·7% (81·4–89·1) in the PET-driven treatment group (hazard ratio [HR] 1·084, 95% CI 0·737–1·596; p=0·65). This similarity was also seen in the per-protocol analysis (86·7% [81·9–90·3] *vs* 85·4% [80·7–89·0], HR 1·144, 0·758–1·726; p=0·74). Grade 3–4 anaemia, thrombocytopenia, and febrile neutropenia were less frequent in the PET-driven group than in the standard group, as were serious adverse events.

The trial has many strengths that make it one of the most important clinical trials completed in Hodgkin lymphoma in the past decade. Adolescents were included, whereas this vulnerable population is often not well represented in paediatric or adult clinical trials, especially in those done in North America. The trial had central review of PET images, which validates the response assessment used and provides confidence in the trial outcome. The trial was well designed and powered to support the study objectives, including non-inferiority of response-adapted therapy, given the understanding that most patients were likely to have a good response to upfront therapy. The response to initial therapy was outstanding, and in patients who were eligible for therapy titration, toxicity was improved. Of equal importance, the outcomes of patients who had incomplete response to induction chemotherapy were better than those seen in similar patient populations in other clinical trials where treatment dose was intensified after two cycles of standard ABVD chemotherapy.[4]

Casanovas and colleagues provide a platform upon which translational research in Hodgkin lymphoma can move forward at an exponential rate with worldwide participation. Subsets of patients, including young patients, those with limited tumour volume or surgically excised tumours, medically compromised patients, and others, could be assessed in individual protocols. Digital data transfer has placed this opportunity at our fingertips and trial participation can be done at an enterprise function level. Although Hodgkin lymphoma is an uncommon disease, there is international interest in collaboration that will permit all investigators to assess subsets of patient, analyse biomarkers, and evaluate outcome with imaging as a common point of validation. This paper sets the tone for future endeavours to improve the care of patients with this disease.[6]

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