GLOSSARY

SURROGATE ENDPOINT
A variable such as a test, score, or measurement, that is used as a substitute for the ideal clinical endpoint; it can reduce the time to achieve the endpoint measurement, and is used to aid the design or evaluation of a clinical trial

PRENTICE'S CRITERION
A set of conditions for evaluating the surrogacy of endpoints

infected patients (viral load) is used to guide antiviral therapy and can be measured by polymerase chain reaction. Chen and colleagues investigated whether serum HBV viral load could predict progression to hepatocellular carcinoma.

In this prospective cohort study, the incidence of hepatocellular carcinoma and the HBV viral load were assessed at baseline and in follow-up examinations (mean follow-up 11.4 years) in patients seropositive for the HBV surface antigen ($n = 3,653$). The investigators identified 164 hepatocellular carcinoma cases; the incidence rate per 100,000 patient-years increased from 108.3 in patients with undetectable viral load (<300 copies/ml) to 1,152.0 for patients with high viral load ($>1 \times 10^6$ copies/ml). After adjusting for confounders such as liver cirrhosis and serum alanine aminotransferase level, the risk of hepatocellular carcinoma was significantly higher in those with high viral load at baseline than in those with low viral load (biological gradient $P < 0.001$). The risk of developing hepatocellular carcinoma was greatest for patients who had persistently elevated HBV viral load.

The authors conclude that elevated HBV viral load is a major risk factor for the development of hepatocellular carcinoma; measurement of a patient's HBV viral load should be used to guide antiviral therapy. Future trials should compare different treatment strategies in patients with high levels of HBV DNA.

Kate Matthews

Original article Chen C-J *et al.* (2006) Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* **295:** 65–73

Surrogate endpoint aids treatment evaluation of invasive bladder cancer

Researchers from Kyoto, Japan, have shown that tumor downstaging is an appropriate SURROGATE ENDPOINT for overall survival when evaluating the effectiveness of neoadjuvant chemotherapy in phase II trials of invasive bladder cancer.

Teramukai and co-workers used data from a follow-up observational study. Of 586 patients, aged <80 years, with clinical stage T2–4, N0, M0, transitional cell carcinoma, 183 were assigned to neoadjuvant chemotherapy followed by radical cystectomy and 403 to cystectomy alone. The authors developed a new criterion for tumor downstaging effect (the difference between clinical stage at diagnosis and pathological stage at the time of cystectomy); this criterion classified patients according to their good, intermediate or poor response to treatment. Overall comparison between patients in whom treatment was most effective and those showing intermediate and poor response produced HRs for overall survival of 1.9 (95% CI 1.0–3.7) and 5.0 (95% CI 2.6–9.8), respectively, following adjustment for prognostic factors.

The relationship between tumor downstaging, effectiveness of neoadjuvant chemotherapy, and overall survival was assessed in accordance with PRENTICE'S CRITERION; tumor downstaging satisfied three of the four conditions of surrogacy. Neoadjuvant chemotherapy had a statistically significant effect on tumor downstaging ($P = 0.001$), but the treatment did not affect survival. These results, however, require validation in randomized clinical trials and are therefore inconclusive. The authors conclude that tumor downstaging could be an appropriate endpoint for evaluating efficacy of neoadjuvant chemotherapy in invasive bladder cancer patients.

Pippa Murdie

Original article Teramukai S *et al.* (2006) Evaluation for surrogacy of end points by using data from observational studies: tumor downstaging for evaluating neoadjuvant chemotherapy in invasive bladder cancer. *Clin Cancer Res* **12:** 139–143

How effective is ferumoxtran-10 MRI in the diagnosis of lymph node metastases?

Detection of tumor spread to lymph nodes is crucial to provide the best treatment to patients with cancer. Current imaging methods used for detecting lymph node metastases, however, are unreliable. Ferumoxtran-10 is a newly developed contrast agent that can identify malignant nodal infiltration even in small lymph nodes. Will *et al.* have performed a meta-analysis to assess the precision of ferumoxtran-10-enhanced MRI as a predictor of lymph node metastases.

Studies that compared either ferumoxtran-10-enhanced MRI or unenhanced MRI with histological diagnosis were identified from the Ovid, EMBASE, Cochrane and MEDLINE