NEWSROUND

Selected reports edited by Hannah Brown

Nodal status is best predictor of effectiveness of neoadjuvant therapy for oesophageal cancer

→ Annals of Surgery

The number of lymph nodes that contain evidence of cancer is the best predictor of the effectiveness of adding chemotherapy and radiation to a treatment plan prior to surgery in individuals with oesophageal cancer, according to a recent study. The authors say their finding is particularly important because the focus of recent pathological studies of response to neoadjuvant therapies has been on the primary tumour rather than nodal sites.

Multimodal neoadjuvant therapy – where suitable patients are given several cycles of drugs and radiation therapy before undergoing surgical procedures to remove their tumour – is increasingly being used by oncologists as a way to boost survival rates from oesophageal cancer which, even with the most radical surgery, remain low: only 50% of patients survive for three years. However, the evidence for which additional therapies work best is confusing and conflicting. What is more, although it is widely accepted that there is a group of patients in whom this approach works well, identifying who these patients are is no easy task.

To help find ways of pinpointing individuals who might respond best, John Vincent Reynolds and colleagues followed the progress of 243 patients who were treated with chemotherapy and radiation before surgery over five years. They paid particular attention to the histomorphological responses of patients, in addition to assessing prognosis using the traditional TNM method of staging, which takes into account tumour size, involvement of lymph nodes (nodal status) and presence or absence of metastases.

The study group consisted of all patients undergoing neoadjuvant treatment for oesophageal cancer at St James' Hospital in Dublin, Ireland. Patients with oesophageal cancer were deemed suitable for multimodal therapy if they fulfilled a list of pre-set criteria, including being younger than 77 years, fit for surgery, and having a tumour of resectable size and location. The patients were given a standard protocol of radiation therapy and concurrent chemotherapy with fluorouracil and cisplatin before undergoing thoracotomy with lymphadenectomy and nodal dissection; the extent of surgery and lymph node dissection depended on the exact location of the tumour. Thirty patients did not proceed to surgery because of disease progression or deterioration in performance status.

Several tissue samples from each patient were extracted during surgery and were subsequently examined for extent of residual cancer, depth of invasion, and lymph node metastasis. The patients were also assigned a tumour stage according to the TNM staging system. All patients were followed up with six-monthly endoscopy and annual CT scans.

Of the 213 patients who underwent surgery, 41 (19%) had a complete pathological response to the pre-surgery therapy, meaning there was no sign of cancer in the tissue samples. Thirty-one (15%) of the remaining patients were classed as having stage 1 disease (the least advanced), 69 (32%) had stage 2 disease, and 72 (34%) had stage 3 disease. After a median follow-up of 60 months, median survival for the whole group was 18 months. But for the group of patients who achieved a complete pathological response, five-year survival was 50%, with a median survival of 56 months. "The achievement of a complete pathologic response following neoadjuvant chemotherapy alone or in combination with radiotherapy for oesophageal tumours is a surrogate marker of survival advantage," explain the authors.

However, the study established that it was nodal status rather than attainment of pathological response that was the most significant determinant of prognosis. When individuals with complete pathological responses were compared with those who had no nodal involvement after neoadjuvant therapy, there was no significant difference in the one-, three-, and five-year survival rates. And within the node-negative group, the combination of complete response with a low tumour stage conferred better survival: individuals with stage 1 disease and no involved nodes (n=65) had a median survival of 67 months and five-year survival of 53%, compared with 25 months and 30% for people with stage 2 and 3 tumours and no nodal involvement after neoadjuvant

treatment. Interestingly, pretreatment clinical stage had no predictive value on histomorphological response.

The authors concluded that, because the study suggests nodal status after neoadjuvant treatment is the strongest determinant of outcome, there is no evidence that an assessment of histomorphological response should be incorporated into a revised TNM system or that traditional methods of assessing prognosis should be altered. However, they added, histomorphological response might be a surrogate for nodal status and residual tumour volume, therefore presenting the option of a non-operative approach in cases where the likelihood of nodal disease is small. According to the authors, the study also raises the question that if patients have no nodal involvement, is neoadjuvant chemoradiotherapy justified at all?

■ Long-term outcomes following neoadjuvant chemoradiotherapy for esophageal cancer. JV Reynolds, C Muldoon, D Hollywood et al. *Ann Surg* May 2007, 245:707–716

Soft tissue sarcomas should be treated in fewer centres to get best outcomes

➜ Annals of Surgery

Soft tissue sarcomas – rare tumours of the connective tissue – should be treated at the few centres which see most cases, in order to give patients the best chance of good outcomes, an analysis of sarcoma management in Florida has concluded.

"STS [soft tissue sarcomas] are rare. This paucity leaves most health care institutions with low case volumes and outdated or inadequate resources, which impede the ability to offer optimal treatment of these rare and often complicated tumors," the authors explain.

Juan Gutierrez and colleagues tested the hypothesis that soft tissue sarcomas are better treated at institutions with higher volumes of cases. They used the Florida cancer data system, a prospective database of all cancer cases in the state of Florida since 1981, to identify all records of soft tissue sarcomas up to 2001. A total of 6,259 cases were extracted and, after duplicates were removed, the researchers arrived at a total of 5,564 unique cases. A final study sample of 4,205 cases was created by excluding individuals who had non-surgical treatments.

Next, the researchers looked at the medical facilities where each person's treatment was done. A total of 256 institutions in Florida performed at least one resection of a soft tissue sarcoma between 1981 and 2001; these were grouped into percentile ranges by surgical procedure volume. Of 4,673 surgical procedures recorded (including repeat procedures, which were excluded from the main analysis), seven institutions treated 1,504 cases (32.2%) and were classified as high-volume centres. The remaining two-thirds of institutions treated 3,169 cases (67.8% of the total) and were classed as low-volume. "Our analysis of 20 years' surgical management of STS in Florida…[showed that] volumes in 213 facilities amounted to less than one case per year, and less than two cases per year were managed at an additional 79 health care institutions," reported the authors.

Patients at high-volume centres were generally younger, with a higher proportion of women, were more likely to have high-grade tumours and were more likely to receive radiation therapy and chemotherapy. When the authors looked at outcomes, they found that 30-day mortality rates were twice as high in low-volume centres than in high-volume institutions; there was a similar disparity with the 90-day mortality rate. Median 5-year and 10-year survival was significantly better for patients treated at high-volume centres (40 months vs 37 months); however, survival of patients with extremity tumours was equal in the two groups of institutions. There was a slight selection bias in favour of the low-volume centres, because tumours managed at high-volume places were higher grade and larger in size. Despite this, higher-volume centres achieved superior outcomes in patients with high-grade lesions and those with tumours over 10 cm in size.

In an additional analysis, the researchers examined outcomes from treatment of extremity tumours alone to establish whether the volume of surgeries done at a centre affected the likelihood of patients keeping their limbs. A total of 1,937 extremity tumours were analysed. At high-volume centres, 90.6% of procedures for these tumours were limb-sparing operations, compared with 86.2% at low-volume centres, suggesting that physicians at low-volume centres were more likely to resort to amputation to protect the patient's survival chances.

"This analysis reveals a direct correlation between hospital surgical volume and both short-term and long-term treatment outcomes for STS. While the observations reported here require confirmation with additional independent data sets, they argue persuasively for exclusive referral of patients with STS to high-volume specialised centres for optimal treatment, survival, and functional outcomes," conclude the authors.

■ Should soft tissue sarcomas be treated at high volume centres? An analysis of 4205 patients. J Gutierrez, E Perez, F Moffat et al. *Ann Surg* June 2007, 245:952–958

Clinical trials give patients positive perceptions of care

➜ Journal of Clinical Oncology

Women with cancer who took part in a randomised controlled trial (RCT) rated the quality of care they received from their doctors higher than patients who did not take part in a trial, according to a recent paper.

A team of French researchers studied a cohort of 455 women with breast cancer, all of whom underwent the same treatment, to investigate the effect on perception of care of enrolment in clinical trials – which is often thought to improve outcomes in general, regardless of protocol. Of the 455 women, 267 had been invited to participate in a RCT (of whom 201 accepted the offer and 66 refused).

The women completed a questionnaire consisting of 60 items describing aspects of care, which they were asked to rate on a five-point scale one month and seven months after the start of chemotherapy. The researchers found that, at the beginning of chemotherapy, women who had been invited to join the RCT rated their doctors' availability and communication higher than did those who were not invited to join the trial. After the treatment, participants in the trial rated their doctors as more supportive and more informative about their illness and treatment than non-participants.

"The main explanation for the positive effects of participating in RCTs is probably that participants benefit from the effects of the informed consent process, the regular data collection process, and medical consultations required to be able to assess the efficacy and adverse effects of drugs during the follow-up period," suggest the authors.

"The standardised methods of information delivery and data collection used in RCTs could possibly be used as an example to improve the level of satisfaction among patients not participating in clinical trials."

■ Assessment of care by breast cancer patients participating or not participating in a randomized controlled trial: a report with the Patients' Committee for Clinical Trials of the Ligue nationale contre le cancer. C Julian-Reynier, J Geneve, F Dalenc et al. *J Clin Oncol* published online 29 May 2007, doi 10.1200/JCO.2006.08.9367

Premenopausal hormone-receptor-positive women can benefit from LHRH agonists

➔ The Lancet

Luteinising-hormone-releasing hormone (LHRH) agonists provide an effective additional class of agents for the treatment of premenopausal women with hormone-sensitive breast cancer, according to the results of a meta-analysis of 16 trials published in the *Lancet*.

"The meta-analysis has established that ovarian suppression is an active treatment in this setting, and one that can be regarded as a reasonable alternative to chemotherapy in women with low-risk disease," write Nicholas Wilcken and Martin Stockler (University of Sydney, Australia) in an accompanying Comment article. "In women with higher-risk disease, chemotherapy followed by tamoxifen should still be the standard approach, with the addition of an LHRH analogue a reasonable consideration for those who remain premenopausal," they suggest.

Jack Cuzick (University of London, UK) and colleagues obtained individual patient data from 11,906 premenopausal women who took part in 16 clinical trials. The researchers focused on the 9,022 hormone-receptor-positive patients followed up for a median of 6.8 years, and found that when LHRH agonists were used as the only systemic adjuvant treatment, they did not significantly reduce recurrence or death after recurrence in hormone-receptor-positive cancers.

However, addition of LHRH agonists to tamoxifen, chemotherapy or both, reduced recurrence by 13% and death after recurrence by 15%. When compared directly with adjuvant therapy, LHRH analogues were of similar benefit. In addition, the effects of the LHRH agonists were greater in younger women than in those older than 40 years.

"Our results broadly support those of the previous analyses, but also show other important details," say the authors. "Of particular importance is the benefit of LHRH agonists after chemotherapy in women younger than 40 years, but not in older premenopausal women, and the equivalence of LHRH agonists with chemotherapy in hormone-receptor-positive cancers, but not in hormone-receptor-negative ones."

■ Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. LHRH-agonists in Early Breast Cancer Overview Group. *Lancet* 19 May 2007, 369:1711–1723

Adjuvant mitotane should be used more to treat adrenocortical carcinoma

➔ New England Journal of Medicine

Adrenocortical carcinoma is a rare, highly malignant cancer that has a high risk of recurrence after radical resection, with very few patients surviving long term. But preliminary evidence from Italy and Germany suggests that adjuvant mitotane may prolong recurrence-free survival in patients with radically resected adrenocortical carcinoma.

The researchers did a retrospective analysis of 177 patients with adrenocortical cancer who had undergone radical surgery at eight centres in Italy and 47 centres in Germany between 1985 and 2005. In total, 47 Italian patients had received mitotane after radical surgery; they were compared with two separate control groups of 55 Italian patients and 75 German patients, none of whom received mitotane.

Twenty-three of the 47 patients (49%) in the mitotane group had a recurrence during a median follow-up of 57 months, compared with 50 of 55 patients (91%) in the Italian control group and 55 of 75 patients (73%) in the German control group.

Patients in the mitotane group had a median recurrence-free survival of 42 months, which was significantly longer than patients in the Italian control group (median of 10 months) and German control group (median of 25 months).

"The large number of patients in this study from a carefully collected database involving multiple institutions, along with systematic follow-up, well-matched control groups, and carefully conducted statistical analysis, makes this retrospective study credible," writes David Schteingart (University of Michigan Medical Center, USA) in an accompanying Editorial. "Although bias inherent in a retrospective study may influence the conclusions, these authors have been careful to minimise and acknowledge this problem."

Previous studies have used relatively high doses of mitotane, an adrenolytic drug with selective activity on adrenocortical cells, which

produced side-effects that were toxic enough to limit its use. However, in the current study, adverse events associated with mitotane were mainly of grade 1 or 2, using a dose of 1–5 g per day.

"Though physicians who are treating patients with adrenocortical carcinoma may continue to request randomised clinical trials concerning adjuvant therapy with mitotane, the study by Terzolo et al. provides the best evidence to date that adjuvant mitotane treatment for adrenocortical carcinoma has benefit after radical surgery, and it should make the therapeutic choice of using the drug more acceptable," says Schteingart.

■ Adjuvant mitotane treatment for adrenocortical carcinoma. M Terzolo, A Angeli, M Fassnacht et al. *N Engl J Med* 7 June 2007, 356:2372–2380

Aromatase inhibitors work best in ovarian cancers with high oestrogen receptor expression

→ Clinical Cancer Research

Endocrine therapies are effective in the treatment of adjuvant and metastatic breast cancer, but their usefulness in the treatment of ovarian cancer remains to be proven. Now, a single-arm phase II has been published that examines the efficacy of the aromatase inhibitor letrozole in patients with oestrogen-receptor-positive ovarian cancer.

The researchers, led by John Smyth (University of Edinburgh, UK), had previously done a trial of letrozole in unselected patients with relapsed ovarian cancer, and had found that patients who responded to treatment expressed more oestrogen receptors. They have now done another trial in which they recruited 44 patients with relapsed ovarian cancer whose tumours expressed oestrogen receptors with a histoscore greater than 150. All the patients received 2.5 mg/day of letrozole until the clinicians saw evidence of disease progression or of clinical or radiological progression.

Forty-two of the 44 patients were evaluable for CA125 response. Following six months of treatment, 7 (17%) of them had responded to treatment, defined as a decrease of >50% in CA125 serum concentrations, and 11 (26%) had not progressed (where progression was defined as CA125 greater than twice the upper limit of normal or greater than twice the nadir following previous chemotherapy). Thirty-three of the patients were evaluable for radiological response: 3 (9%) had a partial remission and 14 (42%) had stable disease at 12 weeks.

"The CA125 response rate increased from 9% in the initial trial of unselected patients to 17% in the present study, and the CA125 stabilisation rate at 12 weeks increased from 25% to 36%, indicating that selecting on the basis of ER [oestrogen-receptor] expression increased the likelihood of response," say the authors.

"However, in view of the fact that the time to CA125 nadir in responders was 10 to 36 weeks and that a significant proportion of patients in this study (17%) received <12 weeks of therapy, we believe that the optimal use of letrozole in ovarian cancer is earlier in the disease course," the authors add.

■ Antiestrogen therapy is active in selected ovarian cancer cases: the use of letrozole in estrogen receptor-positive patients. JF Smyth, C Gourley, G Walker et al. *Clin Cancer Res* 15 June 2007, 13:3617–3622

76-gene signature may pinpoint high-risk cases of early breast cancer

→ Clinical Cancer Research

The TRANSBIG consortium, a network for translational research set up by the Breast International Group, have independently validated a 76-gene signature that can identify breast cancer patients at high risk of early distant metastases.

Currently, patients with early breast cancer often receive chemotherapy and/or endocrine therapy, but only some of them respond to the adjuvant drugs, which can have considerable side-effects. Clinical guidelines cannot reliably identify which patients will respond best and so researchers have been using gene-expression profiling in an attempt to identify prognostic markers.

In 2005, researchers from the Erasmus Medical Centre, the Netherlands, and Veridex, a company that hopes to commercialise such a diagnostic product, described a 76-gene prognostic signature that they claimed could be used to predict the development of distant metastases within five years in patients with node-negative primary breast cancer who did not receive systemic treatment (*Lancet* 365:671–679).

To help validate this marker, the TRANSBIG consortium have done gene expression profiling of frozen samples from 198 node-negative systemically untreated patients, blinded to the patients' clinical outcome. The patients were divided into high- and low-genomic-risk groups based on the genomic signature and to high- and low-clinical-risk groups, as determined by Adjuvant! Online.

A total of 143 patients (72%) were classified into the high-genomic-risk group, whereas 152 patients (77%) were classified into the high-clinical-risk group. The risk criteria were discordant for 69 patients (35%). The proportion of patients remaining free of distant metastases at 10 years was 94% in the low-genomic-risk group and 73% in the high-genomic-risk group. Similarly, the proportion of patients who were alive at 10 years was 87% in the low-genomic-risk group and 72% in the high-genomic-risk group.

"The results of our study clearly show that the 76-gene signature remains a powerful prognostic tool even in this particular setting, where samples were provided by different institutions, the clinical data audited, the experiments done by an independent laboratory, and the data analyzed by an independent statistical office," write the authors.

■ Strong time dependence of the 76-gene prognostic signature for node-negative breast cancer patients in the TRANSBIG multicenter independent validation series. C Desmedt, F Piette, S Loi et al. *Clin Cancer Res* 1 June 2007, 13:3207–3214