NEWSROUND

Selected reports edited by Hannah Brown

Preoperative RT can reduce recurrence in rectal cancer, but has little impact on survival

→ Annals of Surgery

A short, intense course of radiotherapy given before extensive surgery for rectal cancer does not significantly improve overall survival for patients, despite decreasing the likelihood of the cancer re-emerging in the same place, according to the long-term results of a randomised controlled trial.

The trial, which was conducted by a Dutch research group, involved 1,805 patients with clinically resectable adenocarcinoma recruited from all over Europe and one centre in Canada between January 1996 and December 1999. Patients with previous treatment for rectal cancer were excluded, as were those who had had previous radiation or drug therapy to the pelvis. The patients were randomly assigned to preoperative radiotherapy followed by total mesorectal excision (TME) – an extensive surgical procedure now considered the standard of care – or to TME alone. The radiotherapy consisted of 25 Gy delivered in five fractions to the primary tumour and surrounding tissue containing lymph nodes over 5–7 days. Surgery was scheduled to take place in the week after radiotherapy. The primary aim of the trial was to assess the rate of recurrence at the original cancer site (local control), but the researchers also had secondary endpoints including recurrence at distant sites and overall and cancer-specific survival.

An analysis of outcomes was done six years after the trial closed. Median follow-up of surviving patients was 6.1 years. Among the 1,748 patients in whom a total resection had been confirmed, local recurrence risk at five years was 5.6% in the group assigned to radiotherapy before surgery and 10.9% in TME alone patients, corresponding to a reduction in relative risk of almost 50% among patients assigned to preoperative radiotherapy. Distant recurrence risk at five years was 25.8% for patients assigned to radiotherapy plus surgery and 28.3% for surgery alone. None of the subgroup analyses, which included dividing patients by the site of recurrent lesion and the tumour stage as assessed during surgery, produced significant findings that could delineate between the radiotherapy and surgery alone groups. The authors caution, however, that the subgroups were probably too small to detect any outcome differences of statistical significance.

The researchers also looked at survival. As of 1 November 2005, 748 patients had died. Of these patients, 374 (50.2%) died with recurrent disease. At five years, the overall survival rate in irradiated patients was 64.2%, which did not differ significantly from the survival rate in patients who underwent TME alone (63.5%).

The authors conclude: "In our study, increased local control in irradiated patients does not lead to a detectable improved overall survival. Although local recurrences are known to be an important cause of death, an absolute difference in local recurrence rates of 5.3% is apparently too small to have a significant impact on survival."

■ KCMJ Peeters, CAM Marijnen, ID Nagtegaal et al, for the Dutch Colorectal Cancer Group. *Ann Surg* November 2007, 246:693–701

Obesity 'dilutes' prostate cancer marker

→ JAMA

Prostate cancer may be present in obese men even if they have low concentrations of prostate specific antigen (PSA), because the large volumes of plasma associated with being overweight mean PSA is diluted more in their circulation than in normal-weight men, according to a recent study.

Several studies have already found that obese men have lower PSA concentrations than non-obese men. But the mechanism that underlies this difference is unknown. Various theories have been put forward: obese men frequently show lower androgenic activity than normal-weight men, so they may simply be producing less of the substance, even if a cancer is present. But an alternative explanation is

that the larger plasma volumes in obese men actually dilute the serum components, thereby artificially lowering serum PSA levels.

To investigate whether large plasma volumes underlie obese men's lower PSA measurements, Lionel Bañez and colleagues from across Canada and the USA examined three cohorts of men with prostate cancer and looked at the relation between body mass index (BMI), PSA measurements, and plasma volume.

The researchers identified all men who had undergone radical prostatectomy for prostate adenocarcinoma over a period ranging from the mid-1990s to 2006 from the Shared Equal Access Regional Cancer Hospital database, Duke University's Prostate Center database, and the Brady Urological Institute at Johns Hopkins Hospital. Men with lymph-node-positive disease were excluded, as were those for whom no information on BMI was available.

Preoperative BMI was calculated and the researchers made estimates of body surface area and total circulating plasma volume for all patient records, adjusting for cancer-related variables that may affect PSA concentration. In the final study population of 13,734 men, it was established that men with a BMI of 35 or greater had 21%–23% larger plasma volumes relative to normal-weight men, and had lower preoperative PSA concentrations. Men in the most obese group had 11%–21% lower serum PSA concentrations than normal-weight men, in line with the 10%–32% decreased PSA concentration seen in population-based studies of men without prostate cancer.

Next, the researchers investigated whether this finding could be explained by the fact that obese men make less PSA or whether there are alternative explanations for the lower tests of these men. Overall, the PSA mass (the amount of PSA in the blood at the time the PSA measurement is done) did not change significantly with increasing BMI, suggesting that the lower PSA measurements in obese men were a result of the diluting effect of larger plasma volumes.

However, the researchers comment that, because obesity is associated with numerous changes in hormone production and effects, it remains possible that markers for several hormone-related tumours including prostate, endometrial, and breast cancer, "may be dually affected in obese individuals by both hemodilution and altered hormonal stimulation", although they concede that "in the case of PSA, the current data suggest that hemodilution predominates and that hormonal effects are rendered negligible."

Lower PSA values among obese men may have clinical relevance because they may result in fewer obese men undergoing prostate biopsy, leading to fewer cancers detected among this group.

■ Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. LL Bañez, RJ Hamilton, AW Partin et al. *JAMA* 21 November 2007, 98:2275–2280

Chemotherapy and radiotherapy should be standard for localised Hodgkin's lymphoma

➜ New England Journal of Medicine

A combination of chemotherapy and radiotherapy, rather than radiotherapy alone, should now be considered standard treatment for all patients with localised Hodgkin's lymphoma where the tumour is situated above the diaphragm, according to the results of a randomised controlled trial. The trial results further suggest that radiotherapy need only target areas directly involved in the cancer, sparing more extensive treatment of surrounding tissue.

These findings add clarity to speculation about the appropriate treatment of this cancer, after previous results from trials done during the late 1980s and early 1990s showed that clinical staging is sufficient for stratifying early stages of the disease; that chemotherapy followed by involved-field radiotherapy (limited to the areas of cancer, rather than extensive surrounding tissue) should be the standard treatment; and that duration of chemotherapy should be adapted to the severity of the disease.

Christophe Fermé and colleagues at the EORTC and the Groupe d'Études des Lymphomes de l'Adulte initiated the trial to further elucidate treatment options that might improve event-free survival in patients with Hodgkin's lymphoma. Using a set of prognostic factors previously published by the EORTC to stratify patients by severity of disease, the researchers compared subtotal nodal radiotherapy alone with a combination of chemotherapy and radiotherapy in patients preclassified as having good or poor prognosis.

A total of 1,538 patients between the ages of 15 and 70 were enrolled in the trial. All had untreated clinical stage I or II supradiaphragmatic Hodgkin's disease and were being treated at one of 91 centres in Belgium, France, Italy, the Netherlands, Poland, Portugal, Slovenia and Spain.

Of the total patient population, 542 (35%) were categorised as having favourable prognostic factors and 996 (65%) as having unfavourable prognostic factors. Patients in the favourable prognostic factor arm were randomly assigned to receive either subtotal nodal radiotherapy or combination therapy consisting of three cycles of chemotherapy plus involved-field radiotherapy. Patients in the unfavourable prognostic factor arm were randomly assigned to one of three regimens: six or four cycles of chemotherapy plus involved-field radiotherapy or four cycles of drugs plus subtotal nodal radiotherapy.

The chemotherapy regimen used for all the groups was mechlorethamine, vincristine, procarbazine and prednisone in combination with doxorubicin, bleomycin and vinblastine. Taking event-free survival as a primary endpoint, the researchers found that, in the group with favourable prognostic features, response rates to the two treatment regimens were similar. However, among the 446 patients from both groups who had a complete remission, there was a significant difference in rates between the combination group and the radiotherapy alone group: five had a relapse after combination therapy and 61 after subtotal nodal radiotherapy. This equated to a difference in the estimated five-year event-free survival rate of 24%, favouring the combination-therapy group.

For patients with unfavourable prognostic factors, complete remission rates were 83% in the group receiving six cycles of chemotherapy plus involved-field radiotherapy, 85% in the group receiving four cycles plus involved-field

radiotherapy, and 86% in the group receiving four cycles plus subtotal nodal radiotherapy. However, there were no significant differences in the five-year event-free survival estimates or in estimated overall survival.

The researchers conclude from their findings that four courses of a doxorubicin-containing regimen and involved-field radiotherapy should be the standard treatment for this tumour type. Furthermore, they note, in patients with risk factors, four cycles of a doxorubicin-containing regimen are as effective as six cycles, and involved-field radiotherapy yields a disease control rate similar to that with subtotal nodal radiotherapy. "Our study showed that a combination of chemotherapy and radiotherapy should now be considered the standard treatment for all patients with localized stage supradiaphragmatic Hodgkin's disease and that subtotal nodal radiotherapy alone can no longer be recommended," summarise the authors. "The results of our trial show that it is possible to tailor the duration of chemotherapy according to risk factors. Moreover, our findings point to a new role for adjuvant radiotherapy with smaller radiation fields, allowing for the reduction of toxic effects associated with large fields. A remaining question now under investigation is whether patients with early-stage Hodgkin's disease can be cured with chemotherapy alone," they conclude.

■ Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. C Fermé, H Eghbali, JH Meerwaldt et al for the EORTC–GELA trial. *N Engl J Med* 8 November 2007, 357:1916–1927

Thalidomide analogue beats standard multiple myeloma treatment

➔ New England Journal of Medicine

Two clinical trials published side by side in the *New England Journal of Medicine* show that lenalidomide – an oral immunomodulatory drug that is similar to thalidomide but has a different safety profile and more potent biological activity – used in combination with dexamethasone is better than dexamethasone plus placebo for treatment for multiple myeloma.

The two trials, one from Europe and the other from North America, which together provided the evidence base for the Food and Drug Administration's 2006 approval of this combination, investigated the efficacy of lenalidomide plus dexamethasone in the treatment of relapsed or refractory multiple myeloma. In the European trial, 351 patients who had received at least one previous antimyeloma therapy were randomly assigned to receive 25 mg of oral lenalidomide (n=176) or placebo (n=175) plus a course of oral dexamethasone administered in 40 mg doses. In the American trial, 177 patients were assigned to lenalidomide and 176 to placebo, again with 40 mg of oral dexamethasone.

Time to progression was similar in the two trials, and was significantly longer in patients taking lenalidomide versus those on placebo: 11.3 vs 4.7 months and 11.1 vs 4.7 months in the European and American trials, respectively. Median overall survival times were significantly better in patients taking lenalidomide, although in the European trial the median overall survival had not yet been reached at the time of publication. In both trials, grade 3 or 4 adverse events, including neutropenia and venous thromboembolism, were more common in the lenalidomide group than in the placebo group.

The authors of both trials conclude that lenalidomide plus dexamethasone is more effective than placebo plus dexamethasone in relapsed or refractory multiple myeloma. In an accompanying comment, Alan List asserts that the duality of the actions of immunomodulatory drugs on both the malignant clone and the surrounding microenvironment set them apart from more selective drugs, and most likely account for the unanticipated breadth of activity of this class of agents. "Lenalidomide and the immunomodulatory drugs stand as prime examples of potentially dangerous chemical compounds that have been granted a second life with powerful therapeutic applicability," he says.

■ Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. M Dimopoulos, A Spencer, M Attal et al, for the Multiple Myeloma (010) Study Investigators. *N Engl J Med* 22 November 2007, 357:2123–2132

■ Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. DM Weber, C Chen, R Niesvizky et al, for the Multiple Myeloma (009) Study Investigators. *ibid*, pp 2133–2142

■ Lenalidomide – the phoenix rises. AF List. *ibid*, pp 2183–2186

Ten years' survival signals cure in colorectal cancer

➔ Journal of Clinical Oncology

Ten years of survival after resection of colorectal liver metastases can be defined as 'cure' – the time point from hepatectomy after which disease-specific death becomes an extremely rare event – according to a detailed analysis of single-institution experience with this intervention.

In 20%–35% of patients with metastatic colorectal cancer, the liver is the sole site of disease. This makes it possible to attempt curative resection, and this procedure is now considered the standard of care. Five-year survival rates of nearly 40% have been reported with this procedure, compared with a median survival of just 6–12 months in patients with potentially resectable tumours who do not have surgery, or 21 months with chemotherapy. However, these survival estimates are based on retrospective studies.

To counteract weaknesses in previously published estimates of cure-rate, James Tomlinson and colleagues report a large, single-institutional experience with at least 10 years' follow-up. Data on 612 patients who underwent resection of colorectal liver metastases at Memorial Sloan-Kettering Cancer Center in New York, from 1985 to 1994, were used. Of these patients, 132 had no evidence of disease at last follow-up, 24 were alive with disease, 466 were dead, and 73 patients were lost to follow-up.

Analysing survival data, the researchers

established that median survival was 44 months and that the survival curve reached a plateau after 10 years from the time of hepatic resection – demonstrating a minimum cure rate of 17% from this procedure.

Because the enrolled patients underwent resection of their metastases before the introduction of modern chemotherapeutic agents, this was a unique opportunity to investigate the independent therapeutic benefit of surgical resection. There were no preoperative factors that were sufficiently discriminatory to negate the potential for attaining a cure after resection. "A positive margin, however, negated the potential for long-term survival. Identification of novel predictive factors that define tumor biology associated with curable regionally confined metastases clearly is necessary in future attempts to predict outcomes in patients who present with CLM [colorectal liver metastases]," note the authors.

■ Actual 10-year survival after resection of colorectal liver metastases defines cure. JS Tomlinson, WR Jarnagin, RP DeMatteo et al. *J Clin Oncol* 10 October 2007, 25:4575–4580

New drugs can transform patients with liver metastases into surgery candidates

➜ Journal of Clinical Oncology

Patients with liver metastases from colorectal cancer who are initially assessed as being unsuitable for surgery because of the extent of their disease and unresponsiveness to standard chemotherapy can be transformed into surgical candidates after treatment with the biological agent cetuximab [Erbitux], according to a recent study.

The vast majority of colorectal cancer patients who present with liver metastases are not initially candidates for hepatic resection, either because of the distribution of tumours within the liver or because of the presence of disease in other locations. Use of chemotherapy can reduce the burden of disease to an extent where surgery is possible. However, most patients who are classed as having initially unresectable liver metastases do not respond sufficiently well to chemotherapy to become resectable – and this poor first-line response often means these patients are also unlikely to respond well to additional drug treatment.

Combining newer biological agents with cytotoxic chemotherapy might increase response rates and therefore improve resectability in patients in whom chemotherapy alone did not work. To test this idea, René Adam and colleagues chose to investigate systemic chemotherapy with cetuximab in patients unresponsive to first-line chemotherapy to convert patients to resectable status.

A total of 151 patients were switched to receive cetuximab-containing systemic therapy after becoming refractory to their first-line treatment. They were imaged with computed tomography or magnetic resonance scans of the chest, abdomen and pelvis every two months to evaluate tumour responses. Eighteen of the 151 patients (14%) met the criteria for resection of their liver metastases after treatment, although no complete clinical responses were observed. Two of the patients were found, during surgery, to have unresectable disease.

The median follow-up from the initiation of cetuximab therapy was 16.4 months (range 6–31 months). At the most recent follow-up, 25 of the treated patients were alive, including 10 patients who were free of disease. Median overall and progression-free survival from initiation of cetuximab therapy were 20 and 13 months, respectively.

"We have demonstrated the ability to convert 14% of patients from an unresectable status to a resectable situation, with a postoperative five-year survival rate of 33%," comment the authors.

■ Hepatic resection after rescue cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic therapy. R Adam, T Aloia, F Lévi et al. *J Clin Oncol* 10 October 2007, 25:4593–4602

HER2 amplification linked to survival after trastuzumab

➜ Clinical Cancer Research

Patients with locally advanced breast cancers whose tumours contain high numbers of copies of the gene for the human epidermal growth factor receptor 2 (HER2), as assessed by fluorescence in situ hybridisation (FISH), are more likely to have a complete response to treatment with an antibody to the receptor than patients with fewer copies of the gene in their tumours.

Around 20%–30% of breast tumours contain several copies of the HER2 gene, and patients affected by this genetic lesion are more likely to relapse quickly and die sooner than non-affected women. Treatment with trastuzumab (Herceptin), a recombinant monoclonal antibody against HER2, can significantly improve survival and reduce the risk of recurrence in women with various stages of HER2-positive breast cancer, but it is not clear exactly how the extent of overexpression of this gene relates to the survival benefit of treatment.

In a study to ascertain whether there is a relationship between the specific level of HER2 amplification, as assessed by FISH, and the rate of pathological complete response, 93 women diagnosed with HER2-positive locally advanced breast cancer who were treated preoperatively with a combination of trastuzumab plus chemotherapy underwent breast biopsies which were tested for HER2 expression using two methods: immunohistochemistry (IHC) and FISH. The HER2 scores obtained by FISH were subsequently compared with several variables including treatment regimen, patient age, tumour staging, and pathological complete response rates, to determine whether FISH testing could predict response to treatment more accurately than current methods.

Pathological complete response was seen significantly more frequently in high-amplification FISH tumours than in low-amplification tumours – a degree of subclassification that would not have been possible using IHC. "Therefore," the researchers conclude, "FISH may be a

more accurate HER-2 testing method to predict pathologic complete response in the neoadjuvant setting [than IHC]." This technique may also help select those patients for whom trastuzumab confers the greatest clinical benefit, they add.

■ Pathologic complete response to trastuzumab-based neoadjuvant therapy is related to the level of HER-2 amplification. L Arnould, P Arveux, J Couturier et al. *Clin Cancer Res* 1 November 2007, 13:6404–6409

Patients and physicians anxious about opioids

➜ Annals of Oncology

Patients with cancer have concerns about tolerance, addiction and side-effects that limit their uptake of opioid analgesics, according to the results of a qualitative study into patient and physician attitudes to opioids.

It has been documented that health professionals' belief in the inevitability of cancer pain, and fear of hastening death, distract them from using sufficient opioid analgesics to relieve discomfort. To examine patients' views about commencing opioids, a qualitative in-depth interview study was done, focusing on the reasons patients make their initial decision to receive or refuse opioid-based pain relief.

Participants were recruited from a pain management trial that took place in a UK oncology centre during which they were randomised to either cocodamol or the opioid oxycodone, described in the patient information sheet as being similar to morphine.

Twenty-nine patients were approached about the study and 18 took part. Of these 18, six had refused to participate in the drug comparison trial. Interviews took place within two weeks of recruitment to the trial.

Participants described their views about opioid analgesics in detail. For most of them, uncontrolled pain served as a constant reminder of their cancer and caused them to reflect on their anticipated death. Participants viewed morphine as the last resort. This association had led some of them to become frightened when morphine had been discussed in the context of the clinical trial. They anticipated the inevitable consequences of sedation and then death. Thus, pain relief was traded-off against further loss of function and hastened death, and this trade-off was only acceptable when death was imminent.

In conclusion, the authors state, "We found that patients with cancer who were offered morphine for pain relief interpreted this as a signal that their health professional thought they were dying, because opioids were interventions used only as a 'last resort'.

Because participants themselves were not ready to die, they rejected morphine and other opioids as analgesics despite the pain experienced as a consequence."

■ Opioid analgesics for cancer pain: symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. CM Reid, R Gooberman-Hill and GW Hanks. *Ann Oncol* January 2008, 19:5–7

Combined adjuvant treatment best for endometrial cancer

➜ Gynecologic Oncology

According to a retrospective analysis of patients with advanced endometrial cancer, combined adjuvant treatment involving both chemotherapy and radiotherapy gives better outcomes than when either modality is used alone after surgery.

Optimal management for advanced endometrial cancer has yet to be defined and there is an urgent need for new treatment regimens after surgery that can improve survival with acceptable toxicity. While chemotherapy is thought to control distant disease better than radiation therapy, it may not be adequate to achieve local control. Therefore, combined modality therapy with chemotherapy and radiation might give better results than either used alone. Several studies have reported improved clinical outcomes with combined modality therapy; however, there remains some uncertainty about the optimum regimen.

A multicentre retrospective analysis of patients with advanced surgically staged endometrial cancer was done to investigate this issue. Angeles Alvarez Secord and colleagues identified all patients with stage III or IV endometrial cancer who received primary surgical treatment followed by adjuvant therapy with chemotherapy, radiation therapy, or both, at Duke University and the University of North Carolina between 1975 and 2006.

In all, 356 patients with advanced surgically staged endometrial cancer were identified. Adjuvant therapy had been administered to all patients, with 48% receiving radiotherapy alone, 29% chemotherapy alone, and 23% chemotherapy plus radiation. Median follow-up time was 38 months, and 202 patients were alive at last follow-up. Of patients treated with chemotherapy alone, 63% had a documented recurrence or progression compared with 37% for those treated with radiation alone and 31% treated with combined chemotherapy and radiation. Those receiving chemotherapy alone had significantly poorer three-year overall survival and progression-free survival than those who received either radiotherapy alone or combination therapy.

"We believe our study is the largest retrospective series to date to explore the clinical outcome of patients with advanced endometrial cancer treated with adjuvant radiation, chemotherapy, or combination chemotherapy and radiation, following comprehensive surgical staging and cytoreductive surgery," note the authors. "Consistent with other studies in the literature, our findings suggest that combined multi-modality therapy with adjuvant chemotherapy and radiation may improve survival in patients with advanced stage disease compared to either modality alone."

■ The role of multi-modality adjuvant chemotherapy and radiation in women with advanced stage endometrial cancer. A Alvarez Secord, LJ Havrilesky, V Bae-Jump et al. *Gynecol Oncol* November 2007, 107:285–291