

NEWS ROUND

Selected reports edited by Hannah Brown

Chemotherapy for rare childhood brain tumours

→ [The Lancet Oncology](#)

Intensive chemotherapy can be used to delay radiotherapy in children with ependymomas, a rare type of childhood brain tumour that is usually large and difficult to remove. These cancers arise mostly in children younger than five years, so delaying or eliminating the requirement for radiation treatment to the developing brain could reduce the risk of later cognitive problems.

Adjuvant chemotherapy is usually part of the treatment schedule for patients with these tumours, due to the difficulty of complete surgical excision. However, no standard regimen is universally used. Radiotherapy is effective, but its delivery is complicated by the fact that it may cause damage that leads to lower IQ, short-term memory problems and other cognitive defects.

To study maximally intensive chemotherapy strategies that could delay radiotherapy, the United Kingdom Children's Cancer Study Group/International Society of Paediatric Oncology undertook a study in children younger than three years. Radiotherapy was reserved only for those with resistant recurrent tumours.

Eighty-nine children with ependymomas were enrolled from 21 participating centres between 1 December 1992 and 31 April 2003. All patients were first treated with surgery before being given chemotherapy, comprising

blocks of myelosuppressive treatment (carboplatin and cyclophosphamide) alternated with non-myelosuppressive treatment (cisplatin and high-dose methotrexate) at 14-day intervals.

After the treatment, 59 of the patients progressed and 37 of these subsequently died. Median time to progression was 1.6 years (range 0.1–10.2), but five-year overall survival was an encouraging 63.4%. "The median delay to radiotherapy was 20.3 months, and the median age at irradiation was 3.6 years," report the authors, adding, "The original aim of avoiding or delaying radiotherapy in these children without compromising outcome has been achieved. Our results confirm a role for primary chemotherapy in young children with intracranial ependymoma."

According to an accompanying commentary, however, these results are something of a surprise, given that other attempts at deferring radiotherapy have been less successful. What is more, the absence of data for response to chemotherapy is a major limitation in the interpretation of these promising results. "To justify the continuation of such a strategy, the study needs to prove that there are young children that will not be left with impaired neurocognitive abilities as a result of prolonged chemotherapy," the commentators write.

■ Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study. RG Grundy, SA Wilne, CL Weston et al, for the

Children's Cancer and Leukaemia Group (formerly UKCCSG) Brain Tumour Committee. *Lancet Oncol* August 2007, 8:696–705

■ Paediatric ependymomas: should we avoid radiotherapy? [Editorial] E Bouffet, U Tabori, U Bartels. *ibid* pp 665–666

■ Primary radiotherapy for childhood ependymoma? [Editorial] DA Hamstra *Lancet Oncol* September 2007, 8:758–759

Immunotherapy no better than dacarbazine in melanoma

→ [Annals of Oncology](#)

Combined immunotherapy with histamine dihydrochloride, interleukin-2 and interferon-alpha 2b offers no significant benefit in terms of survival and extent and duration of tumour response over dacarbazine treatment for patients with stage IV melanoma.

In vitro and *in vivo* studies have previously suggested that the combination of dihydrochloride and interleukin-2 is more effective at destroying malignant cells than either compound individually. What is more, clinical studies in melanoma show that cytotoxic lymphocytes are more efficiently activated by systemic treatment with the combination than with interleukin-2 monotherapy.

To test this idea further, Middleton and colleagues recruited 241 patients over 18 years old who had histologically proven stage IV melanoma with a life expectancy greater than three months from 43 centres in Australia, Canada, Germany, Israel, Sweden and the UK. Between February 1998 and October 2000, patients were stratified on the basis of liver metastases at baseline (present or absent) and then randomised to either an immunotherapy combination of dihydrochloride, interleukin-2 and interferon- α 2b or to dacarbazine. Follow-up continued until June 2002.

Although the duration of response and survival were slightly longer in the combination group than in the dacarbazine group, these differences were not statistically significant. The results for other secondary endpoints were similar between groups.

"Immunotherapy regimens may yet provide treatment alternatives for patients with stage IV melanoma, but this immunotherapeutic regimen did not improve upon the response rate and overall survival seen with dacarbazine," the authors conclude.

■ Results of a multicenter randomized study to evaluate the safety and efficacy of combined immunotherapy with interleukin-2, interferon- α 2b and histamine dihydrochloride versus dacarbazine in patients with stage IV melanoma. M Middleton, A Hauschild, D Thomson et al. *Ann Oncol* October 2007, 18:1691–1697

Radiofrequency ablation of liver metastases can extend survival

→ *Annals of Surgery*

Radiofrequency ablation – a technique that involves inserting a special needle electrode into tumours to destroy them through heat from the inside – may help improve survival for patients with liver metastases from colorectal cancer whose lesions are unresponsive to chemotherapy and too widespread for surgery, according to an observational study.

Twenty-five percent of patients who present with colorectal cancer already have liver metastases and, within five years of diagnosis, 50% of those initially lacking obvious metastases will have evidence of cancer spread. Because this distant disease is associated with poor outcomes – less than 1% of patients with untreated liver metastases will be alive four years after diagnosis – and because in many patients the only site of metastases at death is the liver, effective treatment of these lesions could have substantial implications for survival.

Allan Siperstein and colleagues from San Francisco and Cleveland investigated the potential of this treatment in patients who were not candidates for surgery and in whom chemotherapy had failed. They designed a prospective study of 234 patients (81 women and 153 men) who were prescribed radiofrequency ablation for metastatic colorectal adenocarcinoma over a 10-year period beginning in May 1997. All of the patients involved in the study had failed chemotherapy and had an average of 2.8 liver lesions.

CT scans were done before and after the procedure and the patients were assessed for their number of lesions, size and location of defects, presence of disease outside the liver, and some liver function tests. Researchers followed the progress of the patients until the study came to an end in December 2006. They noted progression of disease in the treated areas of the liver, evidence of new disease either within or outside the liver, and death. The median follow-up was 24 months and 148 patients died during the study period.

For the whole group, three- and five-year survival data showed that radiofrequency ablation produced 20.2% and 18.4% survival rates, respectively. The number of liver lesions at diagnosis was found to be statistically linked to survival. Patients presenting with between one and three lesions had a median survival of 27 months versus 17 months in those presenting with more than three lesions. Lesion size was also found to be statistically significant: lesions smaller than 3 cm were associated with a median survival of 28 months compared with 20 months for lesions greater than 3 cm. One particularly interesting

observation was the lack of a statistically significant difference in benefit from the treatment when the patients were divided up by stage of disease at presentation, leading the authors to conclude that "all patients despite initial stage derived survival benefit from RFA."

Overall, the authors say of their findings: "Previous to local therapies this subgroup of patients had virtually no survivors at five years, whereas our study demonstrates an 18.4% five-year survival rate."

■ Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. AE Siperstein, E Berber, N Ballem et al. *Ann Surg* October 2007, 246:559–567

CT versus colonoscopy for colon cancer screening

→ *New England Journal of Medicine*

Computed tomography colonography may provide a more targeted screening approach for prevention of colorectal cancer than optical colonoscopy, according to the results of a prospective study.

Researchers from the University of Wisconsin analysed the clinical databases from parallel computed tomography and colonoscopy screening programmes at a single institution, which drew participants from the same geographical region, in order to evaluate the diagnostic yield of each approach. A total of 3,120 consecutive patients who were undergoing computed tomography during a 25-month period and 3,163 consecutive patients who had colonoscopy screening during a 17-month period were included in the analysis.

The researchers also identified all pathologically proven neoplasia that were detected by each screening method from the pool of resected polyps, and compared the prevalence of high-grade dysplasia, invasive adenocarcinoma and overall advanced neoplasia in each study group.

Similar diagnostic yields and detection rates for advanced adenomas were obtained in both programmes, and there was no statistical difference between the groups in terms of the num-

ber of large or small advanced adenomas that were removed. However, the number of polypectomies performed to achieve these similar outcomes differed significantly between the two groups, with more than four times as many polyps removed in the colonoscopy group as in the computed tomography group. Serious adverse events during primary colonoscopy screening included colonic perforation in seven patients (0.2%) and, in four of these, surgical repair was required. During primary computed tomography screening, there were no perforations or other serious complications.

"The marked decrease in the use of [optical colonoscopy; OC] and total rates of polypectomies in the [computed tomography] group suggests that this technique is a safe, clinically effective, and cost-effective filter for therapeutic OC. Furthermore, by combining primary CTC [computed tomography colonography] and primary OC screening efforts, with the choice between tests driven by patient preference, the overall screening compliance for total colonic examination could substantially increase."

■ CT colonography versus colonoscopy for the detection of advanced neoplasia. DH Kim, PJ Pickhardt, AJ Taylor et al. *N Engl J Med* 4 October 2007, 357:1403–1412

Probiotics improve chemotherapy tolerability

→ *British Journal of Cancer*

Dietary supplementation with probiotic bacteria and fibre can help improve the tolerability of chemotherapy for colorectal cancer, according to a recent prospective study.

Regimens containing fluorouracil and leucovorin have long been standard adjuvant chemotherapy agents in colorectal cancer but they cause diarrhoea, which is one of the most troublesome adverse effects related to cancer chemotherapy. Excessive bowel motility may be reduced using drugs such as loperamide and somatostatin analogues, but these treatments are associated with adverse effects, so safer interventions are needed.

Some studies have suggested that administration of micro-organisms such as *Lactobacillus rhamnosus GG* with standard rehydration therapy could reduce the duration of diarrhoea by stimulation of the proliferation of bowel epithelial cells, secretion of protective mucins, and stimulation of local and systemic immune response to pathogens.

This study assessed the efficacy of *L. rhamnosus GG* and guar gum supplementation in reducing fluorouracil-based chemotherapy toxicity. The researchers also compared frequency of diarrhoea related to two different chemotherapy schedules.

A total of 150 study participants who had undergone surgery for either Dukes' B or C colorectal cancer or metastatic colorectal cancer were involved. All patients received adjuvant chemotherapy following surgery and were randomised to either the Mayo regimen (where the drugs are given in bolus injections only) or the simplified de Gramont regimen (in which bolus injections are accompanied by a 48-hour continuous infusion). *L. rhamnosus GG* was administered orally as gelatine capsules twice daily during the 24 weeks of adjuvant cancer chemotherapy, and guar gum containing nutritional supplement was administered daily, on cycle days 7–14, for eight days per month.

The simplified de Gramont regimen was found to be better tolerated than the Mayo regimen, in line with previous findings. Patients who received *Lactobacillus* during chemotherapy reported less abdominal discomfort than those who did not receive it, and these subjects had also fewer chemotherapy-dose reductions, which might have an impact on chemotherapy efficacy. Since *Lactobacillus* supplementation appears to have few or no adverse effects, the capsules are simple to administer, and they are associated with low costs, the authors conclude that "daily oral administration of *L. rhamnosus GG* may reduce the frequency of severe 5-FU-based chemotherapy related diarrhoea, whereas fibre supplementation may be of little benefit."

■ *Lactobacillus* supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. P Österlund, T Ruotsalainen, R Korpela et al. *Br J Cancer* 16 October 2007, 97:1028–1034

Prophylactic mastectomy rates increasing

→ *Journal of Clinical Oncology*

More and more women diagnosed with breast cancer are opting for surgery to remove their non-cancerous breast to cut the risk of new cancers developing, according to an analysis of the prevalence of preventive mastectomy over time.

Todd Tuttle and colleagues from the University of Minnesota used the Surveillance, Epidemiology and End Results (SEER) cancer registry public-use database to examine rates and trends of prophylactic mastectomy of the non-involved breast in women with unilateral breast cancer from 1998 through 2003.

Over the six-year study period, 152,755 women registered in the SEER database were diagnosed with unilateral breast cancer and treated with surgery. Most underwent either breast conserving surgery (57.8%) or a unilateral mastectomy (38.9%), but 4,969 underwent a contralateral prophylactic mastectomy.

Young women were more likely than older ones to opt for this procedure: 6.7% of all surgically treated patients aged 39 or younger underwent non-cancerous breast removal, as compared with only 1.3% of women in their 70s.

Lower tumour grade and negative lymph node status were associated with a significantly higher rate of contralateral mastectomy. Rates increased by 150% for all stages of breast cancer over time, and these trends continued to the end of the study period with no plateau effect.

"These findings represent a dramatic change toward more aggressive breast cancer surgery in the United States," claim the authors. "Still, the rate of BCS [breast conserving surgery] also increased during our study period. Thus, patients are increasingly choosing between minimal surgery or more aggressive surgery (bilateral mastectomy) instead of unilateral mastectomy," they report.

"The decision to undergo [contralateral prophylactic mastectomy; CPM] is complex, and many factors are likely to contribute to its increased frequency. Nevertheless, patients with

unilateral breast cancer have options that are less extreme than CPM. Surveillance with clinical breast examination, mammography, and newer imaging modalities such as breast magnetic resonance imaging may detect cancers at earlier stages... Future prospective studies are critically needed to evaluate the decision-making processes leading to CPM," they conclude.

■ Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. TM Tuttle, EB Habermann, EH Grund et al. *J Clin Oncol* published online 22 October 2007, doi: 10.1200/JCO.2007.12.3141

Radiotherapy plus tamoxifen shows mixed results in breast cancer

→ European Journal of Cancer

Adding radiotherapy to tamoxifen treatment improves outcomes 5-10 years after treatment in women with stage II breast cancer, but late side-effects of radiation mean the combination does not significantly alter the incidence of systemic disease 20 years later, according to the long-term results of a trial first initiated in 1978, when the standard treatment for breast cancer was mastectomy and postoperative radiotherapy.

The original purpose of the study, part of a breast cancer care programme in southern Sweden, was to evaluate the effect of one year of tamoxifen treatment, both as an addition to radiotherapy and an alternative.

Postmenopausal women with stage II breast cancer who were younger than 71 years and had undergone modified radical mastectomy were offered inclusion in the trial. A total of 724 patients were randomised from 1978 to 1985 and, of these, 668 were fully evaluable. Women were randomised to three treatment alternatives: postoperative radiotherapy, radiotherapy and tamoxifen for one year, and tamoxifen alone.

Radiotherapy consisted of 45 Gy to the fossae, 48 Gy to the axilla and parasternal nodes

and 38 Gy to the chest wall. All fields were treated once daily, split into two series, 12+8 fractions, with a three-week interval, commencing within four weeks after surgery. Ten milligrams of oral tamoxifen was given three times daily, starting at the same time as radiotherapy, for patients assigned to both treatments. According to the protocol from 1978, the study endpoints were time to recurrence, type of recurrence and overall survival.

For the long-term analysis, the researchers included additional endpoints of time to systemic disease, incidence of other events, and side-effects. After a median follow-up of 23 years, there was a very clear relative reduction in loco-regional recurrences of 71% for those undergoing radiotherapy, but no effect was evident in patients with no lymph-node metastases.

Radiotherapy as an adjunct to tamoxifen treatment did not significantly lower the cumulative incidence of systemic disease or survival at 20 years. However, the effect varied over the follow-up period: during the first 5-10 years, radiotherapy plus tamoxifen showed better outcomes than tamoxifen alone, but during the period 10-20 years, the survival curves merged and finally crossed over, suggesting radiotherapy influenced late mortality.

The authors speculate that modern radiotherapy techniques may decrease the associated late side-effects and conclude that, overall, the trial "strengthens the case for postmastectomy radiotherapy for breast cancer patients with 1-3 lymph node metastases."

■ Radiotherapy and tamoxifen after mastectomy in postmenopausal women – 20-year follow-up of the South Sweden Breast Cancer group randomised trial SSBCG II.I. F Killander, H Anderson, S Rydén et al. *Eur J Cancer* September 2007, 43:2100-2108

European Commission lifts threat over MRI

→ European Commission

The European Commission has proposed postponing, until 30 April 2012, the deadline for introducing legislation on workers' exposure to

electromagnetic fields. The decision lifts a threat hanging over the use of MRI in Europe and comes in response to a year of heavy lobbying by the Alliance for MRI, a coalition of European parliamentarians, patient groups, leading European scientists and the medical community.

The EU Physical Agents (EMF) Directive was intended to protect the health and safety of people working in the vicinity of strong electromagnetic fields. The unintended effect, however, would have been to effectively end the use of MRI in the diagnosis and treatment of patients and for research. The Alliance had estimated this would affect some eight million patient examinations a year, resulting in unnecessary deaths.

Vladimir Špidla, EU Commissioner for Employment, Social Affairs and Equal Opportunities, said, "The Commission remains committed to the protection of the health and safety of workers. However, it was never the intention of this Directive to impede the practice of MRI. Obviously, the Commission recognises MRI as a technology offering clear benefits to patients, and continues to support MRI research financially. Postponement of the transposition will allow time to review the current Directive and amend those provisions which have been shown to be problematic by recent scientific studies."

Gabriel Kreštin, a leading member of the Alliance for MRI and professor of radiology at the Erasmus University Medical Centre in Rotterdam, welcomed the decision. "We look forward to working with the European Commission prior to the proposal to amend the Directive," she said. "It is essential that the European Commission assesses closely the full impact the directive will have, taking into consideration the social, economic and environmental impact of the legislation. Any new legislation must be evidence-based and founded on sound science. There has been no proven harmful effect of MRI to either patients or workers over the past 25 years, during which time over 500 million examinations have been undertaken."

The Alliance for MRI has indicated that it will be seeking a derogation for MRI from the scope of the EU Physical Agents Directive to ensure the future unimpeded use of MRI, particularly for cutting-edge research and interventional MRI.