newsround

Selected reports edited by Janet Fricker

Study evaluates specificity and sensitivity of lung cancer screening

■ New England Journal of Medicine

The latest data to be published from the US National Lung Screening Trial (NLST) documents exact differences between screening with low-dose computed tomography (LDCT) and chest X-ray (CXR), providing the first thorough evaluation of risks and outcomes associated with each method.

Lung cancer represents the largest contributor to cancer mortality, with experts trying for many years to determine optimal ways to decrease death rates through more accurate and effective screening. NLST is a large-scale, longitudinal clinical trial that, between August 2002 and April 2004, randomised more than 53,400 study participants from 33 centres equally to annual screening for three years with either LDCT (n=26,722) or standard CXR (n=26,732) to evaluate whether lung cancer screening saves lives. To be eligible for the study, funded by the US National Cancer Institute, subjects needed to be asymptomatic, aged between 55 and 74 years, to have a history of at least '30 pack years' of smoking, and either to be a current smoker or to have smoked within the previous 15 years. An earlier publication from the group found that LDCT in comparison to CXR produced a relative reduction in mortality from lung cancer of 20% (95%CI 6.8–26.7, P=0.004). The current publication, describing the results of the first round of screening (first of three) and diagnostic evaluations initiated on the basis of positive findings at the screening visit, was intended to evaluate whether the reduction in mortality achieved through LDCT is worth the potential increase in morbidity.

Results show that a total of 7191 participants (27.3%) in the LDCT group and 2387 (9.2%) in the CXR group had positive screening results. In the LDCT group, 6369 participants (90.4%) had at least one follow-up diagnostic procedure compared to 2176 participants (92.7%) in the CXR group. The diagnostic procedures included imaging in 81.1% of LDCT positive patients compared to 85.6% of CXR patients and surgery in 4.2% of LDCT patients compared to 5.2% of CXR group patients.

Further results showed that stage 1 lung cancer was diagnosed in 158 LDCT participants versus 70 CXR participants and stage IIB to IV lung cancer in 120 LDCT participants versus 112 CXR participants. The sensitivity (proportions of positives correctly identified) was 93.8% for the LDCT group versus 73.4% for the CXR group; while the specificity (proportion of negatives correctly identified) was 73.5% for LDCT group versus 91.3% for the CRX group.

"As expected, more positive screening results, more diagnostic procedures, more biopsies and other invasive procedures, and more lung cancers were seen in the low-dose CT group than in the radiography group during the first screening round. In addition, more early-stage lung cancers, but similar numbers of late-stage cancers, were diagnosed in the low-dose CT group," write the authors.

In a separate press release the lead investigator Timothy Church, from the University of Minnesota School of Public Health, commented that the analysis provides clinicians with additional facts to discuss with patients who share similar characteristics as the NLST participants (current or former heavy smokers over the age of 55). "The results also caution against making blanket lung cancer screening recommendations, because each person's trade-off between the risk of having an unnecessary procedure and the fear of dying of lung cancer is uniquely individual," he adds.

■ The National Lung Screening Trial Research Team. Results of initial low dose computed tomographic screening for lung cancer. *NEJM* 23 May 2013, 368: 1980–91

Molecular tumour profiling diagnoses cancer of unknown primary

■ Journal of the National Cancer Institute

Three different approaches for evaluating molecular tumour profiling (MTP) in patients with cancer of unknown primary (CUP) find that the diagnostic accuracy ranges between 74% and 77%, reports a US study.

Approximately 20% of patients present with a tumour identified in metastatic sites. While for the majority of cases, a clinical history, physical examination, laboratory tests and histologic assessments disclose the primary site, enabling site-directed chemotherapy, in around 4% of cancer diagnoses, primary sites elude determination.

MTP offers the potential to provide a powerful diagnostic tool for identifying the

tissue of origin in patients with CUP. The clinical value of MTP, however, has been difficult to determine, because in most patients the anatomic primary site is never identified. Verification of assay results at autopsy have not proved feasible.

In the current study, Anthony Greco and colleagues, from the Sarah Cannon Cancer Center, in Nashville, Tennessee, set out to estimate the accuracy of the MTP assay in determining the tissue of origin diagnosis. Between March 2008 and January 2010, the investigators undertook a retrospective review of 171 CUP patients on whom they performed MTP using a 92-gene reverse transcription polymerase chain reaction assay capable of identifying 26 different tumour types. Two separate patient groups were considered, one consisting of 151 patients followed prospectively and a second prospective cohort of 24 patients, whose primary sites were identified during clinical follow-up.

Methods used to assess the accuracy of MTP diagnoses in CUP included evaluation of CUP patients who subsequently developed clinically detectable primary sites (latent primary sites); the comparison of specific MTP diagnoses made by immunohistochemistry (IHC) staining methods; and the combination of directed clinical/histological findings and IHC staining obtained after MTP diagnosis was available.

Results show that a single MTP diagnosis could be made in 144 of 149 patients who had adequate tumour specimens to perform the assay. Of the 24 patients who had latent primaries discovered months to years later, 18 were found to have the correct diagnosis by MTP (75%). Diagnoses made by single IHC matched MTP diagnoses in 40 out of 52 patients (77%). The concordance here was particularly noteworthy in colorectal (93%) and breast cancer (100%).

The data, conclude the authors, support the accuracy of MTP assays in CUP diagnosis. "Accurate diagnosis of the tissue of origin will provide important information to better manage all these patients and to guide appropriate therapy in the future as therapy for these tumor types improves," they add.

In an accompanying commentary, Arnold Schwartz and Noam Harpaz, from George Washington University, Washington DC, write that CUPs may be biologically different from their cognate primary tumours. "Consequently identification of primary site of CUPS may only be one component of optimal cancer management," they conclude.

■ FA Greco, W Lennington, D Spigel et al. Molecular profiling diagnosis in unknown primary cancer: accuracy and ability to complement standard pathology. *JNCI* 5 June 2013, 105:782–790

■ A Schwartz and N Harpaz. A primary approach to cancers of unknown primary. *ibid* pp 759–761

Hepatitis B virus reaction only occurs with anthracyclines

■ British Journal of Cancer

Anthracyclines are the only chemotherapy agents that result in reactivation of hepatitis B (HBV), reports a study of 1149 cancer patients from Singapore. Routine screening for hepatitis B, the authors conclude, may not be warranted for low- or moderate-risk chemotherapy regimens.

In 2008 the US Centers for Disease Control and Prevention recommended HBV screening before any form of immunosuppressive therapy including cytotoxics. While HBV reactivation is a recognised complication for patients with solid tumours undergoing cytotoxic therapy, little is known about the exact frequency of HBV reactivation and its associated risk factors. Apart from anthracyclines, the HBV reactivation risks of other commonly used chemotherapy regimens in solid tumours have not been well described.

In the current study, Soo Chin Lee and colleagues, from the National University Cancer Institute, Singapore, set out to compare HBV screening rates as well as reactivation risks in patients receiving several common chemotherapy regimens for solid tumours at a tertiary cancer centre in Singapore. Singapore is a country where HBV is known to be endemic, with a carrier rate of 6% compared to the US carrier rate of 0.3–0.5%.

The medical records of eligible patients who, between January 2007 and December 2010, had received one of six commonly used chemotherapy regimens for solid tumours were reviewed. A total of 1149 patients were identified, including 434 (38%) who received doxorubicin-based regimens, 196 (17%), who received oxaliplatin- or irinotecan-based regimens, 245 (21%) who received carboplatin/gemcitabine and 274 (24%) who received capecitabine chemotherapy. Overall the HBV screening rate was 39%.

Results showed that of the 448 patients who were screened for HBV, 30 (7%) were found to be positive for HBsAg (the hepatitis B surface antigen), and that 28 out of 30 received prophylactic antiviral therapy with no reactivation.

Out of the 1149 patients, three (0.3%) developed HBV reactivation, all of whom were breast cancer patients who originated in the unscreened doxorubicin group (3 out of 214, 1.4%). This was in comparison to 0 out of 487 (0%) of unscreened patients in the other three groups ($P<0.001$). All three patients were admitted for acute hepatitis and had HBV DNA levels $>10^8$ IU/ml at the time of admission.

"Our study showed that the overall clinically apparent HBV reactivation risk in patients with solid tumours treated with chemotherapy is low, even in an endemic region. In particular, none of the 487 unscreened patients who were treated with oxaliplatin- or irinotecan-based chemotherapy, gemcitabine/carboplatin, or single-agent capecitabine developed clinically evident HBV reactivation," write the authors.

While routine HBV screening for patients with solid tumours on high-dose glucocorticoids or high-risk anthracycline-containing regimens is supported, it may not be

necessary for the other lower-risk chemotherapy regimens, even in endemic regions like Singapore. Ideally, they add, these findings should be further evaluated and confirmed by prospective studies.

■ W Ling, P Soe, A Pang et al. Hepatitis B virus reactivation risk varies with different chemotherapy regimens commonly used in solid tumours. *Br J Cancer* 28 May 2013, 108:1931–35

Study defines most effective antibiotic for cancer patients with *Clostridium difficile*

■ Journal of Clinical Oncology

Treatment of *Clostridium difficile* associated diarrhoea (CDAD) is more effective for cancer patients with the antibiotic fidaxomicin than vancomycin.

CDAD, also known as *C difficile* infection (CDI), is an opportunistic infection that occurs mainly in hospitalised patients. A recent study showed that the incidence of CDAD among cancer patients was six-fold higher than in other hospitalised patients, and nine-fold higher for haematopoietic stem cell transplant patients. Depressed immune responses, prolonged hospitalisation, exposure to chemotherapy and repeated antibiotic treatments all contribute to their increased risk.

Over the past three decades the antibiotic treatment choices for CDAD have been metronidazole and vancomycin, but recently fidaxomicin has been approved in the US and Europe for treatment of CDAD. Little is known, however, about the treatment response of cancer patients to these drugs.

In the current *post hoc* analysis Oliver Cornely and colleagues, from University Hospital of Cologne, Germany, explored pooled data from two independent controlled trials that between them had randomly assigned 1105 patients with CDAD to 10 days of oral treatment with fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily). The first study, NCT00314951, was conducted between April 2006 and July 2008 in Canada and the US, and the second study, NCT00468728, between April 2007 and November 2009 in Canada, the US, and Europe.

The investigators defined two subgroups: 183 patients who had cancer (87 in the fidaxomicin arm and 96 in the vancomycin arm) and 922 who did not (452 in the fidaxomicin arm and 470 in the vancomycin arm).

Results showed that the clinical cure rate was 79.2% for patients with cancer compared to 88.6% for patients without cancer ($P<0.001$). The median time to resolution of diarrhoea (TTROD) was 100 hours for patients with cancer versus 55 hours for patients without cancer ($P<0.001$), and furthermore patients with cancer had a 62.3% sustained response rate at 28 days versus 70.9% for patients without cancer ($P=0.020$). Cure rates were similar for patients without cancer treated with fidaxomicin (88.5%) or vancomycin (88.7%, $P=0.913$).

But for cancer patients, fidaxomicin had an 85.1% cure rate compared to a 74% cure rate for vancomycin (OR 2.0, 95%CI 0.95–4.22, $P=0.065$). Furthermore, the median TTROD was 74 hours with fidaxomicin for cancer patients versus 123 hours with vancomycin ($P=0.045$).

"In summary, patients with cancer had significantly lower clinical cure and 28-day post-therapy sustained response rates than patients without cancer, and the differences were greater for patients treated with vancomycin than fidaxomicin," conclude the authors.

"Rapid and sustained resolution of CDAD is particularly important for patients with cancer," they add, "because diarrhea often results in dose reductions or delays of chemotherapy or radiotherapy."

■ O Cornely, M Miller, B Fantin et al. Resolution of *Clostridium difficile*-associated diarrhea in patients with cancer treated with fidaxomicin or vancomycin. *JCO* 1 July 2013, 31:2493–99

Palliative care intervention programmes enable home deaths

■ Lancet Oncology

Introducing a regional intervention programme of palliative care services significantly increased cancer-related home deaths and patient and family assessments of quality of life, a Japanese study has found. The OPTIM (Outreach Palliative Care Trial of Integrated Regional Model) study also found improved communications between healthcare professionals treating terminal patients.

While improvement of palliative care is considered an important public health issue, knowledge around how to best deliver palliative care services remains inadequate.

In the OPTIM study, between April 2008 and March 2011, Tatsuya Morita and colleagues, from Seirei Mikatahara General Hospital, Shizuoka, Japan, implemented a comprehensive programme of interventions for regional palliative care in four regions of Japan. Interventions consisted of four elements: improvement of knowledge and skills, increasing availability of specialised palliative-care services, coordination of community palliative-care resources, and provision of appropriate information about palliative care. The programme did not require any structural or financial changes for implementation. Investigators surveyed patients, bereaved family members, physicians and nurses, both before and after interventions had been introduced. Eligible patients were adults with metastatic or recurrent cancer of the lung, oesophagus, stomach, colon, rectum, pancreas, liver, biliary system, kidney, prostate, bladder, breast, ovary or uterus.

Responses from 859 patients, 1110 bereaved family members, 911 physicians, and 2378 nurses were analysed in the pre-intervention survey, and from 857 patients, 1137 bereaved family members, 706 physicians, and 2236

nurses for the survey after the interventions had been introduced.

The proportion of home deaths increased from 348 out of 5147 (6.76%) before the intervention programme to 581 of 5546 (10.48%) after the intervention programme ($P<0.0001$). Family members of patients who had died at home confirmed that they had wanted to die at home in 194 of 221 cases (87.78%).

Quality of life surveys comparing post-interventions scores with pre-interventions scores showed improvements for both patient-reported quality of life ($P=0.0027$) and family-reported quality of life ($P<0.001$).

After the introduction of interventions, physician-reported and nurse-reported difficulties decreased significantly ($P<0.0001$), with qualitative interviews showing improved communication and cooperation between healthcare professionals because of greater opportunities for interaction at various levels.

"Our study adds important insights about the comprehensive effect of regional palliative care programmes and the crucial value of communication between health-care professionals to improve palliative care at a regional level," write the authors.

The absolute number of home deaths, they add, was still low after the interventions, suggesting that some structural or financial changes are needed in the healthcare system before a further increase in the proportion of home deaths can occur.

In an accompanying commentary, Stein Kaasa, from the Norwegian University of Science and Technology, in Trondheim, Norway, writes, "Recognition of palliative care as an intrinsic part of overall cancer care is as important as improvement of symptom classification and management."

■ T Morita, M Miyashita, A Yamagishi et al. Effects of a programme of interventions on regional comprehensive palliative care for patients with cancer: a mixed methods study. *Lancet Oncol* June 2013, 14:638–646

■ S Kaasa. Integration of general oncology and palliative care. *ibid*, pp 571–572

Pregnancy does not adversely influence breast cancer survival

■ Journal of Clinical Oncology

Women with breast cancer diagnosed during pregnancy showed a similar overall survival to non-pregnant breast cancer patients, a rapid communication abstract has found.

During pregnancy breast cancer is one of the most commonly encountered malignancies, with approximately 0.2–2.6% of all breast cancers occurring in pregnant women. In the first half of the 20th century there was a general belief that breast cancer under the stimulus of pregnancy was especially aggressive and that surgical treatment was pointless and contraindicated. Since then, surgical treatment of breast cancer during pregnancy has become commonplace, and in the last decade, chemotherapeutic treatment during the second and third trimesters has been introduced and deemed not to harm the foetus. However, whether pregnancy itself negatively influences prognosis has remained a subject of debate, and there is still no comprehensive understanding of the interaction between pregnancy and breast cancer carcinogenesis.

In the current study Frédéric Amant and colleagues, from University Hospitals Leuven, Belgium, set out to determine the prognostic impact of pregnancy when breast cancer is diagnosed, and to compare survival between women with breast cancer during pregnancy and patients who were not pregnant. The study combined two international multicentre cohort studies: the German Breast Group and the International Cancer in Pregnancy study. The main analysis was performed using Cox proportional hazards regression of disease-free survival (DFS) and overall survival (OS) on exposure (pregnant or not), adjusting for age, stage, grade, hormone receptor status, human epidermal growth factor 2 status, histology, type of chemotherapy, use of trastuzumab, radiotherapy and hormone therapy. It is the largest cohort study to explore the influence on pregnancy in breast cancer to date, say the authors.

Altogether 447 women with breast cancer in pregnancy were registered, of whom 311 (69.3%) were eligible for the analysis. They were compared with 865 women with breast cancer who were not pregnant. The hazard ratio of pregnancy was 1.34 (95%CI 0.93–1.91; $P=0.14$) for DFS and 1.19 (95%CI, 0.73–1.93; $P=0.51$) for OS. The main Cox model resulted in an average predicted five-year disease-free survival probability of 65% for pregnant patients. According to the model, this would have increased to 71% if these patients had not been pregnant (but all other characteristics were identical). For OS, the average predicted five-year survival probability would have increased from 78% to 81%.

"The observation that patients with BCP [breast cancer in pregnancy] experience survival rates comparable to those of non pregnant patients is important when they are counselled. Breast cancer treatment during pregnancy does not jeopardize maternal prognosis," write the authors.

In an accompanying commentary, Richard Theriault and Jennifer Litton from the University of Texas MD Anderson Cancer Center, Houston, write, "This study provides additional comfort for women and physicians who must care for the pregnant patient with breast cancer. The cancer can be treated, the pregnancy can be maintained, labor and delivery can be successful, and the outcome for mother and neonate can be expected to be favorable."

■ F Amant, G von Minckwitz, S Han et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. *JCO* doi:10.1200/JCO.2012.45.6335

■ R Theriault and J Litton. Pregnancy during or after breast cancer diagnosis: what do we know and what do we need to know? *ibid* doi:10.1200/JCO.2013.49.7347