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Editorial Comment

Use of imaging to detect recurrent cancer: How far should we go?

S.J. Gwyther *

East Surrey Healthcare NHS Trust, Redhill, Canada Avenue, RH1 5RH, Surrey, UK

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The early detection of recurrent cancer is important because alternative treatments can be offered and may lead to improved patient survival and quality of life. However, the patients generally undergoing additional imaging procedures, either in the clinical setting or in the context of a clinical trial, already have metastatic disease and the aim is to determine whether the disease is responding to or progressing on current treatment. For those patients progressing on conventional treatments, a Phase II or III clinical trial offers the opportunity to receive experimental new agents, singly or as combination therapy. In these trials, the protocol typically requires the patient to be imaged in a reproducible and consistent manner, usually by computed tomography (CT) or magnetic resonance imaging (MRI), every two courses during treatment and undergo further imaging beyond that time.

What about those patients with early disease, who have undergone primary treatment, are not receiving any current treatment, have no evidence of detectable disease and are attending the follow-up clinic? These patients may have been cured, or may have microscopic, undetectable disease, which may recur at some stage. How should these patients be followed and to what degree should investigations be instituted to try and detect early recurrent disease? Moreover, does it matter if the disease is detected earlier, or is it simply introducing a lead-time bias? What role should radiology (or medical imaging) play in this group of patients with no apparent evidence of recurrent disease?

Most plain X-ray imaging in the follow-up of patients with the common cancers is in the form of plain frontal chest radiographs (CXR). The use of the CXR in the follow-up of breast cancer patients has been the subject of most publications. The majority of studies undertake are retrospective and have looked at the incidence of detection and the cost-effectiveness of performing CXR on all patients routinely attending the follow-up clinic. In patients with stage I breast cancer, one paper [1] followed 263 patients and detected 10 cases of recurrence, but 6 of these were symptomatic. Despite further treatment, all 6 died between 1 and 15 months after detection. Only 4 cases were detected in asymptomatic patients and 3 of them died between 17 and 30 months after treatment, the fourth patient was still alive 14 months after treatment. Despite the apparent increase in survival in these 4 asymptomatic patients, Vestergaard concluded that CXR was not warranted in patients attending the follow-up clinic, because to detect each asymptomatic case, 400 examinations were necessary. Most patients with recurrent disease present with symptoms and is there any point in treating asymptomatic patients with breast cancer? Another study compared outcomes of patients with early stage breast cancer, who attended follow-up, with and without symptoms and found there was no difference in survival for the two groups, when survival was calculated from the time of primary treatment rather than the time of detection of intra-thoracic metastases [2]. The patients were well matched for age and additional recurrences in the asymptomatic group were detected approximately one year earlier than those in the symptomatic group, but there was no correlation between prognosis and death and earliness of detection of recurrent disease. Other studies have found similar results [3,4].

In this issue of the Journal, Jarvenpaa *et al.* [5] prospectively studied whether there, was any difference in the detection of disease or overall patient outcome depending on who read the plain radiograph – the radiologist or oncologist. All patients with histologically-proven cancer who had undergone primary treatment,

* Tel.: +44-1-737-768511; fax: +44-1-737-780395
E-mail address: gwythersj@aol.com (S.J. Gwyther).

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with no evidence of further disease, were entered into this study, with the exception of patients with testicular cancer. Breast cancer was the commonest cancer, accounting for approximately 60% of the cases. Patients were randomised either to be reviewed in the clinic by the oncologist with plain radiographs, (not just CXR, but any relevant plain films, although 85% were CXR) or to have the plain films additionally reviewed and reported on by a radiologist. Patients were followed for 5 years or until recurrence. Of the 869 patients, 227 recurrences were detected, 55 on plain radiographs, although nearly half (43%) were suspected on clinical examination. How many of the others were detected by the oncologist, rather than the radiologist was not stated but this study suggests that a radiological opinion on plain radiograph is not that important in patients attending the follow-up clinic for various cancers. Moreover, there was no difference in overall survival between the two groups, which is in keeping with most other studies.

The most important factor seems to be whether the patient is symptomatic or not. If they are, the oncologist is in the best position to request further investigations, as appropriate, because he has the X-ray and clinical details. The radiologist usually does not have the benefit of the current clinical details, but most experienced radiologists know the patterns of recurrence for various cancers and can accurately report on detectable, recurrent disease. Although, straightforward and inexpensive, plain radiographs are not very sensitive. To detect bony metastases on plain radiographs, between 50% and 70% of the bone has to be lost before it is visible as a lytic lesion. Similarly, intra-thoracic lesions on CXR need to be approximately 1 cm before they are reliably detected, although they can often be seen in previous examinations when they were smaller if these films are viewed retrospectively. Many lesions occur in the ''hidden'' areas of the chest radiograph, behind the cardiac contour, at the apices or behind the diaphragm, where they cannot easily be seen. Radiographic factors such as film ''penetration'' and processing also affect the ease with which lesions are detected.

In Jarvenpaa *et al.* study, over 34% of all imaging examinations were ''special'' examinations, meaning mammography, ultrasound, CT and MRI, but the authors do not state whether these were the first imaging examinations at follow-up or whether these investigations were instituted as a result of initial plain films or on clinical grounds. Mammography is routinely undertaken annually to determine recurrent or new disease and the films are read by and reported by the radiologist. The follow-up of patients with colorectal cancer is more controversial. Some investigators follow-up early stage patients with clinical examination alone, whilst others take a more aggressive stance and perform CT scans of the thorax, abdomen and pelvis at 6 monthly intervals for 3 years, followed by annual examinations thereafter, to try and detect solitary metastases, or localised disease in the lung or liver.

The possibility of detecting early recurrence and achieving a potential cure is attractive, but has to be weighed against the high radiation dose such examinations inevitably produce. It has been estimated that diagnostic X-rays contribute approximately 14% of all total worldwide radiation exposure [6], although organ-specific radiation doses for CT scans are much higher than plain films. In fact, risk models including Japanese atomic bomb survivors suggest that, CT scans repeated at relatively short time intervals may well induce new cancers in their own right [7]. This is of particular concern in younger patients who will potentially undergo many more examinations. Moreover, these models probably underestimate the incidence of new cancers in a population undergoing repeated CT examinations, as the data are based on the 'average' population. It has been estimated the risk of inducing cancer is approximately 50 cancers per millisieverts (mSv) of effective dose per million people exposed. To put this in context, the effective dose for a CXR is 0.05 mSv and for a CT scan of the thorax is 7.0 mSv [8].

There are some situations where more complex imaging is required. The follow-up of patients with lymphoma poses a different problem. Once the baseline, pre-treatment studies have been performed, there is little need to perform imaging in an asymptomatic patient, but at the end of treatment a residual, para-aortic mass may remain. CT is the usual imaging modality and demonstrates an anatomically, abnormal mass, but, unfortunately, gives no clue as to whether the mass contains active disease or residual scar tissue. In such circumstances, functional imaging is necessary. Positron emission tomography (PET) scanning, using 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) demonstrates increased glycolysis in residual, active disease and so determines whether further treatment is required. In one study of 37 patients with an abnormal para-aortic residual mass, FDG PET scans showed abnormal activity in 13 patients and all went on to relapse, whereas in the 24 patients with no abnormal activity, only one relapsed [9]. The explanation for this one patient in the latter group relapsing is that either there was so little disease present at the time of performing the scan that it was too small to be detected, or that the metabolic activity was not increased and so could not be detected.

In the last 10 years, there have been significant developments in the imaging modalities used to detect and stage cancer at diagnosis and recurrence. For example, when PET is added to CT scanning in lung cancer patients at the initial diagnosis, with a higher stage is advanced disease often detected. This leads to more accurate staging of the patients and prevents unnecessary operations in approximately 20% of those thought to be operable by conventional anatomical (CT) imag-

ing [10]. The same is true for recurrent disease in colorectal cancer patients. Detection of early recurrence in these patients may allow potential resection and cure. However, the addition of PET to the anatomical imaging procedures has shown more extensive and inoperable disease can exist in a further 25% of patients who were thought to be eligible for potentially curable resections following CT and MRI imaging [11].

The emphasises the importance of selecting tumour types such as colorectal cancer and lymphoma where early recurrent disease is detectable by imaging before clinical symptoms occur and in whom a potential cure is realistic. In these patients, "special" imaging, such as CT and PET may be beneficial, despite the potential risk of inducing new cancers, particularly in the young. Even by reducing the radiation dose, with low-dose CT examinations, the radiation dose is substantial. Thus, it is likely that only specific high-risk patient subsets will be selected and followed in this way.

How best to investigate and image the subset of patients with early disease who return to the clinic for "routine" follow-up and who are asymptomatic remains controversial. The tumour type and initial staging at diagnosis are crucial factors. After primary treatment for apparent early breast cancer, the patient is either cured or has undetectable, microscopic disease, so there is little indication for performing any form of routine imaging, with the exception of mammography. More complex imaging modalities are usually reserved for the detection of recurrent disease in symptomatic patients, or in small subsets at high-risk, where potential cure is realistic.

The introduction of multi-disciplinary meetings is a relatively new concept. Although, newly-diagnosed and staged patients are generally discussed, it is an ideal forum in which to discuss clinical problems and decide which investigations are most appropriate in suspected recurrent disease and how best to manage individual patients. However, this necessarily implies a high degree of suspicion for recurrent disease and it is likely this is based on clinical findings and symptoms rather than the result of performing plain X-rays. For the most part, the asymptomatic patient with early stage disease still deserves to be investigated to a lesser rather than a greater degree, unless there are specific concerns or that patient is at a high risk of recurrence. In this case, discussion at multi-disciplinary meetings enables a management plan to be instituted and relevant investigations to be undertaken.

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