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Double-reading of plain radiographs – no benefit with regard to earliness of diagnosis of cancer recurrence: a randomised follow-up study

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Abstract

The aim of this study was to estimate the effect of the radiologist's interpretation of plain radiographs on the earliness of diagnosis of cancer recurrences. Data consisted of patients who had undergone primary treatment and were resident in the Tampere University Hospital Area in Finland during 1991–1997. Consecutive patients were randomised in a double-reading arm (an oncologist and a radiologist independently interpreting radiographs), and in a single-reading arm (interpretation by an oncologist only; if necessary, a radiologist's clinical report was obtained following a separate request). The time of diagnosis of recurrence and death were estimated by the cumulative probabilities of actuarial method with the Wilcoxon (Gehan) test. There were 869 eligible participants, mostly breast cancer patients ($n = 516$). In total, 227 recurrences were diagnosed, and of these 55 on plain radiographs, which is 24.2% of the total number of recurrences. There was no statistically significant difference between the arms in the number of recurrences ($P = 0.85$) or in the time of detecting the recurrence ($P = 0.64$). Altogether, 225 (25.9%) died from cancer and 38 (4.4%) from other causes. There was no statistically significant difference ($P = 0.34$) in survival between the two arms during the follow-up to 5 years. Double-reading of plain radiographs does not offer any extra benefit for the detection of recurrences or for patient's survival compared with single-reading.

Keywords: Cancer recurrence; Survival; Plain radiograph; Interpretation; Randomised study

1. Introduction

Radiological examinations (plain radiographs and specific examinations) have traditionally been part of the overall monitoring of cancer. Plain radiography has been used routinely in follow-up. Despite new radiological techniques, plain radiography continues to be primary in examining the lungs and the skeleton. According to the literature, the significance of plain radiographs alone in the follow-up of cancer and especially for the detection of recurrence is limited [1–7]. The significance of the interpreter of plain radiography has not attracted scientific interest.

In Finland, there is no clear, common and harmonised procedures for interpreting plain radiographs of cancer patients' lungs and skeleton. It is usual for the oncologist and radiologist to view the plain films separately, with the oncologist later receiving the radiologist's report. In addition to radiographs of the lungs, skeletal radiographs are taken as required. The accuracy of the interpretation of the films by the oncologist or radiologist is not known and in part is related to what information is available to the interpreter, in addition to their skill and experience.

To the best of our knowledge, the effect of the radiologist's interpretation of plain radiographs on the

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earliness of diagnosis of recurrence has not been assessed. This study aimed to ascertain the effect of the radiologist's clinical report in interpreting plain radiographs on the earliness of detection of recurrences. The study was based on a randomised, prospective diagnostic design that was specifically conceived for this purpose.

2. Patients and methods

All consecutive cancer patients during the period 1.11.1991–31.5.1995 at the Department of Oncology in Tampere University Hospital were included the trial. All had microscopically confirmed new cancer. The participants were randomised into this study subsequent to primary treatment. Patients with testis cancer were excluded, as well as patients whose follow-up was arranged by other centres. Eligible patients were randomly allocated into two arms, a double-reading arm with a radiologist and an oncologist independently interpreting the plain radiographs, and a single-reading arm with an oncologist interpreting routinely and a radiologist only upon specific request by the oncologist.

The oncologist interpreted the radiographs while the patient was present and had all of the available patient data. The radiologist had only the referral data and the radiographs, according to normal clinical practice.

The total number of randomised patients was 1115. The basis for randomisation was the date of birth recorded in the patient's personal identity number. Patients born on odd-numbered days were allocated to the double-reading arm and those born on even-numbered days to the single-reading arm. The randomisation criteria was not revealed to the clinicians during the study.

Radiological follow-up comprised of plain radiographs of the lungs and skeleton, and specific examinations, such as computerised tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), mammography, and other examinations, all of which were performed and interpreted by a radiologist, at either specifically scheduled or spontaneous outpatient visits. Randomisation had no effect on these other examinations. Clinical follow-up with these examinations was determined by the oncologist and was independent of the research arm to which the patient randomised.

The patients participated in the study after randomisation until the end of follow-up, i.e., either death, moving outside the hospital area, transfer to another hospital for follow-up, or until 31.12.1997. If a recurrence was found, it was confirmed with plain radiographs or an examination, and by the oncologist. Cumulative recurrence and survival probabilities were calculated by the actuarial method. Differences between the cumulative curves were tested using Wilcoxon (Gehan) statistics. Differences in the distributions of background variables by randomised arm were tested using the χ^2 test. The level for statistical significance was set at $P < 0.05$.

The study was approved by the Ethical Committee of Tampere University Hospital.

3. Results

The distribution of rates of response to primary treatment was similar in both arms ($P = 0.40$). Altogether, 1115 patients were randomised and the final study analysis included 869 patients. In total, 246 patients were excluded from the study due to randomisation errors. The most common reason for exclusion was an erroneous randomisation time (randomised before the end of primary treatment or after the first follow-up visit) which occurred in 122 (10.9%) cases. There were 82 patients transferring to follow-up after residual, not primary, treatment and these subjects were therefore excluded. In addition, 15 patients without microscopic confirmation of cancer were excluded. Fourteen patients were randomised, although they were transferred to follow-up elsewhere. Two patients in the double-reading arm died before the first follow-up visit. Ten patients were excluded, because their clinical reports on plain radiographs were issued erroneously without request. One patient with cancer of the testes was excluded due to his cancer type. Altogether, 132 of these patients should have been included in the research, 66 in each arm.

Of the 869 patients included, 452 (52.0%) were randomly allocated to the double-reading arm and 417 (48.0%) to the single-reading arm (Fig. 1). The difference was not statistically significant after allowing for the larger number of odd days in a year. There were 657 (75.6%) women and 212 men (24.4%) in the whole data (Table 1). No statistically significant difference was noted between the arms in the proportions of women and men ($P = 0.29$). Breast cancer was the most common cancer (59.4%) both in the material as a whole and in the respective research arms (Table 2). This also explains the larger proportion of women in the dataset.

The average age of the patients was 58.7 years (range 21–94 years); in the double-reading arm 59.0 years and in the single-reading arm 58.3 years.

The cancer diagnosis was confirmed histologically in 96.7% of cases and by cytology in the remainder.

The number of local tumours was greater in the single-reading arm (247; 66.2%) than in the double-reading arm, where it was 237 (59.1%) ($P = 0.04$). Patients with lymphoma had mainly (70.5%) stages I–II tumours in each arm.

Surgery was the most common single mode of treatment and surgery with radiation the most common combination treatment in both arms (Table 2). The

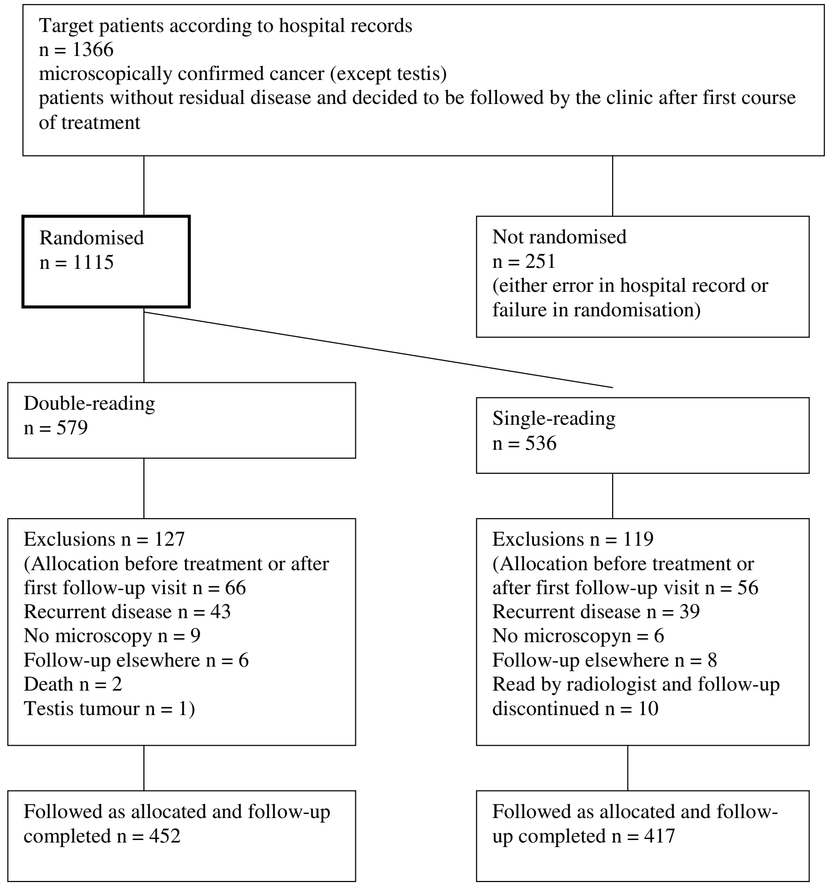

Fig. 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomised controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–9.)

Table 1
Number of patients and percentage distribution by anthropometric characteristics and research arm, all patients in Tampere randomised follow-up trial in 1991–1997

	Double-reading arm		Single-reading arm	
	n	(%)	*n*	(%)
Gender				
Male	117	(25.9)	95	(22.8)
Female	335	(74.1)	322	(77.2)
Age (years)				
54	167	(37.0)	160	(38.4)
55–64	114	(25.2)	105	(25.2)
65–74	104	(23.0)	119	(28.5)
75	67	(14.8)	33	(7.9)
All patients	452	(100.0)	417	(100.0)

disease remained metastatic in 93 patients, so there were 776 patients with the possibility of recurrence.

The total number of radiological examinations in the whole study was 6636 during the five follow-up years. In the double-reading arm, 66.0% were plain radiographs and in the single-reading arm 65.1%. The numbers of visits and plain radiographs were fairly similar in both arms (Table 3). Chest radiographs were the most common plain film examination in each arm (86.0% and 84.3%, respectively). Of all radiological examinations, 2285 (34.4 %) were specific examinations (see Methods); in the double-reading arm 34.0% and 34.9% in the single-reading arm (Table 4).

A recurrence was diagnosed in 227 patients, that is 29.3% of those who had recovered after primary treatment. In the double-reading arm, there were 114 recurrences (28.6%) and in the single-reading arm 113 (29.9%). The number of recurrences was highest in the first follow-up year in both arms (Fig. 2). The number of recurrences at different metastatic sites did not differ significantly between the arms ($P = 0.64$). Almost half of the recurrences (98 (43.2%)) were found at the clinical examination.

During the 5 years' follow-up, 55 recurrences were found in plain radiographs without any differences between the arms being observed ($P = 0.85$). In the double-reading arm, plain radiography served to detect one recurrence per 15 patients. This was one per 134 outpatient visits, and one per 82 plain radiographs. In the single-reading arm, one recurrence was found per 14 patients, which was one per 122 outpatient visits, and one per 77 radiographs. Distant metastases were

Table 2
Number of patients and percentage distribution by characteristics of disease and research arm, all patients in Tampere randomised follow-up trial in 1991–1997

	Double-reading arm		Single-reading arm	
	n	(%)	*n*	(%)
Confirmation				
Histologically	436	(96.5)	404	(96.9)
Cytologically	16	(3.5)	13	(3.1)
Stage of disease[a]				
Local	237	(59.1)	247	(66.2)
Non-local	164	(40.9)	126	(33.8)
Primary site				
Breast	267	(59.1)	249	(59.7)
Lung	59	(13.1)	47	(11.3)
Lymphoma	51	(11.3)	44	(10.6)
Skin	43	(9.5)	45	(10.8)
Thyroid	16	(3.5)	16	(3.8)
Other	16	(3.5)	16	(3.8)
Treatment				
Surgery	105	(23.2)	116	(27.9)
Surgery and radiotherapy	122	(27.0)	121	(29.0)
Surgery, radiotherapy and/or medical treatment	159	(35.2)	123	(29.5)
Radiotherapy and/or medical treatment	60	(13.3)	56	(13.4)
No treatment	6	(1.3)	1	(0.2)
All patients	452	(100.0)	417	(100.0)

tr., treatment.
[a] Some data are missing in this category.

Table 3
Number of patients, visits and plain radiographs before recurrence by research arm in Tampere randomised follow-up trial in 1991–1997

	Double-reading arm	Single-reading arm
Patients	398	378
Visits	3630	3425
Plain radiographs	2207	2144

Only patients with complete response to primary treatment.

Table 4
Number and percentage distribution of specific examinations in Tampere randomised follow-up trial in 1991–1997

	Double-reading arm		Single-reading arm	
	n	(%)	*n*	(%)
Mammography	389	(34.2)	387	(33.7)
Breast ultrasound	207	(18.1)	208	(18.2)
Other ultrasound	381	(33.5)	387	(33.7)
CT	82	(7.2)	78	(6.8)
MRI	11	(1.1)	12	(1.0)
Other	67	(5.9)	76	(6.6)
Total	1137	(100.0)	1148	(100.0)

Only patients with complete response to the primary treatment by research arm.

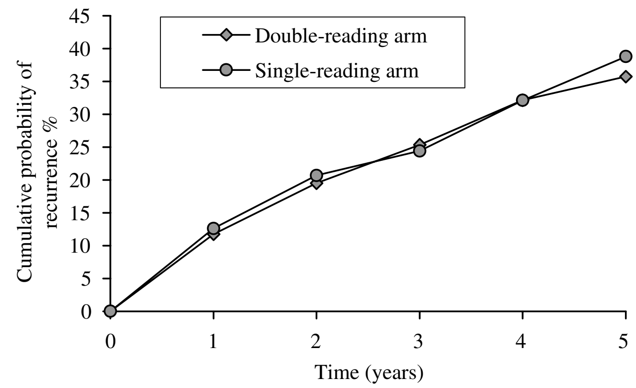

Fig. 2. Cumulative probability (%) of recurrence of cancer in patients in Tampere randomised follow-up trial in 1991–1997. Only patients with complete response to primary treatment.

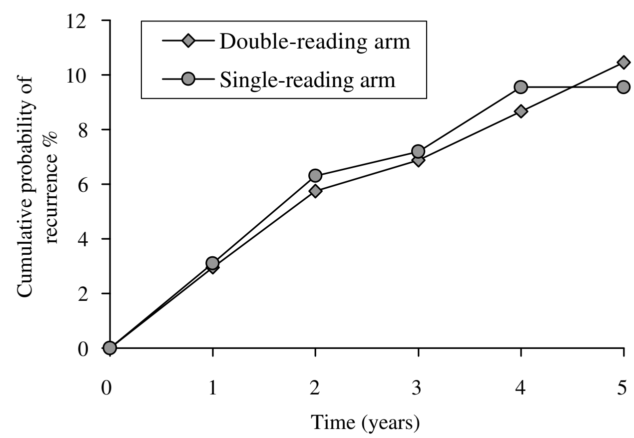

Fig. 3. Cumulative probability (%) of recurrence of cancer found in plain radiography in patients in Tampere randomised follow-up trial in 1991–1997. Only patients with complete response to primary treatment.

observed in 40 cases, 74.1% of all recurrences in the double-reading arm and 71.4% in the single-reading arm. The median time elapsing before recurrence was 1 year 4 months and 4 days in the double-reading arm (range 4 months and 18 days–4 years 10 months and 29 days) and 1 year 3 months and 29 days in the single-reading arm (range 6 months 7 days–4 years and 2 days), with no statistically significant differences ($P = 0.98$). There was also no statistically significant difference ($P = 0.70$) in the cumulative probability of recurrence, which gives an overall indication of no difference in the earliness of diagnosis between the two arms (Fig. 3). As the distribution of different cancer types was similar in both arms (Table 2), a single combined elapsed time was used, instead of distinguishing between the different tumours.

Altogether, 225 (25.9%) patients died from their cancer during the study period, 38 (4.4%) from other causes. Of patients in whom recurrence or a new cancer occurred, 129 (52.4%) died of their disease, 62 (50.0%) in

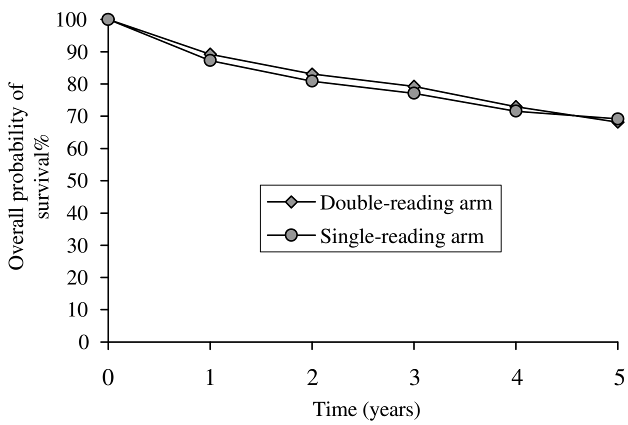

Fig. 4. Cumulative cancer specific survival probability (%) in Tampere randomised follow-up trial in 1991–1997. All patients.

the double-reading arm and 67 (54.9%) in the single-reading arm. Among the entire dataset ($n = 869$), no difference was found in survival between the two randomised arms during the follow-up ($P = 0.34$) (Fig. 4).

In the single-reading arm, a clinical report was requested for 44.4% of all plain radiographs in the arm before recurrence and for 60.1% after recurrence.

4. Discussion

Follow-up radiological examinations comprise plain radiographs of the lungs and skeleton and specific examinations, including clinical reports. On each occasion, selection of plain radiography depends largely on the patient's overall condition and the amenability of the disease to treatment.

The significance of plain radiographs in the detection of recurrences of various cancers has been questioned [1,3–12]. In earlier studies, most of which have been non-experimental and retrospective, patient numbers have varied greatly. Only two prospective, randomised studies could be found dealing with the importance of radiographs in the follow-up of breast cancer patients [13,14]. However, neither of these addressed the importance of the radiologist. Most earlier survival studies have been non-randomised [1,4,9,11,15–17] or their outcome has been ambiguous [4,9,11,17]. Most of them have included breast cancer patient's, with a few studying other primaries such as melanoma [4]. Prospective studies on the effect of radiological examinations or the effectiveness of interpretations of plain radiographs are lacking. There are studies that compare radiological examinations made by non-radiologists and radiologists, but they have analysed statistical and economical aspects, as well as the quality of radiographs and not the accuracy of interpretation and its effect on patients' treatment [18–20].

This present study is the largest to be carried out at a single hospital, and one of the few from which comparability in giving clinical reports has been conferred by randomisation. Randomisation was performed during normal routine practice without dedicated personnel, and therefore it was not possible to completely avoid errors in the randomisation process.

Randomisation divided the patients into two comparable arms with an equal distribution of prognostic factors.

Blinding was complete at the first follow-up visit, but at subsequent visits it was, in principle, possible for the oncologist to find out which arm the patient was in. In reality, the blinding worked well during the whole study, because the oncologists continued to make requests also on the radiographs of the double-reading arm. Such a request was unnecessary if they knew the arm because the radiographs and clinical reports were routinely sent to the oncologist in the double-reading arm. The total number of oncologists in the study was 28. In the study the current, existing practice, i.e., double-reading, was compared with a new method, i.e., single-reading, that could be followed in real clinical practice. In both cases, the oncologist is the first to interpret the radiographs.

There were more local cancers in the single-reading arm, but the difference was not discernible by the response to treatment. This, if anything, would imply an earlier diagnosis of cancer recurrence in the double-reading arm.

In this randomised trial, we found no effect of the radiologist's interpretation compared with that of the oncologist's on the earliness of diagnosis of cancer recurrence. The oncologist interpreting plain radiographs has knowledge of the patient's symptoms and results of other examinations.

The only information available to the radiologist when interpreting the radiographs is the referral data, that is probably written at the previous outpatient visit. The detection of new findings is thus made on a quite different basis when compared with the oncologist is interpretation, who has all the case notes available to him/her. The significance of plain radiographs in finding recurrences is limited; according to the literature most recurrences are detected by history and physical examination [1–7]. In the single-reading arm, there were 35% more requests for a radiologist's clinical report after recurrence than before recurrence. However, the situation after recurrence is very different when compared with the non-recurrent phase. The patient may have symptoms and in any case a dissemination of cancer for which there is greater need to ascertain the response to treatment and the negative effects through the radiologist's assessment than to assess plain radiographs of the non-recurrent phase. An equal number of examinations were made in both arms, all of which were interpreted by a radiologist. The data in our study is from period 1991 to 1997, when the CT and MRI capacity of the Tampere University Hospital was limited. Therefore, these examinations consisted mostly of mammographs and ultrasound reading. Today, CT and MRI are much more widely used. However, our data show that the differences in other diagnostic activities could not compensate for the differences in the reading of plain radiographs, because all examinations were interpreted by a radiologist, regardless of the arm, and the number of examinations was the same in both arms.

There was no difference in the cumulative probabilities of recurrence by follow-up time; this constitutes the main indication of the earliness of diagnosis. According to the literature, history and physical examination have revealed as many as half of all recurring breast cancers [2,17,21–25]. The findings in this study indicate that by clinical examination alone 43% of recurrences were detected. Whatever the reason, we would conclude that double-reading of plain radiographs does not expedite the detection of recurrence, nor does double-reading reveal more recurrences of the disease compared with single-reading. Double-reading did not appear either to offer any clear benefit with regard to the patient's survival compared with single-reading.

Judging from the findings reported here, the contribution of the radiologist could be focused on the interpretation of radiological examinations in the primary diagnosis of cancer, specific radiological examinations, consultation over plain radiographs during follow-up and the meetings between radiologists and oncologists. This would save resources and optimise the use of the radiologist's skills. The radiologist's contribution would be important in uncertain cases, supporting and assisting the oncologist in the decision-making process in follow-up period.

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