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Surgery for Cancer in the Elderly

I.S. Fentiman

ICRF Clinical Oncology Unit, Guy's Hospital, St. Thomas' Street, London SE1 9RT, U.K.

The major risk factor for most common solid tumours is increased age. By the year 2000, approximately half the population in Europe will be over 60 years of age and 70% of cancers will be diagnosed in this patient group. Because older patients were excluded from randomised clinical trials until recently, optimal treatments have not yet been tested in this population. Although screening for cancer in a high-risk group is logical, elderly patients are not offered routine mammographic screening in countries with national breast cancer screening programmes. Problems of compliance can be overcome, and detection of early disease may lead not only to humanitarian improvements, but to economic savings as well. The role of screening in other common cancers, such as prostate cancer, remains to be determined. There are many misconceptions about the role of surgery in older patients; these relate to the biology of cancer, life expectancy in older individuals, the safety of general anaesthesia, and the risks of major surgery. Generally, cancer is not less aggressive in older individuals. If they receive inadequate treatment, most patients will live long enough to have a relapse. They may then die prematurely from metastatic malignancy. Modern anaesthesia has reduced the risks of major surgery and operations performed by experienced surgeons are associated with low operative mortality and a high rate of tumour control. Recent controlled trials of elderly patients with operable breast cancer have demonstrated the importance of local cancer control and the increased relapse rate and mortality in patients receiving suboptimal surgical treatment. © **1997 Published by Elsevier Science Ltd**

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INTRODUCTION

THE FACT that the incidence of cancer rises with age has been thoroughly documented [1]. In the countries of Europe, with their aging populations, the public health and human problem of cancer in older persons will become increasingly urgent in the early years of the 21st century. Unfortunately, screening, diagnosis, and surgical treatment of cancer have usually been less than optimal in elderly patients. This paper discusses why these deficiencies have occurred and how they can be remedied.

EPIDEMIOLOGY

Of the 10 solid tumours that occur most often in males and females, more than 50% are diagnosed in persons over 70 years of age [2]. Since the overall life span of the population is increasing and age is the major risk factor for malignancy, the problem of cancer in the elderly is now assuming greater importance and raising a number of questions about management approaches. Unfortunately, owing to diagnostic delays, a greater proportion of older patients present with advanced stage tumours than do younger patients. A recent study of worldwide trends in cancer mortality in the elderly showed a heterogeneous pattern in different countries and between sexes [1]. In general, mortality rates were lower in females. Although there was a steady or downward trend for overall cancer mortality, there was a rise in lung and other tobacco-related malignancies.

CANCER SCREENING

For patients with a variety of solid tumours, there is evidence that the earlier the diagnosis is made, the greater the probability of cure [1]. The best way to make an early diagnosis is to screen for malignancy, thus making it possible to carry out treatment before the patient is symptomatic. Since the major risk factor for solid tumours is increasing age, it would seem logical to screen the elderly for cancer and possibly remove one source of morbidity and mortality in older individuals (Table 1).

Breast and cervical cancers are the only solid tumours for which mortality has been clearly reduced as a result of screening. However, in the U.K. where mammographic screening is available on a national basis, it is offered only to

Table 1. Major opportunities for reducing cancer morbidity and mortality in older persons

Include patients over the age of 65 years in breast cancer screening programmes
Expand educational programmes so that older patients are more aware of their cancer risks and more likely to undergo screening
Encourage practices that encourage early diagnosis of cancer, such as regular physical examinations and breast self-examination
Discontinue the practice of undertreating cancer in older patients
Discontinue the use of inappropriate therapies in older patients
Include older patients in randomised clinical trials

women aged 50–64 years. Since approximately 50% of cases occur in women who are 65 years or older, this approach misses a substantial proportion of those at risk [2]. The arguments for not screening older women are that they will not comply with invitations to undergo mammography and that, because of comorbidity and a different pattern of tumour behaviour, no benefit would be detectable. However, these assertions are not borne out by available evidence [1].

In a pilot study carried out in a group general practice in Manchester, U.K. 631 women aged 65–79 years were invited to attend mammographic screening and 344 (61%) accepted the offer [3]. Among women aged 50–64 years, 77% went for screening, with a detection rate of 4 cancers per 1000 women screened. In the older group, the detection rate was 12 per 1000.

Despite these positive results, it is clear that public education about cancer is still lacking. A British charity, Age Concern, commissioned a survey of over 1000 women aged 65 years or older [4]. This survey revealed that 36% of these women did not consider themselves to be at increased risk for breast cancer and 28% thought they had no risk. Only 45% had ever had a mammogram and 75% had not requested screening since reaching the age of 65 years.

Screening for prostate cancer has been compared unfavourably with mammographic screening [5]. The available screening techniques are digital rectal examination and the measurement of prostate-specific antigen (PSA) levels. Unfortunately, neither technique meets required standards of sensitivity, specificity, or acceptability. Many older men have histological evidence of prostate cancer that does not lead to clinical disease. Furthermore, the available surgical technique, radical prostatectomy, has not been confirmed to improve survival, and carries a high morbidity in terms of incontinence and impotence.

HISTOLOGY AND AGE

Histological reports of 1869 consecutive Guy's Hospital patients with breast cancer were reviewed to examine age-related histological features [6]. The patients were divided into four groups: 148 patients aged 39 years or under, 355 aged 40–49 years, 984 aged 50–69 years and 382 aged 70 years or older. There was a significant increase in grade III infiltrating ductal carcinoma among those aged $\leq$39 years. On the other hand, lobular, mucoid, and intracystic papillary carcinomas were reported more frequently in the oldest group.

There was also significantly less axillary lymph node metastases, vascular invasion, and lymphoplasmacytic stromal reaction with increasing age, although these latter two findings were not independent of tumour grade. These data suggest that there may be age-related changes in the histology of breast cancer and, in some cases, less aggressive features in elderly patients. However, they also suggest that treatment should be based on histological prognostic features of the primary tumour, rather than age alone.

Table 2. Predictors of an early cancer stage at presentation among patients with various types of cancers in New Mexico [8]

Older age*
Regular medical check-ups
Higher educational level
Greater knowledge of cancer
Breast self-examination (in patients with breast cancer)

*In another study conducted in New Mexico, older patients presented at a more advanced stage than younger patients [7].

STAGE AT PRESENTATION

Evidence from a statewide investigation in New Mexico involving a variety of primary tumours showed that elderly patients presented at a more advanced stage than younger patients [7]. A subsequent study, in which 800 patients over the age of 65 years were interviewed, examined factors responsible for diagnostic delay [8]. There was a direct relationship between length of delay and higher stage at time of diagnosis among patients with breast cancer, but not among patients with other types of tumours. The practice of breast self-examination also was predictive of an earlier stage at diagnosis in patients with breast cancer (Table 2).

For the entire group of patients, including those with colorectal, breast, thyroid, uterine, cervical, thyroid, and buccal cancers, predictors of early stage were older age, regular medical check-ups, educational level, and greater knowledge of cancer. The finding in this study that older patients were more likely than younger patients to have more localised tumours might be spurious because of understaging in the older group.

UNDERTREATMENT OF CANCER

Various studies from different countries have shown a consistently different pattern of treatment of cancer in elderly patients. In the National Hospice Study from the U.S.A., a mortality sample of 1891 cases, with cancers of the breast, uterus, and prostate, showed that older patients were more likely to develop metastatic disease and less likely to have received chemotherapy or radiotherapy than younger patients [9]. A Dutch study examined therapies for breast cancer in 611 cases treated at The Netherlands Cancer Institute and found that patients over the age of 75 were less likely to have received radiotherapy and more likely to have had primary hormonal therapy alone for early-stage disease [10]. There was significantly shorter disease-specific survival in those over 74 years of age.

In an Italian study of 1724 breast cancer patients treated at 63 general hospitals, quality of care was rated using a

diagnostic and therapeutic scale that was based on previously agreed-upon criteria [11]. Approximately one-third of surgical procedures were deemed inappropriate, with one-quarter of patients with stage I/II disease receiving a Halsted mastectomy. The major determinant of egregious therapy was chronological age. Older patients were understaged and less likely to receive conservation therapy, irrespective of their overall health status.

RANDOMISED TRIALS

Until recently, it was standard policy in European Organization for Research and Treatment of Cancer (EORTC) trials to exclude patients over the age of 65 years or in some instances, over the age of 70 years. The primary rationale for this approach was the desire to reduce non-cancer deaths that might compromise the evaluation of potential new therapies. As a result, no guidelines for optimal treatment in older patients have been available, and this omission may have contributed to the problem of undertreatment in this age group. Presently, this policy no longer applies and the decision is made, by protocol, to exclude elderly patients only if the investigative treatment demands it. A retrospective study of single agent phase II trials in the treatment of advanced solid tumours conducted by the EORTC examined the extent to which elderly patients (≥ 65 years old) were enrolled in these trials, and whether advanced age was associated with increased drug toxicity [12]. Of 2344 patients enroled in 16 trials, 22% were 65 years or older, and 8% were 70 years or above. There was no significant difference in response rates between older and younger patients, nor was there evidence of increased drug toxicity in the elderly group. There was an increased rate of treatment discontinuation for the older patients because of treatment refusal and loss to follow-up.

Results are now available from prospective randomised trials examining the treatment of elderly women with operable breast cancer (Table 3). Such studies were performed as a result of evidence that breast conservation treatment was as effective as mastectomy and because uncontrolled studies had suggested that tamoxifen might be an alternative to mastectomy in older women [13–15].

Several European groups, mainly British, conducted a variety of clinical trials, all of which compared the therapeutic benefit of tamoxifen with that of some type of surgery in elderly women with operable disease. The first published trial was conducted at St. George's Hospital, London, and initially included 116 patients [16]. Results were reported after a median follow-up of 3 years, when both relapse-free and overall survival were similar in both groups. The investigators concluded that tamoxifen was equally effective as surgery. The study was criticised because the surgery was not standardised [17]. For patients with smaller cancers, total mastectomy was performed in 18% and wide excision in 82% of patients whereas, for those with larger tumours, total mastectomy was carried out in 67% and wide excision in 33% of patients.

An update of this study has shown that at a median follow-up of 6 years, in 100 patients treated with tamoxifen and 100 with surgery, local relapse or progression occurred in 56% of patients in the tamoxifen group and only 44% of the surgery group [18]. There was no significant difference in time to progression in either treatment group at a mean follow-up of 6 years. Thirty-nine patients in the tamoxifen group who experienced progression of disease or recurrence after regression chose to crossover to undergo surgery. Of those 39 patients, 21 treated with surgery did not experience a recurrence of their disease; overall, of patients originally treated with tamoxifen, 60% remained disease-free, a rate similar to that of those originally randomised to surgery (56%) [18].

Another randomised trial was conducted at City Hospital, Nottingham, U.K. [19]. Patients were treated with either tamoxifen 40 mg daily or by wedge mastectomy. The surgical procedure consisted of a subtotal mastectomy, without axillary dissection. The trial included 135 patients, 68 treated with tamoxifen and 67 by wedge mastectomy. At a median follow-up of 24 months, 47% of the tamoxifen group were alive without recurrence, compared with 70% of the wedge mastectomy group. Mortality rates for the two groups were similar: 11% versus 15%. After a mean follow-up of 65 months, there was a statistically significant increase ($P < 0.0001$) in the failure rate for local control in the tamoxifen arm; 59% of patients developed local relapse or progression, compared with 30% of patients in the wedge mastectomy group [20]. Mortality rates for the two groups were 41% in the tamoxifen group and 42% in the mastectomy group.

Table 3. Breast cancer clinical trials comparing the use of tamoxifen with surgery in elderly patients

Study site or sponsor	Total number of patients	Treatments	Results
St. George's Hospital, London [16]	116	Tamoxifen versus surgery	At a median follow-up of 3 years, relapse-free and overall survival were similar in the two groups
St. George's Hospital, London [18] (continuation of previous study)	200	Tamoxifen versus surgery	At a median follow-up of 6 years, local relapse or progression occurred in 56% of the tamoxifen group and 44% of the surgery group; rates similar in both groups after tamoxifen progression or relapse crossed over to surgery
City Hospital, Nottingham [19, 20]	135	Tamoxifen versus wedge mastectomy	At a median follow-up of 2 years, 47% of the tamoxifen group and 70% of the mastctomy group were alive without recurrence; at a mean follow-up of 65 months, 59% of the tamoxifen group and 30% of the mastectomy group had a local relapse or disease progression; mortality was similar for the two groups
Cancer Research Campaign [21]	446	Tamoxifen versus tamoxifen + optimal surgery	At a mean follow-up of 41 months, a change of management was needed in 21% of the surgery group and 46% of the tamoxifen group; 29% of tamoxifen patients and 21% of surgically-treated patients had died

The Cancer Research Campaign (CRC) conducted a British multicentre trial in which both arms received tamoxifen, one as sole treatment and the other in combination with optimal surgery, which varied from wide excision to modified radical mastectomy [21]. At a mean follow-up of 41 months, 446 patients were available for assessment. A change of management was necessary in 44/212 (21%) of the tamoxifen-plus-surgery group and 101/222 (46%) of the tamoxifen-only group. Furthermore, significantly more ($P = 0.046$) patients on the tamoxifen-only arm than on the tamoxifen-plus-surgery arm had died (29% versus 21%).

The EORTC Breast Cancer Cooperative Group has conducted two parallel trials of elderly women with operable breast cancer. In EORTC 10850, patients were treated with either local excision and tamoxifen or modified radical mastectomy. In EORTC 10851, the therapeutic options were tamoxifen alone or modified radical mastectomy. It was decided to run two trials because of differing philosophies concerning the management of breast cancer in elderly patients. EORTC 10850 was intended to test the value of removing the primary tumour and then using tamoxifen as adjuvant therapy in the hope of preventing relapse within the breast and inhibiting the progression of axillary lymph node metastases when present. In contrast, the objective of EORTC 10851 was to determine whether patients could be treated without surgery or admission to hospital. The analysis of these trials, as well as the quality-of-life study, are ongoing.

CONCLUSION

At last it is possible to base treatment of older patients on results from controlled clinical trials. These studies have shown the benefits of good local control, which may affect not only the quality of life but also the quantity of life in older women. Use of suboptimal treatments may place older patients at increased risk of dying from breast cancer. It is essential that upper age limits be removed from the majority of clinical trials so that the best surgical treatments for cancer in patients of all ages can be determined.

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