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Selection of Patients may Limit the Generalizability of Results from Cancer Trials

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Despite the development of apparently effective curative strategies according to results from clinical trials, survival rates for major cancer types have improved only slowly during recent years. Patient selection is discussed as an important reason for this observation. From 1989 to 1995 the Norwegian Radium Hospital entered 85 patients in an international multicentre trial assessing cisplatin-based neoadjuvant chemotherapy in T2-T4a bladder cancer. Forty-three eligible patients, among whom there were 36 non-consenting patients, and 106 ineligible patients received comparable local treatment outside the trial. The 3-year overall survival rates for the above three groups were 62%, 58%, and 31%, respectively ($p < 0.001$). Differences in overall as well as cancer-specific survival could be demonstrated, even after adjustment for prognostic factors. There was a significant difference in overall survival ($p = 0.01$) between the 85 trial patients and the 36 eligible patients who refused trial inclusion. Results and treatment recommendations from a trial can be transferred to daily practice only if eligibility criteria and selection of patients are taken into account. By registering patients undergoing comparable treatment outside a trial, the overall applicability of the treatment in question can be assessed.

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In clinical oncology, a large multicentre randomized trial is regarded as the best method for comparing the efficacy of two or more management systems. If the trial is well designed, randomization will ensure internal validity. Every expert is of course aware that trial results should only be extrapolated to patients fulfilling the eligibility criteria of the trial. However, in daily oncological practice, and sometimes because of the demands of individual patients, clinicians may feel encouraged and urged to follow emerging treatment recommendations, which strictly speaking, are valid only for patients eligible for the trial. Thus, the original eligibility criteria of the trial could easily be neglected, and the risk of treatment failure and major complications subsequently increased.

The impact of the trial results on clinical practice and the overall importance of observations gained during the study depend on the generalizability of the experimental conditions among the entire population of patients with the disease in question. Generalizability may be reduced if a large number of patients seen in daily practice are ineligible, or if many eligible patients are not entered in the study (1). Eligible patients may refuse to be randomized because they prefer one therapy to another, or the physician may omit randomization because of some treatment preference. This is sometimes referred to as non-consent bias (1). Often the number of patients included in a randomized trial is thus only a limited proportion of eligible patients (2–8). They represent an even smaller fraction of all available patients with comparable disease seen during daily practice and who receive therapy principally identical with the trial's control arm, being the current standard treatment. In this situation generalization of the final trial results and of any important observations about toxicity becomes questionable (9). However, when reporting results of a clinical study, the exclusion and outcome of non-entered patients with the same treatment as those in the trial are rarely considered.

An assessment of the generalizability of trial results may primarily be achieved by comparing the patients included in the trial with those patients who met the eligibility criteria, but were not randomized (3, 10). Secondarily, it may be of interest to know what proportion of all available patients with the malignancy studied was in fact eligible for the trial. It is often stated that patients enrolled in a trial have a more favourable outcome than those not included, irrespective of the specific treatment that is evaluated (1, 11, 12). Even though trial patients and non-trial patients receive the same standard treatment, differences in outcome are observed. However, the reasons for such variations are only rarely discussed in detail, and few

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clinical trial reports include information on non-randomized patients.

For some tumour types, as for breast (13) or colon cancer (14), benefit from adjuvant strategies has been demonstrated in large trials and/or by meta-analyses and subsequent standard treatment has been based on these favourable study results. A more general application of these adjuvant therapies has been possible even in patients not fulfilling the eligibility criteria of the trials. The reason is that the recommended treatment (anti-oestrogens for breast cancer, modulated 5-FU regimens for colon cancer, short-term preoperative radiotherapy for rectal cancer) displays a broad therapeutic ratio, without major risk of toxicity. However, before a more toxic treatment, possibly effective in a clinical trial, can be safely adopted as 'standard therapy' in general oncological practice, one has to consider to what degree the eligibility criteria for the trial patients comply with those relevant for patients seen during daily clinical work. There are reasons to believe that this basic rule is frequently neglected in routine oncological practice.

The aim of the present study was to exemplify these considerations and to demonstrate the potential limits of generalizability of observations in the International Bladder Cancer Trial on neoadjuvant chemotherapy (15). The survival rate of trial patients was compared with that of non-participants, comprising eligible, but non-randomized patients as well as ineligible patients registered during the same period. All patients underwent the same curatively intended local treatment, either cystectomy or high-dose radiotherapy, which are the standard treatments for this condition.

MATERIAL AND METHODS

The Norwegian Radium Hospital (NRH) serves as a referral cancer centre for bladder cancer patients from a geographically defined area in southern Norway, with a population of 1.8 million inhabitants. However, patients referred to the NRH are only those who are thought likely to benefit from radiotherapy and/or chemotherapy in combination with surgery. In 1985 about 50% of all patients with muscle-invasive bladder cancer diagnosed in the region during one year were referred to the hospital for combined modality treatment, the selection of patients depending on the decision made by the local referring urologist. (16).

Patients

In 1989 clinicians at the NRH agreed to participate in the International Bladder Cancer Trial, which assessed the role of neoadjuvant CMV (cisplatin, methotrexate, vinblastine) chemotherapy for muscle-invasive bladder cancer (15). At the same time, it was decided that the reason for non-participation should prospectively be registered for all non-included patients with operable muscle-invasive bladder cancer seen at the Department of Oncology during the trial period.

All referred patients with non-metastatic muscle-invasive bladder cancer underwent the same diagnostic work-up. In all patients, muscle infiltration was confirmed histologically in the pretreatment biopsy, and all patients underwent clinical T-categorization (17) that remained unchanged based on subsequent results from imaging by CT, if done. Routine haematological and biochemical investigations comprised haemoglobin, blood serum count, thrombocytes, alkaline phosphatase and serum creatinine. Bone scans were performed in the case of clinical suspicion of skeletal spread or increased serum alkaline phosphatases. Pelvic CT was routinely done only in patients who were to receive definitive radiotherapy.

Treatment principles

In all patients of T2-T4A N0/NX M0 category the primary local treatment consisted of total cystectomy or definitive radiotherapy to the bladder (18, 19), cystectomy being the primary 'treatment of choice'. All patients in whom cystectomy was planned underwent preoperative pelvic radiotherapy to anterior–posterior pelvic fields (4 Gy × 5 given during one week), followed by the operation within 7 days after discontinuation of preoperative radiotherapy. The surgical technique was the same as that described for the neoadjuvant chemotherapy trial (15). In patients with locally operable tumours, definitive radiotherapy was used only exceptionally, usually if the patient refused cystectomy or in patients whose general condition or co-morbidity did not allow major surgery. As in the International trial, the target volume comprised the bladder only, with a 2-cm large safety margin. A daily dose of 2 Gy was given, 5 times per week, the target dose being 60 Gy. All radiotherapy was given at the NRH, whereas total cystectomy was performed either at the NRH, or at a local hospital by the referring urologist. The neoadjuvant chemotherapy consisted of three 3-weekly CMV cycles (day 1: methotrexate 30 mg/m^2, vinblastine 4 mg/m^2; day 2: cisplatin 100 mg/m^2; day 8: methotrexate 30 mg/m^2, vinblastine 4 mg/m^2) with toxicity-related dose modifications.

Follow-up

All patients were seen at the NRH 3 months after treatment. Thereafter, individual follow-up schedules were designed at 6–12 month intervals, either at the NRH or at the local referral hospital. Salvage cystectomy was considered in irradiated patients who developed an operable bladder recurrence, but this was done only in exceptional cases.

Trial inclusion

Whenever a patient's TNM category had been determined, inclusion in the International Trial was considered as the

first priority. The reason for final non-inclusion was documented in the medical record and by a specific register, kept along with the register for trial patients. Patients above the age of 75 years were a priori considered ineligible. The Regional Ethics Committee approved the trial, and all patients included gave their written informed consent to participate.

Statistical analysis

The primary endpoint of the present analysis was overall survival. Patients were followed from their first visit to the NRH (inclusion of eligible patients in the trial) until death or 1 June 2000. Overall and cancer-specific survival rates were estimated by the Kaplan–Meier method and analysed using the log-rank test. Cox's proportional hazards model was used to adjust the comparison of groups for known prognostic factors. All analyses were performed by the 'intention to treat' principle and stratified by primary treatment (radiotherapy or cystectomy). In the International Trial the increase in 3-year overall survival with neoadjuvant chemotherapy was estimated to 5.5% (CI −0.5%, 11%) only. Chemotherapy (yes or no) was nevertheless included as a covariate in the present analyses. Demographic variables were compared between groups by the χ^2 test and one-way ANOVA, as appropriate.

RESULTS

From December 1989 to May 1995 a total of 234 patients with operable muscle-invasive bladder cancer patients were seen (Table 1). Among these, 85 patients entered the trial (group I), whereas 36 eligible patients refused inclusion in the trial, as they did not accept the experimental chemotherapy. These 36 patients were grouped along with 6 eligible patients in whom the oncologist in charge decided that neoadjuvant chemotherapy should be given, and with one eligible patient who was not included in the trial as a result of doctor's error (group II). Trial patients were significantly younger and had a better performance status than eligible, non-randomized patients. Group III comprised 106 patients whose bladder tumour was judged to be technically operable by cystectomy, but who were deemed to be ineligible for the trial, usually owing to higher age or significant co-morbidity. Ineligible patients were thus older than eligible patients, their performance status was poor, and they had higher levels of serum creatinine. No association with gender or T-category was demonstrated. Ineligible patients were more often treated by radiotherapy only, as their co-morbidity frequently did not allow major surgery (Table 2). Of the 36 patients refusing to participate, 29 had a cystectomy whereas 7 were given radiotherapy as primary treatment.

Table 1

Demographics

	Trial	Non-trial		Total
	Group I	Eligible Group II	Ineligible Group III	
Number	85 (36%)	43 (18%)	106 (45%)	234
Age	62 ± 8.4	67 ± 7.7	73 ± 5.9	68 + 8.8
Males/Females	74/11	32/11	83/23	189/45
Performance status				
0	69 (81%)	28 (65%)	62 (59%)	159
1	16	15	39	70
2	–	–	5	5
Known co-morbidity				
No	39 (46%)	21 (49%)	17 (16%)	77
Cardiovasc/pulm	24	12	60	96
Renal	–	1	2	3
Other	22	9	27	58
T category				
T2	31 (36%)	16 (37%)	37 (35%)	84
T3	47	25	63	135
T4a	7	2	6	15
Creatinine (μmol/l)	90 ± 15	89 ± 22	120 ± 44	103 ± 35
Haemoglobin (g/dl)	13.4 ± 1.9	13.4 ± 1.6	12.8 ± 1.8	13.1 ± 1.8
Reason for non-inclusion				
Refusal		36		
Chemotherapy wanted		6		
Doctor's error		1		
High age			30	
Renal insufficiency			46	
Cardiovasc/pulm			10	
Performance status			5	
Other			15	

Table 2

Treatment and outcome

	Trial	Non-trial		Total
		Eligible	Ineligible	
No. of patients	85	43	106	234
Planned treatment				
Cystectomy	69	33	43	145
Radiotherapy	16	10	63	89
Chemotherapy	36	6	1	43
Estimated 3-year overall survival (%) and 95% confidence interval	62 [52, 73]	58 [43, 73]	31 [22, 40]	47 [41, 54]

The 3-year overall survival for all 234 patients was 47% (Table 2). In Fig. 1A and B it is shown that overall and cancer-specific survival differed between the three groups ($p < 0.001$), as might be expected. A pairwise analysis confirmed that ineligible patients had a shorter survival time than the other two groups, whereas there was no significant difference between trial patients and other eligible patients. The hazard ratio for patients included in the study relative to those who were ineligible was 0.38 (overall survival). Similar results were obtained when analysing disease-free survival (data not shown). Even when including treatment (chemotherapy or not) and important prognostic factors (T-category, performance status, and age) in a Cox proportional hazards model stratified by primary treatment, a difference in overall and cancer-specific survival between the three groups of patients could be demonstrated. The hazard ratio between included patients and ineligible patients was now 0.63, still demonstrating a statistically significant difference. No significant interaction between trial participation and chemotherapy treatment was found.

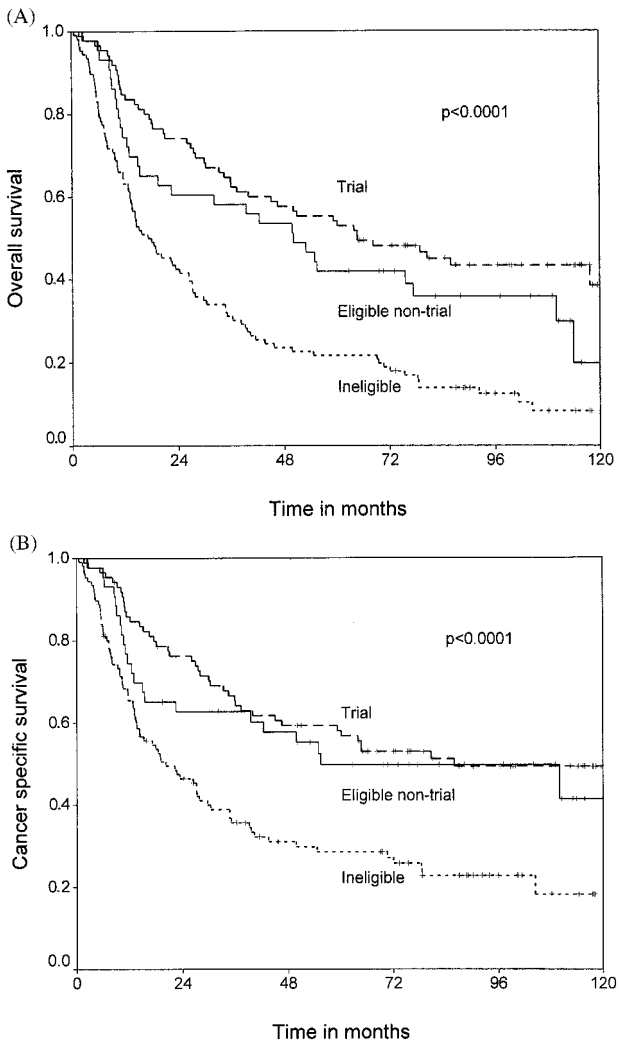

Fig. 1. Overall (A) and cancer-specific (B) survival by patient group. The dashed line represents trial patients (n = 85), the solid line eligible non-randomized patients (n = 43), and the dotted line ineligible patients (n = 106).

A comparison between the 85 trial patients and the 36 patients who refused to participate in the trial is presented in Fig. 2. A statistically significant difference in overall survival was demonstrated ($p = 0.014$). No significant difference in cancer-specific survival was found ($p = 0.134$). Patients refusing to participate were older than trial patients (mean 68 vs. 62 years), which may be the main explanation for the survival difference observed.

DISCUSSION

The primary aim of the International Bladder Cancer Trial (15) was to evaluate the efficacy of neoadjuvant chemotherapy on overall survival. The trial was powered to document a 10% difference in overall survival between the trial arms, should it exist. The estimated improvement was only 5.5%, but as the 95% confidence interval was estimated to -0.5% to 11%, a 10% increase in survival could not be excluded. The trial's 3-year overall survival was 53%. The 3-year overall survival of trial patients at NRH was 62%, and the overall survival of all patients seen at the hospital was 47%, which is in agreement with other published series considering total cystectomy or definitive

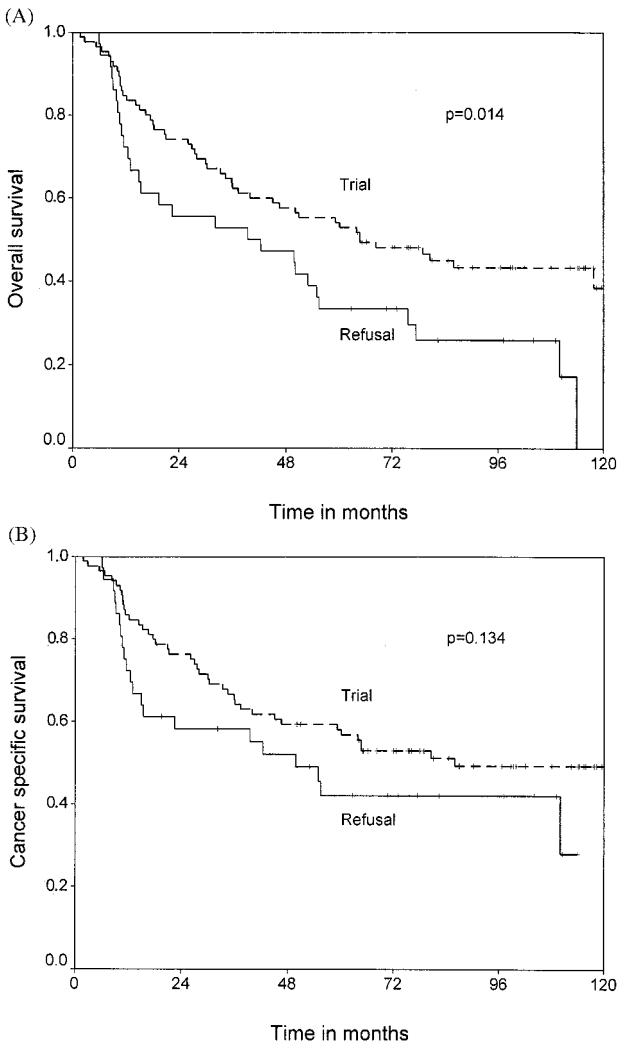

Fig. 2. Overall (A) and cancer-specific (B) survival by consent. The dashed line represents trial patients (n = 85) and the solid line patients who refused to be randomized (n = 36).

radiotherapy as curative treatment (18–24). This figure seems to have remained relatively unchanged during the past decade.

Although not formally statistically significant, the above result may lead some clinicians to consider CMV as standard treatment in patients with T2–T4A bladder cancer. The question, then, is how relevant the results of the trial would be to patients seen in their practice. An important factor that determines the answer to this question is whether patients entered in the trial are representative of those seen in the community. Generalization of trial results may be particularly suspect when only a small proportion of eligible patients are accrued (8). Another important aspect is tolerability to the experimental treatment which may differ between trial patients and patients in the community.

To evaluate external validity, it would have been of interest to compare the chemotherapy effect between trial and non-trial patients. However, no formally significant effect of chemotherapy was found in the multicentre trial, and the number of patients at the NRH was too small to properly assess a possible difference in the effect of neoadjuvant therapy. Thus, we were unable to demonstrate that ineligible patients might not derive the same survival benefit from neoadjuvant chemotherapy as the trial patients. It can therefore not be precluded that ineligible patients may experience the same (small) benefit as trial patients. Nevertheless, as non-included patients were older and more likely to have reduced kidney function, it seems fair to assume that the potential survival benefit would be reduced because of the increased toxicity of cisplatin-based chemotherapy necessitating major close reductions.

Chemotherapy-related toxicity was described as 'acceptable' (15). The toxicity of neoadjuvant CMV chemotherapy was, however, by no means insignificant in the International Bladder Cancer Trial. Toxicity-related dose reductions of cisplatin and methotrexate had to be made in 20% of the patients, though they had a normal kidney function at trial entry. Inspection of the reasons for excluding our patients from the trial indicates that CMV chemotherapy would have been dangerous and even intolerable for most of them.

If the number of patients eligible for a certain trial greatly exceeds the number of ineligible patients, any beneficial results of the experimental treatment will certainly influence the future standard therapy of the cancer type in question. Perhaps of more relevance to assessing generalizability of trial results is the accrual of a reasonably large proportion of eligible patients. In the Swedish Rectal Cancer Trial, 52% of eligible patients were included (25). Both overall and cancer-specific survival in the group of non-randomized eligible patients was comparable to survival in the trial's control arm. This indicates that the data from the trial are representative of the entire Swedish population of patients with rectal cancer.

Our experience of patients with bladder cancer differs from that of the Swedish Rectal Cancer Trial. Fifty-five percent of the patients with local curatively intended treatment seen at the NRH were eligible for the trial, and of these eligible patients, 66% were included. This group had a significantly better overall survival than that of eligible patients who refused to participate. Trial patients are thus probably not representative of the whole population of eligible patients. Non-participants were older than trial patients and this may explain their poorer outcome. The group of ineligible patients had shorter overall survival, as would be expected.

A difference in survival rate between ineligible patients and the two groups of eligible patients was observed even when adjusting for treatment and known prognostic factors. Differences in follow-up routines and secondary treatments might partly explain this. Trial patients usually have more frequent specialist follow-up visits than those not included in a trial and may develop a more obligatory

doctor–patient relationship. This might secondarily result in improved quality of cancer-related and non-cancer-related healthcare, even when treatment becomes mainly palliative. These results could be taken to support the general oncological view that cancer patients should be included in trials as often as possible, not only for research purposes but also in view of the more favourable outcome of trial patients.

It has previously been shown that patients with muscle-invasive bladder cancer who were eligible for adjuvant cisplatin-based chemotherapy had a 5-year survival of 50–60% (26). For the large group of ineligible referred patients, survival was significantly inferior to that for eligible patients. Our observations are largely in agreement with these findings. The prognosis might be even worse for non-referred patients, as these persons are usually older and often present with more severe co-morbidity than our group III patients.

The nature and extent of extrapolation of results are rarely considered in the planning of clinical trials or in the presentation of trial results, and surprisingly few investigators have discussed to what degree results from large trials can be generalized. It has previously been emphasized that patients enrolled in a clinical trial cannot be regarded as a random sample of the population fulfilling the inclusion criteria (27, 28). The pretreatment characteristics of randomized and excluded patients may differ substantially with respect to clinical variables that potentially affect outcome (29). Patients who are willing to be entered into clinical trials differ from those who refuse randomization (1, 5, 6, 30), as confirmed by our study. However, for most trials, no records concerning non-included eligible and ineligible patients are kept (3), and assessments of the generalizability of trial results are thus not possible or at least limited. Better survival for trial patients as compared to eligible non-participants has, however, been demonstrated in a nephroblastoma trial (12), a sarcoma trial (1), and a pooled analysis of several non-small cell lung cancer trials (11). These observations are supported by our analysis.

CONCLUSION

This mono-institutional experience with the clinical management of patients with T2–T4a operable bladder cancer confirms previous results that patients included in a clinical trial display better overall survival than eligible patients who refuse to be included, despite similar treatment. Furthermore, ineligible patients with similar tumour burden and with similar treatment not surprisingly have considerably lower overall and cancer-specific survival. We recommend that clinical investigators register reasons for non-participation in clinical trials. The outcome of non-included patients undergoing treatment comparable to that in the trial should also be recorded.

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