

# Palliative Chemotherapy or Watchful Waiting? A Vignettes Study Among Oncologists

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**Purpose:** To determine the preferences of oncologists for palliative chemotherapy or watchful waiting and the factors considered important to that preference.

**Methods:** Sixteen vignettes (paper case descriptions), varying on eight patient and treatment characteristics, were designed to assess the oncologists' preferences. Their strength of preference was rated on a 7-point scale. An orthogonal main effects design provided a subset of all possible combinations of the characteristics, allowing estimations of the relative weights of the presented characteristics. A written questionnaire was sent to a random sample of oncologists (N = 1,235).

**Results:** The response rate was 67%, and 697 questionnaires were available for analysis. Eighty-one percent of the respondents were male. The mean age was 46 years. We found considerable variation among the

oncologists. No major associations between physician characteristics and preferences were found. Of the patient and treatment characteristics affecting treatment preference, age was the strongest predictor, followed by the patient's wish to be treated and the expected survival gain. Other patient and treatment characteristics had a limited effect on preferences, except for psychological distress, which had no independent impact.

**Conclusion:** Patients will encounter different decisions depending on their oncologists' preferences and their own personal background. Therefore, to ensure adequate information for decision-making processes, decision aids are proposed.

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DURING THE PAST decade, there has been little improvement in survival for the most common types of cancer. As a result, approximately half of all cancer patients will become eligible for palliative treatment at some point in time.<sup>1</sup> Many patients will receive palliative chemotherapy, endocrine treatment, surgery, or radiation therapy, not with curative intention, but primarily to ensure an optimal quality of life and/or sometimes increase their length of survival.<sup>2,3</sup> In palliative oncology, chemotherapy and watchful waiting are often equivalent options.

Palliative chemotherapy not only has limited efficacy but side effects as well. The efficacy of palliative chemotherapy in clinical trials is often evaluated by its ability to induce a tumor response. However, tumor shrinkage does not necessarily imply a benefit to patients.<sup>4</sup> There have been optimistic expectations about the success of chemotherapy in the treatment of metastatic tumors of adults. However, "pessimists

have been right and the optimists wrong"<sup>4</sup> about the subsequent achievements of chemotherapy as a treatment for metastatic solid tumors of adults. The effect of palliative chemotherapy on survival is modest.<sup>2</sup> With regard to the effect of treatment on quality of life, researchers have found different outcomes. In some studies, palliative chemotherapy seemed to enhance a patient's quality of life significantly.<sup>5-9</sup> However, Ramirez et al<sup>10</sup> reported that after palliative chemotherapy, only 26% of breast cancer patients felt better. Finally, there are also studies that reported no improvement or deterioration of quality of life as an effect of palliative chemotherapy.<sup>11-14</sup> Thus, physicians may have a dilemma when proposing palliative chemotherapy, and patients may have a dilemma about whether to accept it.<sup>3,15</sup> Still, such treatment is offered to many patients and often accepted by them.<sup>16</sup>

The other, alternative option is watchful waiting. Such a wait-and-see policy focuses on the quality of life of patients by providing symptomatic treatments, thus minimizing their physical complaints. However, although equivalent to a certain extent to palliative chemotherapy, in medical practice, watchful waiting is not often explicitly discussed with patients.<sup>16</sup>

Data on patient preferences for palliative chemotherapy or watchful waiting are sparse.<sup>17</sup> Whereas this might be considered unfortunate, patients with a life-threatening disease often want to leave important decisions to their physician.<sup>18-21</sup> Consequently, the preference of physicians is weighty in actual decision making. However, we know even less about the preferences of physicians in palliative oncology.

Generally accepted guidelines about offering palliative chemotherapy are usually lacking. Little is known about the magnitude of practice variation and about considerations that play a role in attitudes towards palliative chemotherapy.

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Variation among oncologists is usually found when no option is evidently preferable<sup>22</sup> and may be thus expected.

We studied the strength of preference for palliative chemotherapy versus watchful waiting for treating patients with incurable cancer among a large random sample of oncologists. We approached the clinical reality by using vignettes to enable us to confront all the specialists with the same "paper patient." Additionally, the impact of physician, patient, and treatment characteristics on their preferences was assessed. The study was carried out between July and November 1999 in the Netherlands. Medical specialists who treat cancer patients indicated their strength of preference for palliative chemotherapy versus watchful waiting by evaluating 16 vignettes of patients with incurable cancer.

METHODS

Participants

All members of the Society of Medical Oncology (n = 262), the Society of Pulmonologists and Tuberculosis (n = 346), the Society of Surgical Oncology (n = 332), the Society of Radiotherapy and Oncology (n = 150), the Society of Gynecological Oncology (n = 108), and the Head and Neck Cancer Society (head and neck surgeons, n = 37) were eligible for the study. All clinicians (N = 1,235) were sent a questionnaire.

Questionnaire

The questionnaire contained items on physician characteristics, including specialty (medical oncology, pulmonology, surgery, radiation oncology, gynecology, or head and neck surgery), sex, age, employment status, and type of hospital (academic teaching, nonacademic teaching, or nonteaching). Additionally, we asked what percentage of their patients was being treated for malignancies. After 6 weeks, a reminder was sent to nonresponders.

We used a set of vignettes to assess the strength of preference for palliative chemotherapy versus watchful waiting and to establish the influence of physician, patient, and treatment characteristics on these preferences. A vignette is a paper case description in which patient, disease, and treatment characteristics are given (Table 1). The selection of relevant factors and the wording of the vignettes were based on in-depth interviews with three medical oncologists and on the outcomes of a pilot study. Eight patient background and outcome parameters were selected. All factors varied at two or three levels: (1) age (40, 60, or 80 years), (2) physical condition (World Health Organization [WHO]-0, WHO-1, or WHO-2), (3) psychologic distress (little anxiety and/or depression v severe anxiety and/or depression), (4) patient's wish to be treated (no v outspoken wish to be treated), (5) expected toxicity of chemotherapy (mild v severe toxicity), (6) disease-related complaints expected in the future (few v many complaints), (7) chance of tumor response (15%, 25%, or 50%), and (8) possible chemotherapy-related survival gain (no survival gain v survival gain of 3 months or more). The case descriptions could thus be cancer-specific because relevant considerations in the decision-making process were covered by the factors included. For each vignette, the respondents rated their strength of preference for palliative treatment versus watchful waiting on an anchored 7-point scale ranging from a strong preference for watchful waiting (1) via a neutral position, implying no preference for either alternative (4), to a strong preference for palliative chemotherapy (7).

The eight characteristics and their respective levels result in 864 combinations. We reduced this number to 16 using an orthogonal main effects design. This design provides a subset of all possible combina-

Table 1. Case Description: An Example

Patient 4						
Imagine you are the physician of the patient who is described below. This patient has metastatic cancer. Cure is not possible. There are two options left: palliative chemotherapy and watchful waiting. Could you describe your preference?						
Age	60 years					
Physical condition	Complaints (WHO = 1)					
Psychological distress	Very anxious and/or depressed					
Patient's wish to be treated	Strong outspoken wish for treatment					
Toxicity of the chemotherapy	Severe toxicity					
Expected complaints	Minor increase					
Chance of tumor response	25%					
Survival gain	3 months or more					
How strong is your preference for palliative chemotherapy or watchful waiting for this patient?						
1	2	3	4	5	6	7
strong preference for watchful waiting			no preference			strong preference for palliative chemotherapy

tions of patient and treatment characteristics and allows estimations of the relative weights for each level of the presented characteristics on the preference score. Main effects of the case characteristics on the preference score can be estimated using this design. However, interaction effects of case characteristics cannot be evaluated.

To avoid order effects, the vignettes were randomly presented to respondents in three different orders. The anchoring points, preference for watchful waiting (1) and preference for palliative chemotherapy (7), were randomly reversed as well.

Statistical Analyses

The characteristics of the sample were summarized using descriptive statistics. Differences between proportions were analyzed with the  $\chi^2$  statistic. After recoding, higher preference scores systematically indicated a stronger preference for palliative chemotherapy. The strength of preference for each vignette was analyzed using a mixed linear model with a null model case as a fixed factor and individual respondents as a random factor. The physician, patient, and treatment characteristics were added as main effects afterwards. In the model-building phase, the Akaike Information Criterion<sup>23</sup> in combination with the maximum likelihood estimation was used. The final models were estimated using restricted maximum likelihood to obtain appropriate SE. Finally, the least-square-mean and corresponding SE were estimated from the model, whereby cases were split into their characteristics and corrected for the neutral preference value. The analyses were performed in S-plus for Windows using the function linear mixed effects model (LME, version 8.0; MathSoft Inc, Cambridge, MA), whereas computation of least-square-mean was performed with a S-plus function designed for this study. Statistical uncertainty was expressed in 95% confidence intervals (CIs).

RESULTS

Participants

Of the 1,235 questionnaires that were sent to the physicians, 826 (67%) were returned. Of those, 101 were from specialists stating that they did not treat cancer patients (any

**Table 2. Characteristics of the Sample (n = 697)**

	No.	%
Specialty		
Medical oncologists	157	23
Pulmonologists	176	25
Surgeons	173	25
Radiation oncologists	98	14
Gynecologists	73	10
Head and neck surgeons	20	3
Sex		
Male	562	81
Female	135	19
Age		
≤ 40 years	202	30
41-50 years	275	40
≥ 51 years	208	30
Employment		
Employed	310	45
Solo or group practice	337	49
Combination	36	5
Type of hospital		
Academic	251	37
Teaching	245	36
Nonteaching	175	26
Percentage of oncology patients treated		
< 50%	340	50
50-89%	138	20
≥ 90%	202	30

NOTE. Because of missing data and truncations, the numbers and percentages do not always add to 697 and 100%, respectively.

longer), 12 had not been delivered, and 16 were incompletely returned. Thus, 697 questionnaires were used in the analyses. There was no significant difference in response rate between the different specialties ( $P = .12$ ;  $\chi^2$  statistic). The characteristics of the 697 respondents are listed in Table 2. The majority of the responding physicians were male (81%), with a mean age (SD) of 46 (7.9) years. Almost all specialists working in an academic hospital were employed by the hospital, whereas specialists in nonacademic hospitals usually worked in a solo or group practice.

Cancer patients constituted a widely varying percentage of the patients seen by the different specialists. All radiation oncologists, 17% of the surgeons, 33% of the medical oncologists, 20% of the gynecologists, 37% of the head and neck surgeons, and 5% of the pulmonologists saw almost exclusively (> 90%) cancer patients.

#### *Strength of Preference for Palliative Chemotherapy*

The mean overall preference for palliative chemotherapy for the 16 case descriptions combined was 3.70 (95% CI, 3.59 to 3.81), indicating a slightly stronger preference for watchful waiting. On average, as is presented in Fig 1, the respondents favored palliative chemotherapy in seven cases (especially in case 3) and opted for watchful waiting in eight

cases (especially in case 2). There was no clear preference for either alternative in case 12. In one of 16 cases (case 2), more than 90% of the physicians strongly preferred watchful waiting (score 1 or 2). In three other cases (cases 4, 5, and 11),  $\geq 66\%$  reported a strong preference for watchful waiting (score 1 or 2). In other cases, there was more variation among the physicians.

#### *Impact of Physician Characteristics on Treatment Preference*

No associations between most physician characteristics and the preference scores for the 16 vignettes were observed. In other words, neither sex, age, employment status, type of hospital, nor percentage of cancer patients in practice affected the preference scores of respondents. However, a significant, albeit small, independent effect ( $P < .01$ ) was demonstrated with regard to specialty. On average, radiation oncologists (mean preference score, 3.41; 95% CI, 3.35 to 3.55) were more often in favor of watchful waiting as compared with the other specialists (mean preference score, 3.75; 95% CI, 3.68 to 3.81).

#### *Impact of Patient and Treatment Characteristics on Treatment Preference*

Figure 2 shows the independent impact of the case (patient and treatment) characteristics on the preference of the respondents. As compared with the reference group of patients of 60 years of age, being 80 years old had the strongest independent impact on the oncologists' preferences, with a mean increase of preference score in favor of watchful waiting of  $-1.25$  points (95% CI, 1.01 to 1.49). In contrast, when the patients were 40 years old, there was a significant shift of the preference towards palliative chemotherapy (mean increase of 0.68 points; 95% CI, 0.44 to 0.91).

Preference was also influenced by the patients' wish to be treated. If the patient had no outspoken wish to be treated, watchful waiting was preferred more often (mean decrease of 1.07 points; 95% CI, 0.75 to 1.29) compared with the reference scores of patients with an outspoken wish.

As compared with the situation in which no survival gain was expected, a survival gain of  $\geq 3$  months was strongly associated with the preference for palliative chemotherapy (mean increase of 1.13; 95% CI, 0.91 to 1.35).

All but one of the remaining case characteristics had a significant, albeit smaller, independent impact on the preference scores. Mild toxicity of the treatment led to a stronger preference for palliative chemotherapy as compared with severe toxicity. When patients were suffering from a worse physical condition or when an increase of disease-related complaints was expected, a stronger preference for palliative chemotherapy was reported. If there was 50% chance of tumor response, the preference for palliative

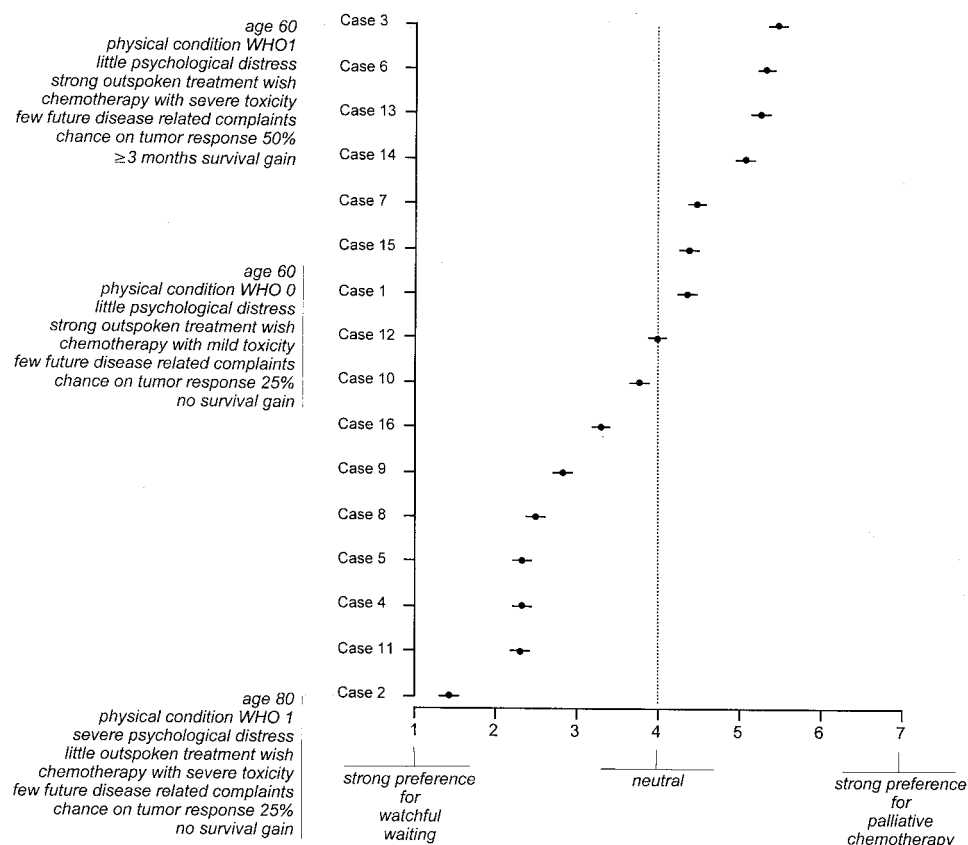


Fig 1. Mean preference score (95% CI) for palliative chemotherapy or watchful waiting.

chemotherapy was stronger than in cases with a smaller chance of tumor response. Psychologic distress was found to have no independent influence on treatment preferences.

DISCUSSION

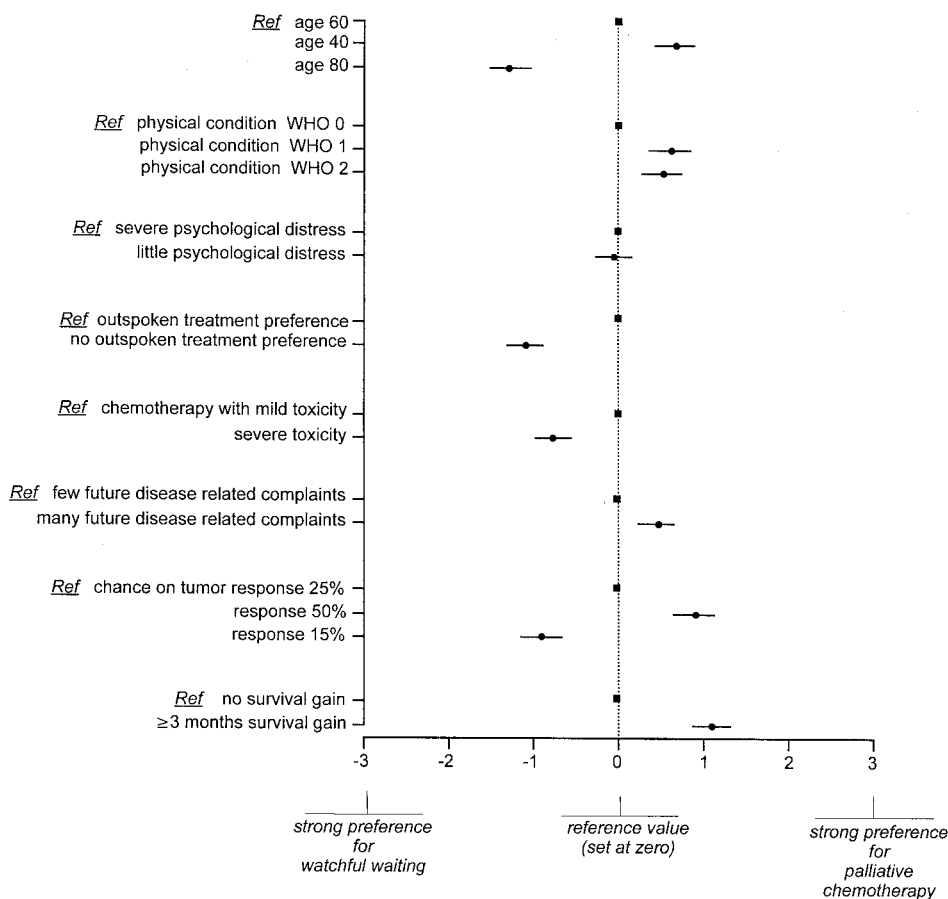
Diversity in patterns of practice and considerations that play a role in deciding about palliative chemotherapy may be expected, but little is known about them. We therefore studied the strength of preference for palliative chemotherapy versus watchful waiting, two alternative options for patients with incurable cancer, among a large random sample of oncologists. To sum up the dilemma with these two alternative options, physicians chose palliative chemotherapy in a situation with a possible survival gain of  $\geq 3$  months with existing physical complaints and when future complaints are expected. Watchful waiting was preferred in cases where they expect severe toxicity of chemotherapy, where there is no explicit wish of the patients to be treated, and when patients are of older age.

It is difficult to assess the influence of different considerations of specialists on their actual palliative treatment preferences. Therefore, we approached the clinical reality by using vignettes, ie, paper case descriptions. This approach enabled us to confront all specialists with the same

“patients.” It has proven useful in earlier studies among oncologists and provides insight into their treatment preferences.<sup>24-27</sup> Peabody et al<sup>28</sup> recently compared vignettes, standard patients, and chart abstractions and concluded that actual clinical practice can be measured in a valid manner by using such vignettes.

The physicians’ preference scores were well distributed. This result indicates that we succeeded in eliciting preferences for both palliative chemotherapy and watchful waiting. The small CIs reveal a considerable consensus among physicians with regard to individual patient profiles. However, in only 25% of the cases, an agreement percentage of  $\geq 66\%$  was achieved. In a comparable study, Lind et al<sup>29</sup> found a higher level of agreement, but they nevertheless interpreted this as considerable heterogeneity. According to these authors, personal values might be at stake. On the other hand, practice variation, especially when equivalent options are available, is often seen.<sup>30</sup>

With the exception of specialty, physician characteristics such as sex, age, employment status, type of hospital, and number of cancer patients treated did not influence preference scores. To some extent, these findings are in contrast



**Fig 2.** Independent impact of patient and treatment characteristics on the preference score for palliative chemotherapy or watchful waiting of the respondents.

with the outcomes of a smaller study performed by Tannock et al<sup>26</sup> in which both sex and age had an impact on the preference of physicians for chemotherapy. Their results might be explained by the fact that their physicians were younger and were more often female. Additionally, their scenarios referred to adjuvant rather than palliative chemotherapy. Our only significant finding regarding physician characteristics is that radiation oncologists have, on average, a stronger preference for watchful waiting. This might be explained by the fact that radiotherapy is usually intended to relieve symptoms in the short term with a minimum of side effects, whereas palliative chemotherapy may induce tumor shrinkage in the long term only and may result in substantially more severe side effects.

It is important to understand which patient-, disease-, or treatment-related characteristics are relevant for the oncologists' preference for palliative chemotherapy. Palliative care means striving to achieve or maintain an acceptable quality of life as long as possible. Palliative chemotherapy tries to relieve or postpone symptom distress, and thus enhance quality of life, by reducing tumor size. Watchful waiting

tries to maintain the quality of life by using treatments directed against specific symptoms only when they occur. In line with its objective, it can be expected that palliative chemotherapy is preferred when a patient has (tumor-related) physical complaints or if major physical complaints are expected in the near future. Present or future physical complaints were indeed found to be indicative for a stronger preference for palliative chemotherapy in our study.

The rate of response to chemotherapy and the possible survival gain associated with it are also expected to influence preferences for palliative chemotherapy. This expectation was supported by our results. Palliative chemotherapy was more strongly preferred when there was a survival gain of 3 months or more and a tumor response of 50% rather than 25% or 15%. However, the toxicity of the chemotherapy cannot be ignored, and a trade-off between burden and benefits of the therapy is unavoidable. Our results show that severe toxicity of the chemotherapy was indeed associated with a stronger preference for watchful waiting.

In the trade-off process, the wish of the patient to be treated also plays a role. In cases where patients did not

have an outspoken wish to be treated, the preference for watchful waiting among physicians increased significantly. This result is fortunate in times when shared decision making becomes increasingly important.<sup>31-33</sup>

Interestingly, older age had the strongest impact on the preference scores towards watchful waiting. It is questionable whether this preference is rational or whether age discrimination was a factor. The literature on the effects of palliative chemotherapy in the elderly is sparse.<sup>34-38</sup> Some studies indicate that in lung cancer patients, the elderly in particular benefited from chemotherapy.<sup>35,37</sup> Another study found that elderly patients tolerated chemotherapy as well as younger patients.<sup>38</sup> Although one should bear in mind that in these studies a selection bias could be present based on performance status or other factors, it nevertheless seems unjustified to withhold palliative chemotherapy on the basis of age alone.

The presence of psychologic distress did not influence the oncologists' preference for either palliative chemotherapy or watchful waiting. This result can be considered as positive because no evidence can be found in the literature that indicates an effect of such distress on the effectiveness of chemotherapy. Even though depressive patients seem to be less willing to undergo chemotherapy,<sup>39</sup> Kramer et al<sup>40</sup> recently showed that emotional function does not influence response to palliative chemotherapy.

Some limitations of our study merit discussion. Not all characteristics that might influence the physicians' preferences could be included in the vignettes. For example, cost-effectiveness of the therapy or social circumstances of the patient were disregarded, even though these aspects might have an impact on the decision-making process.<sup>41,42</sup> Also, because of the orthogonal study design, only main effects could be measured. Therefore, possible interactions between the different case characteristics are unknown, eg, the effect of older age and the wish to be treated<sup>42</sup> or the co-occurrence of physical complaints and emotional distress.

We found that the preferences for treatment among oncologists vary from a strong preference for palliative chemotherapy to a strong preference for watchful waiting. However, in daily

clinical practice, watchful waiting is offered less frequently.<sup>16</sup> Different explanations might account for this discrepancy between our findings and clinical reality. First, referral bias may be at stake. In daily practice, medical oncologists see mostly patients who are referred to them for chemotherapy and, thus, expect such treatment. It may then be less obvious to propose watchful waiting as an alternative. Second, there may be a difference between preferences expressed in a paper case and the decisions made in daily clinical practice. The wish of the patient to be treated is an important factor, which was confirmed by our results. It is interesting to note that in our study, when there was no explicit preference of the patient to be treated, the preference towards watchful waiting became stronger. Slevin et al<sup>43</sup> found that cancer patients often wish to be treated for small chances of response. In fact, cancer patients were found to be reluctant to "do nothing."<sup>44</sup> Therefore, physicians may anticipate a strong wish to be treated and propose chemotherapy to patients, even if they would prefer watchful waiting themselves.<sup>44,45</sup>

Given the patient's wish to be treated, one might wonder how well patients are being informed about the alternative treatment option of watchful waiting. Silvestri et al<sup>46</sup> found that patients are willing to choose supportive care, watchful waiting, when they knew that the survival gain would only be 3 months. The question arises of how physicians can inform their patients adequately with regard to such treatment and their own preferences. Given the uncertainty of the side effects of palliative chemotherapy and the possibilities of watchful waiting, a systematic counseling procedure may be needed to prepare patients for decision making.<sup>31,47,48</sup> In such procedure, information on the present health condition, probabilities of certain health outcomes with or without palliative chemotherapy, side effects, and the opinion of others can be discussed. The use of a decision aid, such as decision boards, interactive videodiscs and CD-ROMs, or group presentations, may then be supportive for both the patient and the physician.

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## CORRESPONDENCE

### Increased Risk of Malignant Mullerian Tumor of the Uterus Among Women With Breast Cancer Treated by Tamoxifen

*To the Editor:* It has been well documented that women taking tamoxifen experienced a two- to three-fold increased risk of uterine cancers, which are mainly endometrial adenocarcinoma.<sup>1</sup> We recently received a mailing from a pharmaceutical company alerting health care professionals of a relationship between tamoxifen use and increased risk of a very rare form of uterine sarcoma, ie, malignant mixed mullerian tumor (MMMT). This alert was based mainly on the recent publication by Wickerham et al,<sup>2</sup> which appeared in the June 1, 2002, issue of the *Journal of Clinical Oncology*. We investigated whether such patterns could be observed in the Swiss canton of Geneva. Since 1970, the Geneva cancer registry has systematically collected information on all patients diagnosed with cancer in the population (about 400,000 inhabitants). Data concern patient and tumor characteristics and outcome, in terms of second primary cancer occurrence and survival. Since 1985, detailed information on primary cancer treatments (given within 6 months after diagnosis) has been recorded. We considered all women diagnosed with histologically confirmed invasive and/or in situ breast cancer between 1985 and 1999, after exclusion of patients with a survival of less than 1 year. The study cohort included 3,972 women. Tamoxifen was given to 1,664 women (42%). Standardized incidence ratios of uterine cancer were calculated as the ratio of observed and expected cases.<sup>3</sup> As observed cases, we considered women who developed corpus uteri cancer at least 1 year after the initial diagnosis of breast cancer. The expected number of cases was calculated by applying the Geneva female corpus uteri cancer incidence rates by 5-year period and age group to the cohorts of women treated with tamoxifen versus not. The number of person-years was 6,446 in the tamoxifen group and 14,581 in the group not treated with tamoxifen. Twenty-two women developed uterine cancer after breast cancer. As expected, we observed an increased risk of corpus uteri cancer in both cohorts, which was somewhat more pronounced among women who received tamoxifen (Table 1). The risk of corpus uteri cancer was 2.8-fold (95% confidence interval [CI], 1.4 to 5.0,  $P < .01$ ) increased among women treated with tamoxifen and 1.6-fold (95% CI, 0.8 to 2.8,  $P = .10$ ) increased among women who did not receive tamoxifen. Two cases of MMMT uteri cancer were observed. Both cases occurred in the tamoxifen group, conferring to this cohort of women a 29.0-fold increased risk (96% CI, 3.5 to 104.9,  $P < .01$ ) compared with that expected in the general population. This corresponds to one corpus uteri MMMT per 650 women treated with tamoxifen for 5 years. This study therefore confirms the strong increased risk of MMMT uteri cancer among women treated with tamoxifen and the importance of their close surveillance. However, the two cases of uterine MMMT represented less than 20% of all MMMT cases observed during the

period ( $n = 11$ ). Therefore, additional research is needed to identify other risk factors for this rare cancer.

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### Revisiting Truth and Consequences: What to Do When the Patient Doesn't Want to Know

*To the Editor:* We often put our best experiences (and patients) forward as examples of good medical care. However, Drs Neff, Lyckholm, and Smith have graciously written about their frustrating experiences.<sup>1</sup> We can only commend them in this regard. However, we believe we should revisit the case presentation. We acknowledge our limitations for we were not there, and we can reassure the authors that their experience is common to all who care for terminally ill patients. With that said, four points can be addressed: plan of care, communication, physician responsibility, and futility.

*Plan of care:* The ancillary services seemed to have failed to enter into the decision-making process. Surgery was not to be, as "the patient, dying of metastatic cancer, was continued on futile treatment and hoped for surgery that 'not only was not going to occur, but probably didn't exist.'"<sup>1</sup> In addition, the palliative specialist, Dr Smith, was deferring to the oncologist.<sup>1</sup> Therefore, it seems that a plan of care, although covertly made, was not made common knowledge to the patient or mother. Certainly there was a plan of

**Table 1. Risk of Corpus Uteri Cancer After Breast Cancer**

Breast Cancer Patients	Pathological Type											
	Adenocarcinoma			MMMT			Other Sarcoma			Total		
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
With tamoxifen ( $n = 1,664$ )	9	3.67	2.5* (1.1-4.7)	2	0.07	29.0† (3.5-104.9)	0	0.11	0	11	3.94	2.8† (1.4-5.0)
Without tamoxifen ( $n = 2,308$ )	10	6.49	1.5 (0.7-2.8)	0	0.16	0	1	0.26	3.8 (0.1-21.2)	11	7.05	1.6 (0.8-2.8)
All patients ( $N = 3,972$ )	19	10.22	1.9† (1.1-2.9)	2	0.22	8.9* (1.1-32.1)	1	0.37	2.7 (0.1-15.1)	22	11.00	2.0† (1.3-3.0)

Abbreviations: SIR, standardized incidence ratios (observed/expected); 95% CI, confidence interval at 95%.

\* $P < .5$ .

† $P < .01$ .

care, established by default. Antitumor therapy was appropriately avoided, but because of failure by both the surgeon and the oncologist to act, procedures (total parenteral nutrition and cardiopulmonary resuscitation [CPR]) deemed inappropriate that should have been suspended were continued by default. There was a failure to establish and communicate an appropriate plan of care to the patient within the context of her illness.

**Communication:** The lack of communication of an appropriate plan of care led to duplicity and limited patient autonomy.<sup>2-4</sup> If the patient knew the appropriate plan of care for where she was in the trajectory of her illness, it would have given her the opportunity and the freedom to act on the plan by agreement, by disagreement with the second opinion, by arbitration through the medical ethics committee, or by transfer of care. The communication, even if unilaterally initiated, could have been handled with compassion and respect.

**Physician responsibility:** Physicians cannot be excused from the responsibility of professional care (and standard of care) because of a lack of communication, communication barriers, or patient demands.<sup>3-5</sup> We cannot shrug our responsibility by stating "I am getting tired of being held responsible for fixing all of society's ills." Physicians are free moral agents and are not victimized by either patient autonomy or societal issues, whatever they may be. Principles that deny physicians any power to act on professional value leave physicians powerless to refuse to perform actions which harm patients or which are below the standard of care and are morally reprehensible.<sup>4-6</sup> "Physicians would be complicators of substandard care without accountability."<sup>4</sup> A patient's negative right to refuse treatment cannot by itself imply any positive right to demand treatment. Such a right without qualification (standard of care) would violate the negative rights of physicians whose services are sought.<sup>4</sup> It is not obvious that the routine application of CPR (as a standard of care) represents either good medicine or good ethics.<sup>7</sup> It is a fallacy to believe that providing CPR by default is a value-free judgment.<sup>7</sup> Physicians have both the right to make value judgments and the responsibility to communicate such decisions to patients based on the standard of care, even if such conversations are initiated unilaterally.<sup>4</sup>

**Futility:** Physiologic futility is centered on probability (diminishing returns, which rarely reach zero).<sup>8</sup> The degree of certainty must be absolute before the futility card is played. Otherwise, a value judgment related to the course of care is squarely within the purview of the patient and the physician's moral agency is severely limited. This leads to the nonsensical practice of both offering CPR and making efforts to have patients retract its use by logic, pleading, and—even worse—as a final resort, a feeble attempt at resuscitation, ie, the "slow code." If CPR is the alternative to certain death and physiologic futility is the reigning principle, then codes could never be stopped because there is always a chance. Physicians would be morally obligated to offer any and all experimental therapies and surgeries to terminally ill patients for whom conventional therapy has failed.<sup>4</sup> Eligibility criteria for such treatment consist only of patient consent.

Medical futility revolves around the goals of medical therapy and the reasonable benefits expected from therapy.<sup>9-11</sup> Futility in this context is treatment that will not produce the benefits sought by the patient.<sup>10</sup> Futile therapies are those that result in temporary and fleeting benefits and that do not improve conditions, or "treatment which prolongs the dying process and offers no realistic chance of improvement."<sup>10</sup> In this case, both total parenteral nutrition and CPR were medically futile. Both can generate harm, as demonstrated by swollen legs, shortness of breath, loss of dignity, and (potentially but not realized) bone fractures, without benefit.

What could have been done differently? Within the context of a family meeting, the patient and mother could have been informed that resuscitation was not medically appropriate for various reasons and that CPR would not be performed. Further discussion would probably have ensued, centered on her clinical course and reasons why surgery and chemotherapy were inappropriate. The patient could have either agreed with the course of action of aggressive palliative care or expressed her disagreement, which in most instances can be resolved by second opinion, ethics consultation, or (rarely) transfer of care. The palliative specialist would have maintained a sense of integrity.

In summary, the failure to communicate can lead to a wide range of adverse effects by violating both the physician's sense of appropriate care and the patient's autonomy (did we really know she wanted CPR?).<sup>11</sup>

communicate with patients, but communicate we must if we are to avoid a greater harm.

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## Nail Toxicity Related to Weekly Taxanes: An Important Issue Requiring a Change in Common Toxicity Criteria Grading?

**To the Editor:** Two articles regarding chemotherapy with weekly taxanes in women with metastatic breast cancer were published in the August 1 and November 15, 2001, issues of the *Journal of Clinical Oncology*.<sup>1,2</sup> Both articles concluded that treatments with weekly paclitaxel<sup>1</sup> and docetaxel<sup>2</sup> were well tolerated and demonstrated reasonable activity. The most important reported toxicities were hematologic toxicity, neurotoxicity, and fatigue. There was only one mention of nail disorders: Perez et al<sup>1</sup> documented 17% grade 1 and only 3% grade 2 toxicity. Hainsworth et al<sup>2</sup> did not report nail disorders at all. The common toxicity criteria of the National Cancer Institute (version 2.0) describe only two grades of nail changes: grade 1, discoloration, ridging (koilonychia), or pitting; and grade 2, partial or complete loss of nail(s) or pain in the nailbeds.

In February 1998, we started a phase II trial of weekly paclitaxel in metastatic breast cancer using the Perez schedule<sup>1</sup>: paclitaxel 80 mg/m<sup>2</sup> over 1 hour administered weekly (4 weeks = 1 cycle) without rest periods (data submitted). Fifty-eight patients were entered onto this trial. Toxicity was acceptable, but we noted a higher incidence of onychopathy than previously reported. Nail toxicity occurred in 16 patients (27.6%), mostly (75%) of grade 2. Eleven (68.7%) of these patients had received four or more consecutive cycles of chemotherapy. In two cases, chemotherapy delay was required in order to manage nail disorders, which were painful and caused a severe limitation of function. In one patient, onychopathy was the dose-limiting toxicity. A variety of clinical patterns was seen in different patients. Usually, the nails of the hands and/or feet showed an initial dark discoloration, and after that, nail raising and paronychia with exudation and subungual hemorrhage also appeared. This clinical pattern progressively disappeared after discontinuation of chemotherapy. An onycholysis was also observed in one patient.

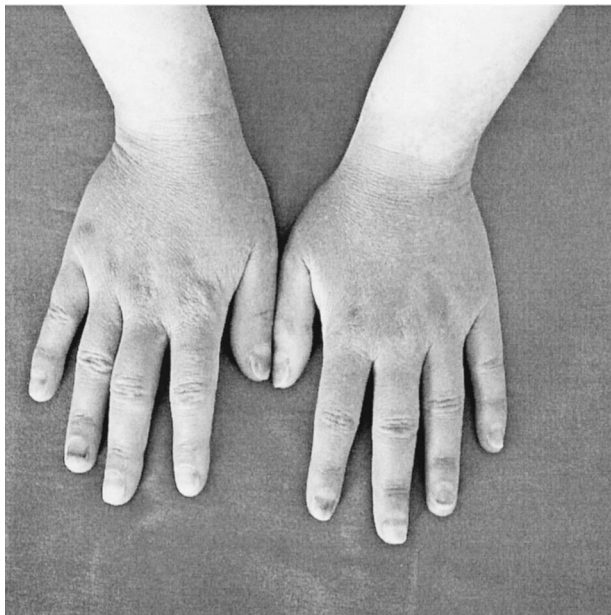


Fig 1. Onychopathy with dark pigmentation and onycholysis.

depicted in Fig 1. This toxicity, which plays an important role in the quality of life of patients, is typical of the weekly schedule of taxanes and has affinity with toxicities related to the protracted continuous infusion of drugs, such as the hand-foot syndrome, which is correlated with fluorouracil. Taxanes are now important drugs in breast cancer treatment and are frequently used with weekly schedules because of the lesser hematologic toxicity reported. It is important, therefore, to recognize nail changes early in order to avoid a worsening of the patient's quality of life and to prevent permanent discontinuation of chemotherapy. Furthermore, we suggest expanding the common toxicity criteria regarding nail disorders to three grades, similar to the situation for hand-foot syndrome: grade 1, discoloration, ridging (koilonychia), or pitting; grade 2, partial loss of nail(s) (onycholysis) or pain in nailbeds not interfering with function; and grade 3, partial loss of nail(s) (onycholysis) or pain in nailbeds interfering with function, or complete loss of nail(s).

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**In Reply:** Our trial<sup>1</sup> used the current common toxicity criteria version 2.0 descriptions for grading of nail toxicity, with 3% of patients developing partial or complete loss of nail(s) or pain in nailbeds. The recommendations for redefining the grading of nail toxicity by Spazzapan et al are reasonable, as they better

of toxicity as part of clinical trials, which now requires we only report grade 3 to 5 toxicities.

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## Very-Long-Term Survival Rates of Patients With Cancer

**To the Editor:** Long-term survival is an essential outcome measure in cancer surveillance. Five- and 10-year survival rates are often reported by cancer registries, and they are increasingly accessible for researchers, clinicians, and patients. Although the occurrence of late cancer deaths (ie, deaths beyond 10 years after diagnosis) is well known, longer-term survival rates, such as 15- or 20-year survival rates, have only occasionally been reported. This may be due to several reasons. First, the proportion of cancer patients surviving the first 10 years after diagnosis was very low for many forms of cancer in the past. Second, for many forms of cancer, life expectancy of patients would have been quite limited, even in the absence of the cancer, because of the relatively high average age of cancer occurrence. Third, few cancer registries have had series sufficiently long enough to generate long-term survival estimates in the past. Fourth, with traditional survival analysis, even the most recent estimates of very-long-term survival rates would have pertained to patients diagnosed many years ago and may have been quite outdated at the time they could be derived.

However, in the past decades, perspectives of long-term survival have substantially improved for patients with various forms of cancer, for reasons such as earlier diagnosis and more effective therapy. Furthermore, as a result of decreasing rates of other causes of death, mainly death from cardiovascular disease, remaining life expectancy at the average age of cancer occurrence has also increased, making long-term survival estimates more meaningful than before. Estimates of long-term survival rates also become more possible with the increasing time length of cancer registration series in many parts of the world. Finally, recent development in the methodology of survival analysis, particularly the introduction of period analysis of survival rates, has opened new perspectives on deriving up-to-date, long-term survival estimates.<sup>1,2</sup>

Recently, we showed that period analysis, in contrast to traditional survival analysis, provides estimates of survival curves for up to 10 years after diagnosis that are very close to the survival curves later observed for patients who are diagnosed with cancer at the time these estimates are available.<sup>3</sup> We now extend our previous analysis to evaluate the possibilities of deriving up-to-date estimates of survival for up to 20 years after diagnosis and to provide recent 20-year survival estimates for the most common forms of cancer.

As in our previous report,<sup>3</sup> our analysis is based on patients reported to the Finnish Cancer Registry between 1953 and 1997. Analyses were carried out separately for the most common forms of cancer, and they were restricted to patients under the age of 75 years at the time of diagnosis, because very-long-term survival is of less concern for very old patients whose life expectancy is rather limited even in the absence of cancer. To focus on excess deaths caused by cancer rather than all deaths, relative survival rates,<sup>4</sup> derived according to Hakulinen's method,<sup>5</sup> rather than absolute survival rates are reported.

The analyses were carried out in two steps. In the first step, we derived 20-year relative survival curves for the most recent cohorts of patients who had been followed up for 20 years by the end of 1997, that is, patients diagnosed in 1977 and earlier years. To increase the precision of estimates, this analysis included patients diagnosed in the 5-year interval from 1973 to 1977. The 20-year relative survival curves actually observed for these patients were then compared with the most up-to-date estimates of 20-year relative survival curves that could have been obtained from the registry data at the time of diagnosis of these patients, that is, from 1973 to 1977, either by traditional cohort analysis (including only patients diagnosed from 1953 to 1957 for whom 20-year follow-up could have been complete from 1973 to 1977) or by period analysis (including patients diagnosed from 1953 to 1977).

1953 to 1977 with their entire survival experience from 1953 to 1977), or period analysis (including only survival experience from 1973 to 1977 of patients diagnosed between 1953 and 1977). In the second step, analogous analyses were carried out to derive 20-year survival curves that could be obtained by cohort analysis, complete analysis, or period analysis 20 years later, that is, with cancer registration and mortality follow-up completed by the end of 1997. Survival curves are presented for eight very common forms of cancer only: cancers of the stomach, colon, rectum, lung, breast, corpus uteri, ovaries, and prostate. Although prognosis varies strongly among cancer sites, the general patterns were very similar for the other common types of cancer for which survival curves are not shown.

Figure 1A shows the most up-to-date estimates of 20-year relative survival curves that might have been obtained in 1973 to 1977 by cohort analysis, complete analysis, and period analysis compared with the 20-year relative survival curve meanwhile observed for patients diagnosed with the most common gastrointestinal cancers and lung cancer in that period. Overall, the 20-year relative survival rate of patients diagnosed with stomach cancer from 1973 to 1977 would have been only approximately 14%. However, estimates of 20-year survival curves obtained from 1973 to 1977 by cohort analysis would have been even more pessimistic. The same applies, though to a lower extent, to estimates

obtained by complete analysis. By contrast, period analysis would have almost perfectly predicted the 20-year relative survival curve observed 20 years later for patients diagnosed from 1973 to 1977. Twenty-year relative survival curves of patients diagnosed with colorectal cancer from 1973 to 1977 turned out to be more favorable. In particular, they were much more favorable than the most up-to-date estimates based on cohort analysis and complete analysis available from 1973 to 1977 would have suggested. Again, the period estimates available from 1973 to 1977 would have much better predicted the 20-year relative survival curves meanwhile observed for patients diagnosed at that time. Long-term prognosis was particularly poor for patients diagnosed with lung cancer from 1973 to 1977. Although survival curves obtained by different types of analysis from data available from 1973 to 1977 were not so different for this form of cancer, survival curves obtained by cohort and complete analysis, in contrast to those obtained by period analysis, were again overly pessimistic even for this form of cancer.

Figure 1B shows the same types of survival curves for the most common gynecologic cancers as well as for prostate cancer. For breast cancer, 20-year survival rates are higher than for most other forms of cancer, but the survival curve does not flatten out within 20 years after diagnosis, that is, there is still some major proportion of late deaths. A similar pattern holds for prostate cancer, albeit at much lower levels of survival. For all forms of cancer, the

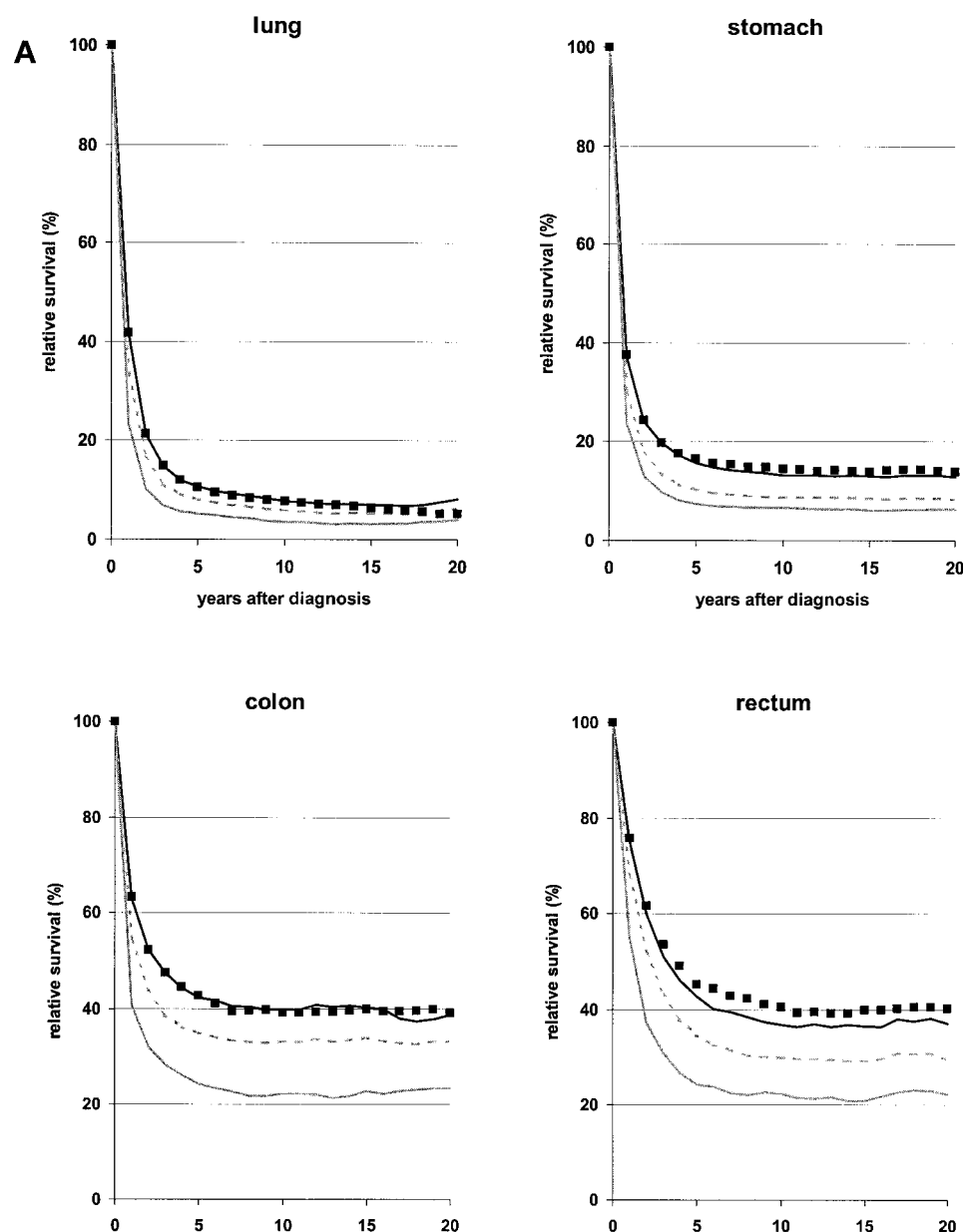


Fig 1. Twenty-year relative survival curves for patients diagnosed from 1973 to 1977 (black squares curve) compared with survival curves obtained from 1973 to 1977 by cohort (solid grey curve), complete (dashed grey curve), and period analysis (solid black curve). (A) Common gastrointestinal cancers and lung cancer; (B) common gynecologic cancers and prostate cancer.

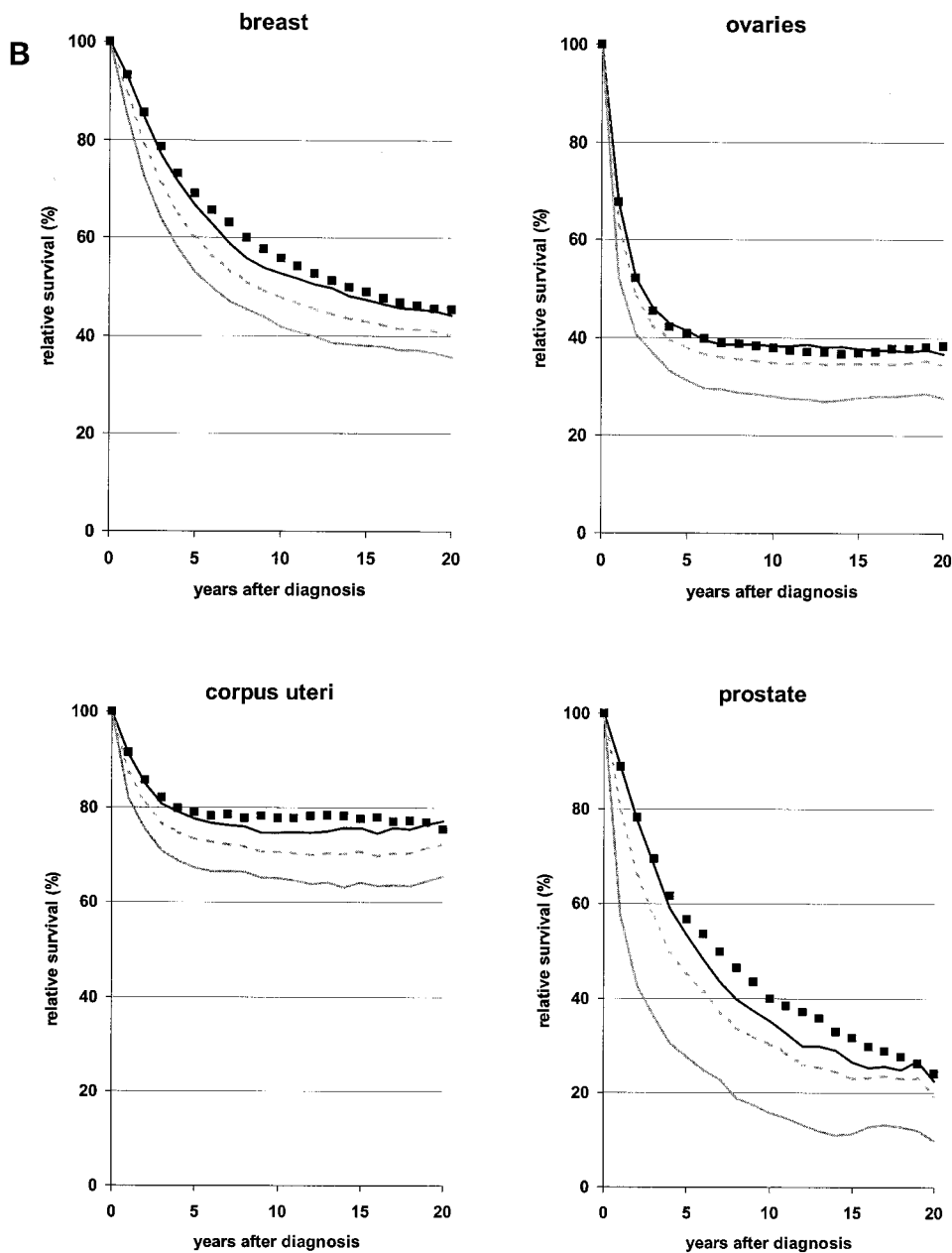


Fig 1. (cont'd)

characteristic shape of the survival curve meanwhile observed for patients diagnosed from 1973 to 1977 would have been quite well captured by the different estimates available from 1973 to 1977. However, in all cases, cohort analysis would have provided overly pessimistic estimates of long-term survival expectations. The same applies to complete analysis, albeit to a lesser extent. By contrast, period analysis would again have given quite up-to-date estimates of 20-year survival expectations in all cases.

Obviously, it will take another 20 years until we know the 20-year survival curves of patients diagnosed from 1993 to 1997. However, from the experience outlined above, we are quite confident that the 20-year survival curves for 1993 to 1997 derived by period analysis quite closely predict the survival experience of patients diagnosed in that period. These survival curves are shown in Fig 2, A and B, along with the estimates of 20-year survival curves obtained from 1993 to 1997 by cohort analysis and complete analysis. With the exception of lung cancer, all survival curves are considerably higher than those obtained 20 year earlier, which indicates major improvement in prognosis between the 1970s and the 1990s. Furthermore, again with the exception of lung cancer, estimates of 20-year survival obtained by the traditional methods of survival analysis are substantially lower than those obtained by period analysis.

would continue to provide overly pessimistic estimates of long-term survival expectations for newly diagnosed patients. The differences are particularly large for stomach, colon, breast, and ovarian cancers.

In summary, our analysis suggests that derivation of up-to-date survival estimates has now become feasible even for very-long-term survival rates, and we suggest that it should be routinely included in monitoring of progress against cancer in the increasing number of cancer registries with long-standing time series of high-quality data.

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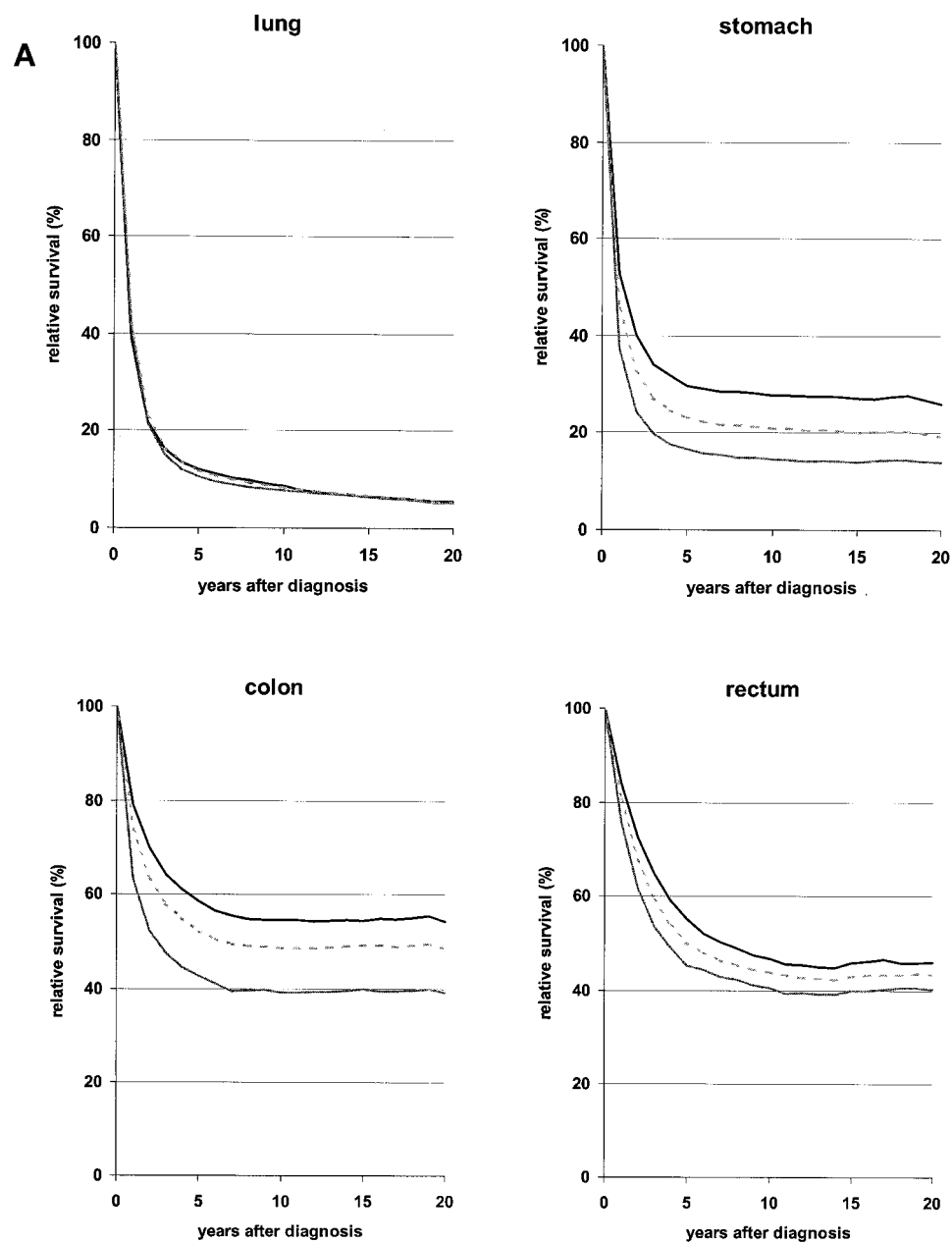


Fig 2. Recent estimates of 20-year relative survival curves obtained with data up to 1997 by cohort (solid grey curve), complete (dashed grey curve), and period analysis (solid black curve). (A) Common gastrointestinal cancers and lung cancer; (B) common gynecologic cancers and prostate cancer.

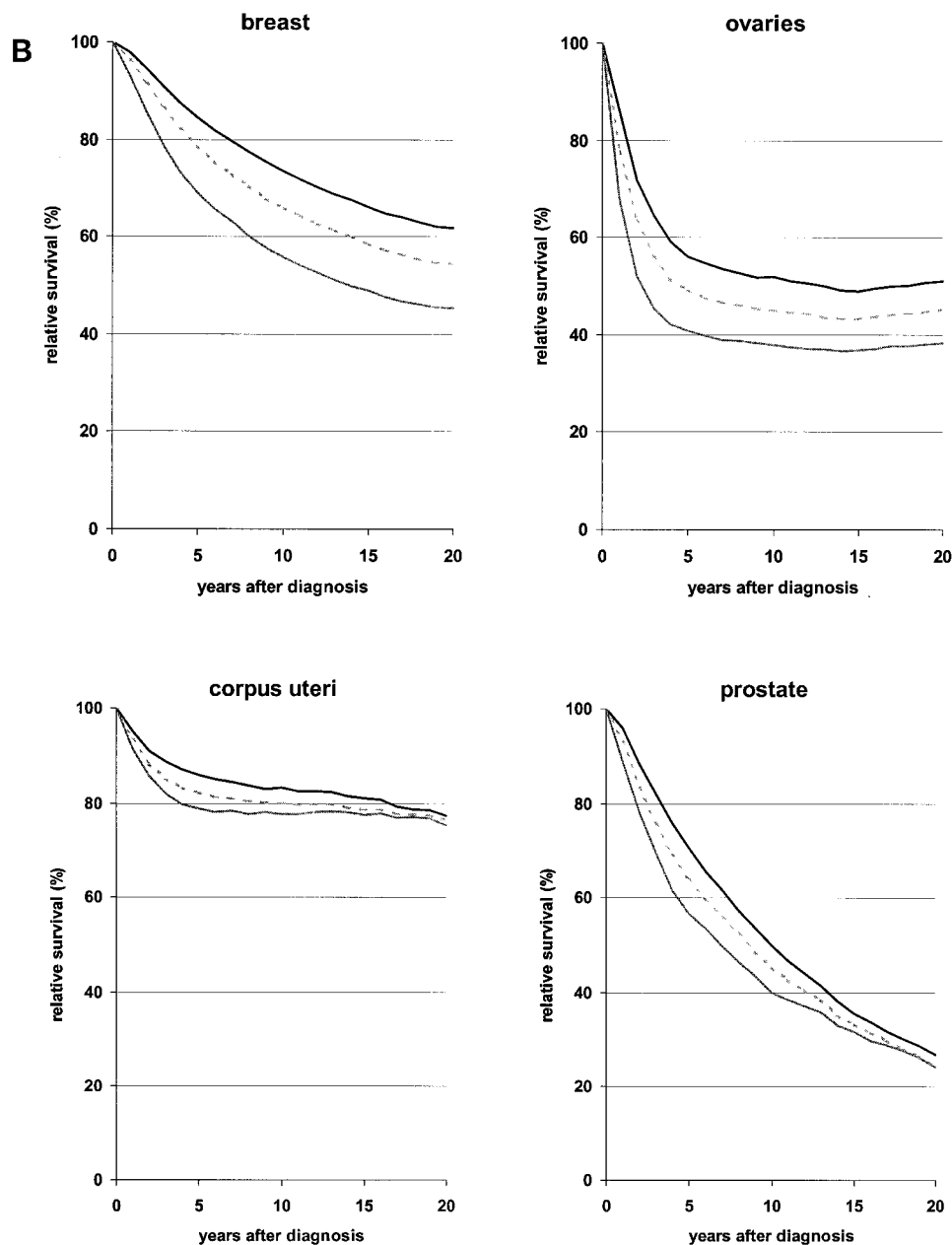


Fig 2. (cont'd)

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## ERRATUM

In the September 1, 2002, article by Koedoot et al, entitled "Palliative Chemotherapy or Watchful Waiting? A Vignettes Study Among Oncologists" (*J Clin Oncol* 20:3658-3664, 2002), there was an error.

Figures 1 and 2 were inadvertently switched.

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