# Cost-effectiveness in the diagnosis and treatment of carcinoma of unknown primary origin

*Original Research*

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**Between 2% and 9% of patients with cancer present with metastatic nonsquamous cell carcinoma of unknown primary origin. Traditionally, a series of investigations is undertaken to locate the primary origin of the tumour, although many of these tests are often painful or distressing to patients, unsuccessful in locating the primary site and costly to the health care system. Moreover, even if a tumour is found it usually cannot be treated surgically. However, a small number of cancers of unknown primary origin can be cured, arrested or effectively palliated with systemic treatment. This study compares the costs and outcomes of the current practice of comprehensively searching for the primary tumour with those of an alternative, limited approach that identifies only the primary tumours for which relatively effective systemic therapy exists. Decision trees were constructed for the two diagnostic approaches and their associated therapeutic options. Costs and probabilities were integrated with published data on the survival of patients with each type of cancer. The results indicate that the comprehensive diagnostic strategy may increase 1-year survival rates from 11.0% to 11.5%. On the basis of Ontario cost data it is calculated that the additional costs of a comprehensive search for 1000 patients will range from approximately $2 million to $8 million, depending on the subsequent treatment strategy.**

**Dans 2% à 9% des cas de cancer, il s'agit de métastases d'un épithélioma non-squameux dont le site d'origine est inconnu. La recherche de celui-ci comporte habituellement une série d'examens qui sont pénibles pour le malade, fort coûteux et peu efficaces dans la découverte de la tumeur primitive. De plus, celle-ci fût-elle décelée, elle serait ordinairement inaccessible à la chirurgie. Dans un petit nombre de cas, cependant, elle reste susceptible de guérison, d'arrêt ou de palliation grâce à un traitement par voie générale. On compare ici les coûts et les résultats de la recherche intensive des tumeurs primitives selon le style actuel à ceux d'une recherche limitée à celles pour lesquelles on peut offrir un traitement relativement efficace par voie générale. On a conçu des arbres décisionnels pour l'une et l'autre méthodes et les thérapeutiques mises en oeuvre. On y considère coûts et probabilités en rapport avec les données déjà publiées sur la survie des malades pour chaque type de cancer. En guise de résultat, on indique que la recherche diagnostique intensive d'une tumeur primitive porte de 11,0% à 11,5% le taux de survie de 1 an. Aux prix ontariens, pour 1000 malades il en coûtera de 2 à 8 millions de $, selon le traitement ultérieur choisi.**

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Treatment decisions in oncology are strongly influenced by knowledge of the natural history, the histologic type, the stage and the primary site of the tumour. The clinical management of patients who present with disseminated neoplasms for which the site of origin cannot be determined is a major challenge.

← For prescribing information see page 1067

For the purpose of this study a patient with carcinoma of unknown primary origin is defined as one who presents with histologically confirmed metastatic nonsquamous cell carcinoma (e.g., adenocarcinoma, anaplastic carcinoma or poorly differentiated carcinoma) and for whom thorough history-taking, physical examination (including pelvic, rectal and breast examinations), chest roentgenography and urinalysis do not identify the primary site. We have excluded patients presenting with squamous cell carcinomas because the primary site of the tumours, the prognosis and the ultimate treatment of patients with metastatic squamous cell carcinoma of unknown primary origin can be quite different.[1]

Carcinoma of unknown primary origin is not uncommon, occurring in between 2.6% and 9.6% of patients with tumours.[2,3] Usually many investigations are undertaken to locate the primary origin of the tumour; these may include radiologic examination of the upper gastrointestinal tract, barium enema, intravenous pyelography, mammography, thyroid scanning and bronchoscopy. The main arguments for undertaking a comprehensive diagnostic strategy are that (a) finding the primary site might lead to specific antitumour treatment, (b) finding an occult primary tumour might prevent local complications (e.g., bleeding from the primary tumour, obstruction or perforation of a viscus), and (c) finding the primary site might give a better guide to prognosis and help the physician communicate with the patient. The arguments against the comprehensive strategy are as follows: (a) it exposes many patients to unnecessary investigations, considerable discomfort and inconvenience; (b) even with a meticulous search, the primary site is not often found; (c) if found, the tumour is usually a cancer for which there is no effective systemic treatment;[4,5] and (d) it consumes resources that might better be used in other ways.

The dilemma of whether or not to search for a primary tumour is summarized by Moertel,[6] who points out that "many hundreds of dollars for computerized tomography, angiography, flexible fibroscopy and the like are an investment in futility when the end result is only the discovery of an obscure carcinoma of the pancreas for which no effective therapy exists"; moreover, "treatment of unknown disease with arbitrarily selected cytotoxic drugs may produce expense and discomfort far in excess of diagnostic approaches that would allow treatment to be applied rationally".

There are a number of cancers that, although disseminated at presentation, can be cured, arrested or consistently palliated with systemic therapy; in men these include prostatic carcinoma, testicular (germ-cell) carcinoma, small-cell carcinoma of the lung and lymphoma, and in women breast carcinoma, ovarian carcinoma, choriocarcinoma, small-cell carcinoma of the lung and lymphoma.[7,8] A number of these neoplasms (e.g., lymphoma, germ-cell carcinoma and small-cell carcinoma) may present as undifferentiated or poorly differentiated carcinomas, and an effort must be made to detect potentially curable tumours.

The main object of our study was to compare the costs and outcomes of the current practice of a comprehensive search for the primary tumour with an alternative approach of a more limited investigation to identify only the carcinomas for which relatively effective systemic therapy exists — that is, therapy that is known to increase survival or consistently control symptoms by arresting growth of tumours that present at a metastatic stage. We recognize that any tumour has the potential to be treated and hence can be referred to as treatable. However, in our analysis we have restricted the use of the term "treatable" to only the carcinomas that are responsive to therapy, as we have defined above.

We developed a framework (a decision tree) for exploring diagnostic and treatment options for carcinomas of unknown origin, synthesizing current epidemiologic knowledge on test and treatment outcomes and estimating the costs of diagnosis and management with each approach. This work can also be used to provide clinical practitioners with a systematic framework for considering diagnostic and treatment choices, to identify the potential aggregate resource savings (for Ontario) from adopting a limited investigation strategy and to identify areas in which knowledge is lacking and for which further research would be worth while.

## Diagnostic strategies

The comprehensive and limited diagnostic strategies are summarized in Table I. Their difference lies in the intent of the limited strategy to identify only the carcinomas for which effective systemic therapy currently exists. Specifically, electron microscopy of the metastasis is used to identify treatable small-cell carcinomas or lymphomas, the latter diagnosis being aided by immunocytochemistry. In men measurements of serum acid phosphatase (for prostatic carcinoma) and human chorionic gonadotropin (HCG) and $\alpha$-fetoprotein (for testicular carcinoma) complete the limited investigation, whereas in women this objective is served by mammography and estrogen-receptor assay (for breast cancer) and pelvic ultrasonography (for ovarian carcinoma). The comprehensive strategy, on the other hand, seeks to identify all primary sites and requires additional investigations, such as radiologic examination of the upper gastrointestinal tract, barium enema, intravenous pyelography, thyroid scanning and bronchoscopy. However, the carcinomas identified by these tests (including metastatic cancers of the stomach, colon, pancreas, liver and kidney, non-small-cell lung cancer and other less prevalent cancers) do not respond well, if at all, to treatment; consequently, survival is not likely to be extended as a result of therapeutic interventions.

The diagnostic investigation of a patient with an occult primary tumour may vary depending on the presenting metastatic site. A woman presenting with an axillary metastasis warrants mammography to detect an occult primary breast tumour,[10] whereas the same patient presenting with a solitary supraclavicular metastasis is more likely to have a primary tumour in the lung or gastrointestinal tract than in the breast.[9,10] A small percentage of patients presenting with metastatic adenocarcinoma in a lymph node in the mid- or upper neck will have a primary tumour originating in the salivary glands, usually the submandibular gland,[10] but it is rare for a primary tumour in the salivary gland to present with a metastatic node and not an easily detectable primary tumour. However, since this does occur, albeit infrequently, patients presenting with nonsquamous cell carcinoma in a lymph node in the mid- or upper neck should have a careful head and neck examination to rule out the possibility of the primary tumour's arising in the major or minor salivary glands. Patients in this group are best managed surgically and are not included in this analysis.

Similarly, metastatic adenocarcinoma presenting in neck nodes (and, not uncommonly, in a solitary supraclavicular node), particularly in younger patients, can arise from a primary tumour in the thyroid. The pathologist usually has no difficulty in distinguishing well differentiated metastatic thyroid cancer from other types of adenocarcinoma. Moreover, radioisotope scans (or even the newer generation of more sophisticated sonograms and computerized tomography [CT] scans) rarely pick up a primary tumour in the thyroid that cannot be detected by a careful physical examination.[11] Accordingly, we have not included thyroid scanning in our limited search for treatable primary tumours. In addition, there are patients who present with a mid- or upper neck node that on biopsy is found to be truly undifferentiated carcinoma and in whom the primary site is usually presumed to be the upper aerodigestive tract.[12] This group of patients usually receives the same treatment as patients with squamous cell tumours and is therefore excluded from our analysis.

Patients with carcinoma of unknown primary origin often present to a family practitioner, general internist or surgeon, any one of whom might perform diagnostic investigations to search for the primary tumour prior to referral to an oncologist. Although the oncologist might not repeat these tests but, rather, review the results with a radiologist, we have assumed that no prior investigations have been performed. This is unlikely to bias our analysis, because prior investigations would probably be equally (that is, randomly) distributed for both the comprehensive and the limited strategies.

Finally, although newer imaging techniques, such as CT scanning and, more recently, magnetic resonance imaging, may be useful in locating the primary cancer, they have not been included in our limited investigation because insufficient information is available on their diagnostic capabilities when applied specifically to patients with carcinoma of unknown primary origin.[13]

**Table I—Diagnostic strategies for patients with nonsquamous cell carcinoma of unknown primary origin**

| Patient's sex | Comprehensive investigation* | Limited investigation*[4,7,9] | Site of treatable primary tumours |
|---|---|---|---|
| Male | Measurement of serum levels of: | Measurement of serum levels of: | |
| | Acid phosphatase | Acid phosphatase | Prostate |
| | Alpha-fetoprotein | Alpha-fetoprotein | Testis |
| | HCG | HCG | Testis |
| | Electron microscopy | Electron microscopy | Lung (small cell or lymphoma) |
| | Immunocytochemistry | Immunocytochemistry | Lymphoma (testis or prostate) |
| | Radiologic examination of upper gastrointestinal tract | | |
| | Barium enema | | |
| | Intravenous pyelography | | |
| | Abdominal CT scanning | | |
| | Thyroid scanning | | |
| | Bronchoscopy | | |
| Female | Mammography | Mammography | Breast |
| | Estrogen-receptor assay | Estrogen-receptor assay | Breast |
| | Pelvic ultrasonography | Pelvic ultrasonography | Ovary |
| | Electron microscopy | Electron microscopy | Lung (small cell or lymphoma) |
| | Immunocytochemistry | Immunocytochemistry | Lymphoma |
| | Radiologic examination of upper gastrointestinal tract | | |
| | Barium enema | | |
| | Intravenous pyelography | | |
| | Abdominal CT scanning | | |
| | Thyroid scanning | | |
| | Bronchoscopy | | |

*HCG = human chorionic gonadotropin; CT = computerized tomography.

## Treatment strategies

There are four broad treatment choices in cancer therapy: chemotherapy (which, for our purposes, also includes hormonal manipulation), radiotherapy, surgery and symptomatic care. Most of these options are, in theory, applicable to the treatment of carcinoma of unknown primary origin, although the precise regimens differ according to the suspected site. Radiotherapy or surgical removal of the primary tumour (if found) may be required following initial palliative therapy for local pain or to avoid the development of an obstruction caused by tumour growth. Although it is recognized that surgical removal of a primary tumour in some sites (e.g., the salivary gland) is of value and that radiotherapy can be very effective in certain malignant diseases (e.g., metastatic breast cancer), the preferred option for carcinoma of unknown primary origin is likely to be either chemotherapy or symptomatic care.

If the primary site of the tumour is found patients are usually placed on a chemotherapy regimen recommended for the specific tumour. If the primary site is not found physicians act in a number of ways: some prescribe multiagent chemotherapy, one of the broad-spectrum combinations of drugs used in carcinoma of unknown primary origin;[14,15] others give symptomatic care (i.e., follow-up consultations and attention to symptoms such as pain, nausea and vomiting) on the basis that, given the poor prognosis of most patients with metastatic disease, the unpleasant side effects of the cytotoxic drugs would far outweigh the benefits from a potential minimal extension of life.

A third option is to treat patients as though they had a treatable (responsive) primary tumour and give the appropriate systemic treatment based on the possible location of the tumour. We did not include this option because there is no information as to how frequently it is used, nor is it the treatment strategy currently advocated in the literature.[14,15]

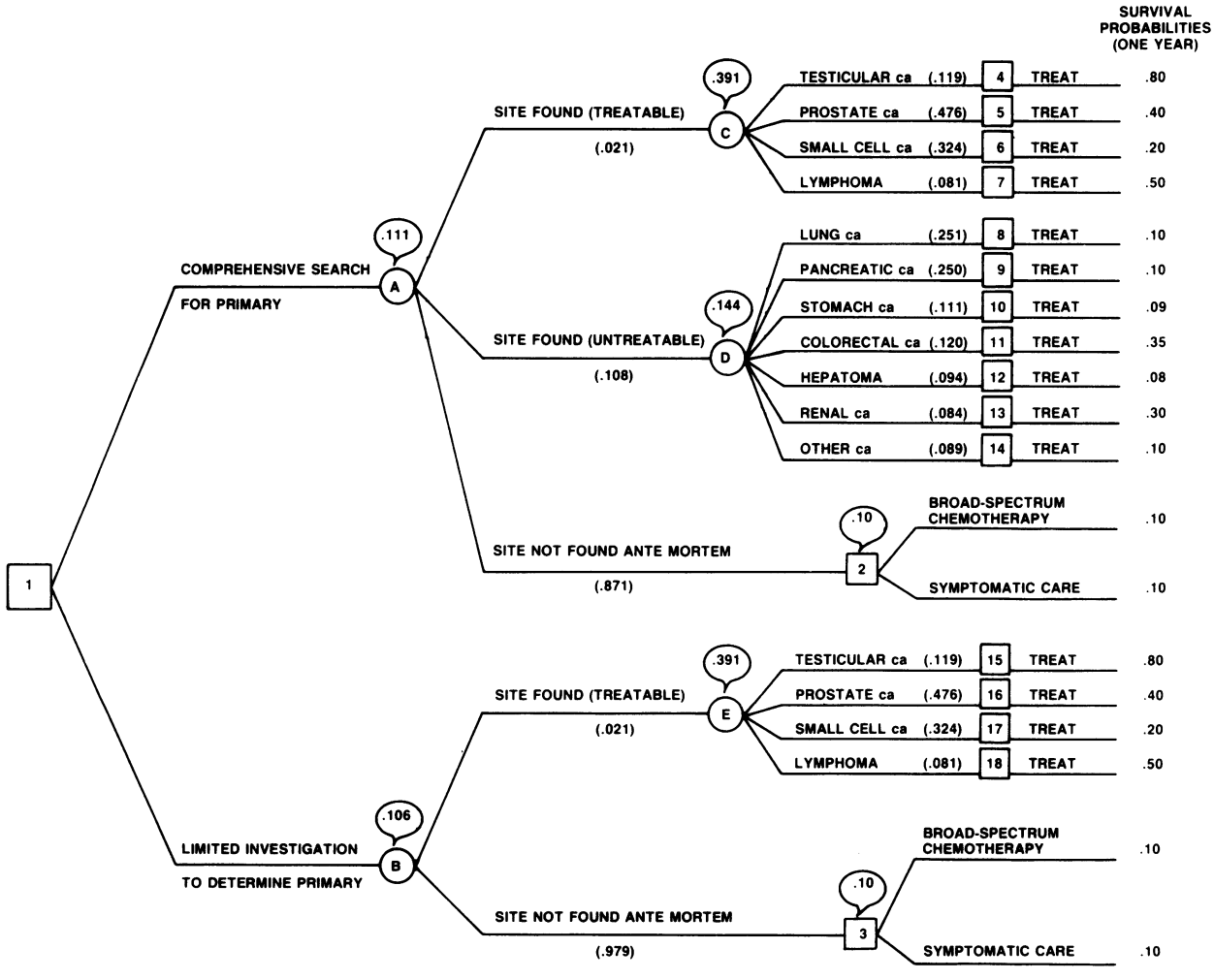


**Fig.1—Decision tree for investigation of carcinoma of unknown primary origin in men. Squares with numbers represent choice nodes (points at which clinician may make decision); numbers in parentheses are probabilities of specified choices; circles with letters are chance nodes (points at which possibilities of various outcomes arise); and numbers in balloons are expected 1-year survival rates.**

## Methods

### *Analytic framework*

A decision tree is a model of the temporal and logical flow of steps in the management of clinical problems.[16,17] It comprises four structural elements, as follows:

- The clinical starting point, which refers to the group of patients for whom the analysis is conducted.
- Alternative management options — for example, diagnostic tests or therapies. A choice (decision) node, represented by a small square, denotes a point at which a decision must be made among several alternative courses of action.
- A set of events, represented by a chance node or small circle, whose probability is beyond the control of the decision-maker.
- A set of outcomes or valued end-points determined by the clinical research question (e.g., percentage survival or recurrences averted). The expected value (represented by a "balloon") of a particular strategy is calculated by multiplication and addition of probabilities, known as "folding back".

For this analysis the outcome of interest is the difference in 1-year survival rate when the comprehensive strategy, rather than the limited strategy, is used to search for the primary tumour.

### *Decision tree*

The decision tree for the diagnostic and therapeutic options for men is shown in Fig. 1.

The main diagnostic choice is made at choice node 1. If a comprehensive search is performed there are three possible outcomes (at chance node A): the primary site of a treatable carcinoma will be found, the primary site of an untreatable carcinoma will be found, or no site will be found.

If a treatable primary tumour is found appropriate systemic therapy would be administered. (Given the demonstrated effectiveness of systemic therapy, symptomatic care is not likely to be

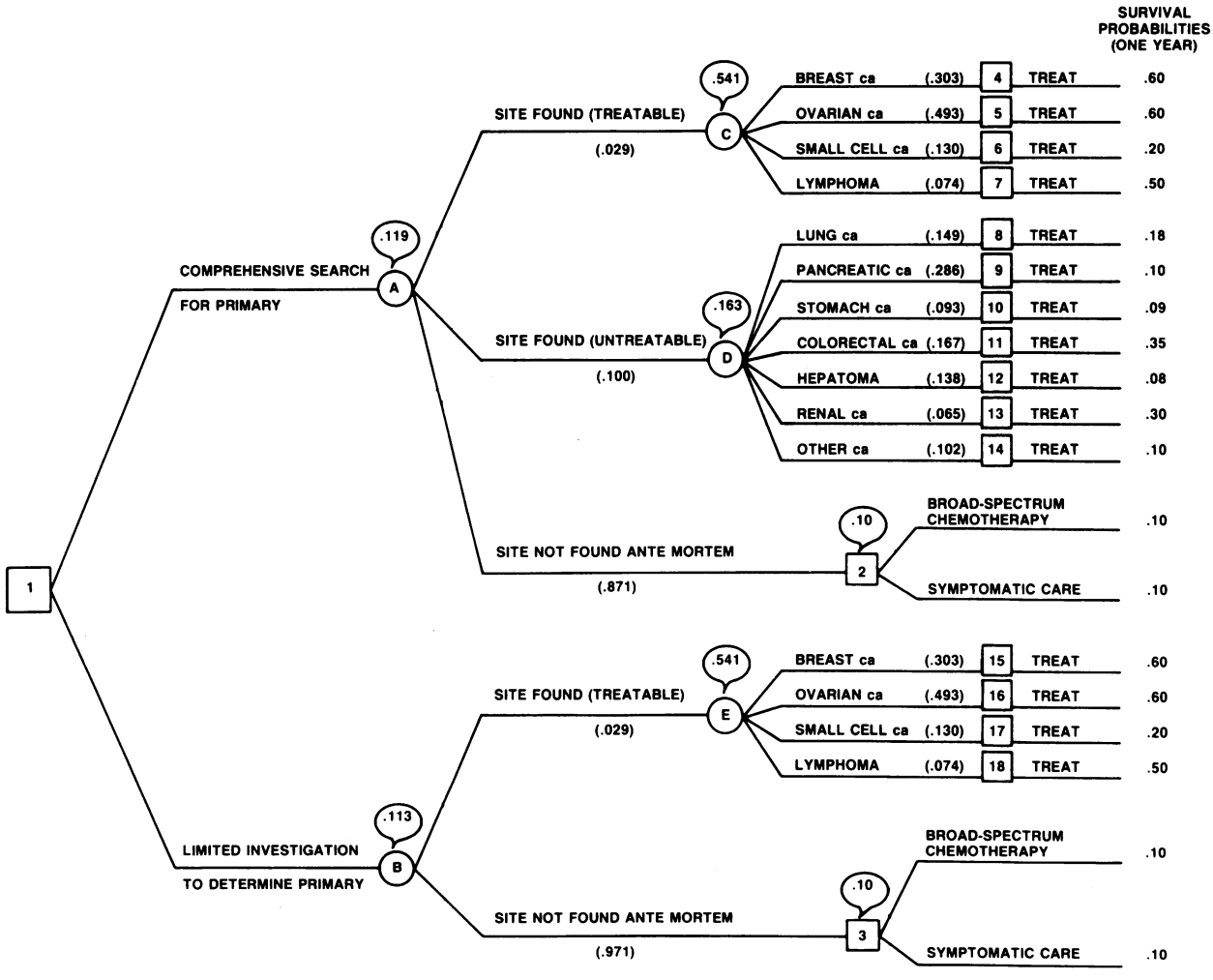


**Fig. 2—Decision tree for investigation of carcinoma of unknown primary origin in women. Symbols as in Fig. 1.**

considered.) In men multiagent chemotherapy is used for metastatic testicular carcinoma, lymphoma and small-cell carcinoma of the lung, and estrogens are used for prostatic cancer.

If an untreatable primary tumour is found we have assumed that systemic therapy would be administered. Chemotherapy is preferred, except for renal cell carcinoma, for which the treatment is infarction of the kidney followed by surgery and administration of progesterone.* We have not considered symptomatic care as an option, because presumably a patient would not be subjected to extensive investigations to locate untreatable primary carcinomas if site-specific therapy was not contemplated.

If no site is found ante mortem the carcinoma can be treated with broad-spectrum chemotherapy or symptomatic care (choice node 2). We have assumed that the chemotherapeutic agent used is FAC (5-fluorouracil, Adriamycin [doxorubicin] and cyclophosphamide),[15] which has a wide spectrum of activity and is commonly used in clinical practice for patients with carcinoma of unknown primary origin.

The options under the limited diagnostic strategy are restricted to treatment for the smaller number of primary tumours that would be found, with either chemotherapy or symptomatic care given to the remainder.

Conceivably, a third option available at choice node 1 is not to search for the primary site at all. However, we did not explicitly consider this option, because, given current practice standards, it is not clinically acceptable.

The decision tree for women is essentially the same as that for men, except that the treatable cancers differ, as indicated in Table I and Fig. 2. In women multiagent chemotherapy is preferred for ovarian carcinoma, lymphoma and small-cell carcinoma of the lung, whereas chemotherapy or hormonal therapy, or both, is used for disseminated breast cancer. Although choriocarcinoma is treatable, it has not been included, because it commonly presents post partum and has not been reported as one of the primary sites of origin.[15,18-21]

### *Probability of finding the primary site*

A key factor in estimating the outcomes of the diagnostic and therapeutic options is the probability of finding the primary site of the tumour with either the comprehensive or the limited strategy. Five empirical studies of searches for the primary sites in patients with carcinoma of unknown origin have been reported in the literature.[15,18-21]

Table II shows that the studies vary both in the overall proportion of sites found and in the distribution of cancers by site. If Table II is simplified to a $3 \times 5$ contingency table[22] with primary sites combined to yield three broad categories (i.e., above the diaphragm [mainly the lung and breast], below the diaphragm and miscellaneous), then the overall chi-square value is 18.54 ($p < 0.05$), which indicates that there is a statistically significant difference in the distribution of tumour sites among the five studies. The statistical significance of this result is attributed primarily to the discrepancies in the sites above the diaphragm (the contribution to the overall chi-square value is 11.71).

In general, the probability that an investigator will find the primary site ante mortem depends on (a) the true prevalence of cancer, by site, in the patient population surveyed; (b) the range of investigations performed; and (c) the sensitivity of the investigations (i.e., the ability of the test to detect the condition if it is present).

Reconciliation of the data in the five studies is difficult for several reasons. First, there was a low prevalence of certain cancers in the patient population; it is therefore possible that the studies with a small number of patients did not find any cancers in a particular site, even though these cancers exist in the population as a whole. Second, none of the studies gave an adequate description of the inception cohort: only two indicated the male/female breakdown,[18,21] and all of the studies suffered from a referral bias — that is, the patients surveyed reflected the particular interest of the investigator and not the overall population of patients with carcinoma of unknown primary origin. Third, there was some variation in the range of procedures performed, although most of the studies included the majority of the tests suggested in our comprehensive strategy. Finally, all the studies reported postmortem as well as antemortem findings, and in each study this confounding factor was handled differently.

Thus, in order to estimate the prior probability of finding the primary tumour ante mortem,

**Table II—Distribution of primary sites of cancer**

| Site of cancer | Schildt et al[15] (n = 51) | Moertel et al[18] (n = 162) | Osteen et al[19] (n = 67) | Nystrom et al[20] (n = 266) | Stewart et al[21] (n = 87) |
|---|---|---|---|---|---|
| Lung | 4 | 1 | 18 | 28 | 7 |
| Pancreas | 6 | 16 | 6 | 30 | 1 |
| Stomach | 1 | 5 | 2 | 12 | 3 |
| Colon/rectum | 1 | 5 | 5 | 15 | 5 |
| Liver | 1 | 4 | 2 | 16 | 2 |
| Kidney | 2 | 2 | 2 | 9 | 2 |
| Lymphoid tissue | 0 | 0 | 4 | 0 | 0 |
| Testicle | 1 | 0 | 0 | 0 | 2 |
| Prostate | 1 | 1 | 4 | 4 | 2 |
| Breast | 0 | 2 | 3 | 3 | 0 |
| Ovary | 0 | 0 | 5 | 4 | 4 |
| Other | 1 | 6 | 4 | 8 | 2 |
| Total | 18 | 42 | 55 | 129 | 30 |

*The choice of therapeutic regimens is consistent with current practice and with evidence reported in the literature. We can provide, on request, a list of the studies we used to determine the treatment for each site of cancer.

we made the following assumptions:

- Unless otherwise indicated the proportions of men and women surveyed in a given study were the same as those for new cases of cancer in all sites.[23] In 1981 the American Cancer Society estimated 815 000 new cases in the United States, 403 000 in men and 412 000 in women,[23] or 49.4/50.6, which we have rounded to 50/50 for ease of calculation. (The proportions of men in the two studies that reported this statistic were 62%[18] and 52%.[21])
- The distribution of primary tumour by site was that observed in the five studies as a whole.
- Because the studies that found the lung as the primary site did not report the histologic type of the cancer, we have assumed that small-cell carcinoma of the lung represents 20% of the lung tumours presenting as carcinoma of unknown origin.[24]
- The probability of finding the primary site ante mortem when a comprehensive search was undertaken was, according to our "best guess", the average of the probabilities observed in the three studies that reported the antemortem findings separately (i.e., 13.7%, 8.3% and 26.4% respectively; mean 12.9%).[15,20,21]

### *Survival*

The estimated survival rates (proportions of patients alive 1 year after diagnosis) were derived from data currently available in the literature. We identified the ranges of survival rates by site and made our "best guess" from the mean of these values* (Figs. 1 and 2).

We encountered a number of difficulties in generating the survival rates for metastatic cancers: the natural history of untreated metastatic carcinoma is not readily available; the use of historical data may not reflect current survival rates because of recent improvements in supportive therapy; the patient numbers in the natural-history studies are often small, so our confidence in the reported results is limited; and the source of the information (i.e., surgical or medical series) must be taken into account when interpreting the survival data. For example, patients with metastatic cancer in a surgical series may have been selected for surgery because they were generally healthier or, conversely, because of a complication (i.e., obstruction or bleeding). These complicating factors could bias survival, the extent of the bias depending on the relative importance of each factor in a given study.

In some instances the 1-year survival of an untreatable cancer could exceed that of a treatable cancer. Although this might at first seem odd, it should be emphasized that our definition of a treatable tumour depends not on an absolute survival rate but, rather, on the increment in the probability of survival following systemic treatment. Thus, although the survival rate associated with, say, renal cancer presenting as carcinoma of unknown primary origin is higher than that associated with small-cell carcinoma of the lung, we have labelled the former as untreatable, since the survival rate is not significantly affected by the use of systemic therapy. The survival rate associated with metastatic small-cell carcinoma, however, increases with therapy, even though the absolute rate is less than some of those associated with untreatable tumours.

### *Costs of diagnosis and therapy*

The costs were calculated from the point of view of the Ontario Ministry of Health, which is responsible for funding almost all hospital and medical expenditures in Ontario. Omitted from the cost estimates are patients' access costs (patients need not incur any direct expenses for medical and hospital care in Canada, given the existence of universal and comprehensive public health care insurance), indirect costs resulting from production losses and "psychic" costs associated with pain and discomfort. If these costs had been included they would likely have been greater for the comprehensive strategy than for the limited one.

The estimated cost of the limited investigation comprises the costs of routine tests, the costs of additional tests required to detect treatable cancers and physicians' fees for consultations and reassessments. The estimated cost of the comprehensive investigation includes the costs of routine tests, the costs of additional tests required to detect both treatable and untreatable cancers, physicians' fees, and the costs of hospital stays necessitated by the tests to identify untreatable cancers.

The costs of therapy are the sum of outpatient visit costs, physicians' fees, and costs of laboratory tests, drugs and, when necessary, hospital stays. These costs relate to the therapy given immediately following the diagnostic procedure and exclude the costs of terminal care in the hospital, home or hospice. Costs are calculated separately for men and women since different cancer sites are involved and drug doses differ slightly.†

Whenever possible, costs were obtained from the Ontario Health Insurance Plan of Benefits Schedule[25] and the Ontario Ministry of Health's hospital statistics.[26] Per-diem hospital costs were adjusted to reflect the different resources used by hospitals for patients with carcinoma of unknown primary origin. All costs are in 1983 Canadian dollars.

*These data are taken from numerous papers, the full details of which can be obtained from us on request.

†A detailed breakdown of the individual cost components included in the total cost estimates is available from us on request.

## Results

### *Survival*

We combined the data on the probability of finding the primary site of the cancer and the effectiveness of the resultant therapy to compare expected survival rates for men and women following the comprehensive and the limited diagnostic and treatment strategies. For example, in Fig. 1 the expected value of the strategy at choice node C, 0.391, is calculated from the sum of the products of the probabilities of detecting treatable cancers and the associated 1-year survival rates ([0.119 × 0.80] + [0.476 × 0.40] + [0.324 × 0.20] + [0.081 × 0.50]). Similarly, the expected value at node A, 0.111, is calculated from the sum of the products of the probabilities of survival and detecting all cancers when the comprehensive strategy is used ([0.021 × 0.391] + [0.108 × 0.144] + [0.871 × 0.10]). For men the comprehensive strategy would result in an increase in the probability of survival of 0.005 (0.111 − 0.106) (Fig. 1); in other words, additional diagnosis and treatment would result in another five patients' per 1000 being alive 1 year after diagnosis. This increment is a result of finding only a few additional primary sites combined with the associated low incremental survival rate for most of the therapies for untreatable cancers. For women the comprehensive strategy would result in an increase in the probability of survival of 0.006 (0.119 − 0.113) (Fig. 2). The incremental survival rate for women, six patients per 1000, is about the same as that for men.

### *Cost-effectiveness*

The incremental cost of the comprehensive diagnostic strategy is the same for men and women — $1768 per patient ($455 in fees and $1313 in hospital stays) — because the diagnostic strategies for untreatable carcinomas are not sex-specific. In 1981 there were 17 446 new cases of cancer registered at treatment centres in Ontario.[27] Depending on the proportions of these cancers that are assumed to be carcinomas of unknown primary origin (2.6% to 9.6%), the approximate potential annual savings in diagnostic costs from using the limited rather than the comprehensive strategy would be between $800 000 and $2 900 000.

The costs of treating patients with both strategies depend not only on the diagnostic strategy used but also on the therapy provided. For example, the physician may take the view that if the site is not found there is nothing to gain from giving nonspecific multiagent chemotherapy and instead would opt to provide symptomatic care. Alternatively, he or she may decide to treat every patient, irrespective of whether the site is found, with either tumour-specific therapy if the primary site is located or multiagent broad-spectrum chemotherapy if the site remains obscure.[14,15]

Thus, we can define four strategies for treatment, the costs of which are shown in Table III. A very conservative approach (strategy I) to the management of 1000 patients with carcinoma of unknown primary origin (an approximation of the annual number of such patients in Ontario) would cost approximately $761 000. With this strategy only the tumours for which relatively effective systemic therapy exists would be searched for and treated if found; the result would be 110 patients alive 1 year after diagnosis (assuming that, of the 1000 patients, 500 men would have a survival rate of 0.106 and 500 women would have a rate of 0.113, as indicated in Figs. 1 and 2). Patients for whom the primary tumour was not found would receive symptomatic care.

The opposite extreme would be a strategy by which an extensive search was undertaken and every patient treated, either with tumour-specific therapy (if the primary tumour was found) or broad-spectrum combinations (if the tumour was not found). This comprehensive approach (strategy IV) represents an expenditure of approximately $7 851 500 ($8 612 500 − $761 000) per annum in excess of the cost of the limited aproach. Theoretically, an additional five patients would be alive 1

Table III—Costs and effects on survival of limited and comprehensive diagnostic and treatment strategies for 1000 patients with carcinoma of unknown primary origin

| Strategy* | Cost | Effects (no. of patients surviving 1 year after diagnosis) |
|---|---|---|
| I | | |
| Limited investigation, treatment option 1 | 761 000 | 110 |
| II | | |
| Limited investigation, treatment option 2 | 7 348 500 | 110 |
| Incremental costs and effects | 6 587 500 | 0 |
| III | | |
| Comprehensive investigation, treatment option 1 | 2 737 000 | 115 |
| Incremental costs and effects | 1 976 000 | 5 |
| IV | | |
| Comprehensive investigation, treatment option 2 | 8 612 500 | 115 |
| Incremental costs and effects | 7 851 500 | 5 |

*Treatment option 1 is to use symptomatic therapy, option 2 to use broad-spectrum chemotherapy if the primary site of the tumour is not found.

year after diagnosis, and approximately 20 more could be told the primary site of the tumour and given tumour-specific therapy (although the prognosis would probably be poor). This strategy would represent an expenditure of approximately $1 570 000 for each additional patient.

Strategy II uses a limited investigation for diagnosis (searching only for the treatable cancers) but a comprehensive one for treatment. If the primary site is found tumour-specific chemotherapy is given; if the site is not found broad-spectrum chemotherapy is used. This approach would cost approximately $6 587 500 ($7 348 500 − $761 000) more than the limited strategy, and there is no evidence that it would increase survival.

Strategy III, a comprehensive strategy for diagnosis and a limited strategy for treatment (i.e., only if the primary tumour is found), would cost another $1 976 000 ($2 737 000 − $761 000) and result in about five more patients' surviving 1 year after diagnosis. In addition, the primary site of the tumour would be known in 10 additional patients.

*Sensitivity analysis*

We recognize that the accuracy of our results depends on both the accuracy of the assumptions we made to derive them and on the precision of the data we used in the probability and cost estimates. We therefore conducted a series of sensitivity analyses around the parameters of uncertainty to test the robustness of our results to variations in both the assumptions and the data.

We recalculated the expected survival rates with a higher probability of finding the primary site than the 0.129 we used originally. Specifically, it was assumed that this probability was equal to the highest antemortem value (0.264) in any of the five studies.[21] The incremental probability of survival 1 year after diagnosis then becomes 0.011 rather than 0.005.

We also examined the implications of assuming a different distribution of sites of untreatable primary cancer. As mentioned earlier, there is significant variation in the distribution of primary sites as identified in studies that report the origin of the tumour, and this variation is primarily due to discrepancies in the distribution of sites "above the diaphragm". We therefore used the results from the study by Osteen and colleagues,[19] who reported a relatively higher prevalence of sites above the diaphragm, to estimate the expected survival rates with a different distribution of sites. This had virtually no effect on expected survival rates — that is, the expected survival rate for men at chance node A changed from 0.111 to 0.1109.

We made a basic assumption in determining our initial results; that is, that broad-spectrum chemotherapy and symptomatic care were of equal effectiveness. Although there is no reliable clinical evidence to indicate the superiority of either treatment for patients with carcinoma of unknown primary origin we explored the implications of assuming that chemotherapy was twice as effective as symptomatic care. The effects (number of patients still alive 1 year after diagnosis) were recalculated with a 1-year survival rate of 0.05 for symptomatic care and 0.10 for broad-spectrum chemotherapy for both the comprehensive and the limited approach to diagnosis. As anticipated, the expected number of survivors decreased substantially when symptomatic care was chosen. With strategy I (limited investigation, symptomatic care) the number of survivors would decrease from 110 to 61 per 1000 patients. The corresponding figure for strategy III (comprehensive investigation, symptomatic care) would decrease from 115 to 72. (With strategies II and IV the figures are unchanged because no change was assumed in the effectiveness of broad-spectrum chemotherapy.) Thus, when the survival rate with symptomatic care is assumed to be 10% the incremental effectiveness between strategies III and I represents five additional patients' being alive 1 year after diagnosis. When the survival rate is decreased to 5%, however, the incremental effectiveness represents 11 additional patients.

Strategies II and IV appear more attractive when differential effectiveness between chemotherapy and symptomatic care is assumed. Both would result in significantly more survivors 1 year after diagnosis than would strategies I and III; as well, they would cost considerably more. It should be emphasized, however, that although evidence from the literature is lacking with respect to the relative effectiveness of broad-spectrum chemotherapy and symptomatic care in patients with carcinoma of unknown primary origin, it is likely that the survival rates with the two types of therapy are equally poor. None the less, our results emphasize the need for further research and empirical evidence on these two treatment alternatives.

To derive our initial results we assumed that patients in whom the primary site is not found have the same probability of surviving 1 year after diagnosis (10%) with the comprehensive and the limited investigations. The literature provides no reliable evidence on survival rates for this group of patients. We therefore re-estimated the results assuming, somewhat arbitrarily, that when the site is not found the survival rate is higher for the patients for whom the limited investigation is used than for those for whom the comprehensive investigation is used. This may be true, because the comprehensive investigation identifies, and subsequently allows the treatment of, some untreatable carcinomas that respond, albeit minimally, to therapy. Consequently, the remaining patients for whom the site is not found may have a lower survival rate than those who remain after the limited investigation is undertaken. Our results indicate that altering the survival rate from 10% to 5% for the patients in whom the site is not found in the comprehensive investigation changes the expected value at node A in Figs. 1 and 2 from

0.115 to 0.072. In other words, the comprehensive strategy would be both more costly and less effective (72 survivors v. 110 with the limited strategy); thus, strategies III and IV would be virtually impossible to defend in terms of either effectiveness or efficiency.

We also considered the possibility that the survival rates for patients with untreatable carcinomas were underestimated. The results were therefore recalculated assuming that the 1-year survival rates for the patients with untreatable primary tumours were twice those originally assumed, all other survival rates being unchanged. The probability of 1-year survival for the patients given a comprehensive investigation would increase from 0.115 to 0.131; therefore, the comprehensive investigation would yield 21 more survivors (131 − 110) at the end of 1 year. Of course, this doubling of the initial survival rates is an extreme example; even if some of the initial rates were underestimated it is unlikely that the "true" rates would be twice as high.

We also considered the effect of using alternative broad-spectrum chemotherapeutic regimens on the costs. To derive our original estimates of expected costs and outcomes we assumed that FAC was administered if the primary site was not found and broad-spectrum chemotherapy subsequently chosen.[10] However, it has been suggested that a combination of doxorubicin and mitomycin C be administered in these circumstances;[9] we thus re-estimated our results assuming that the less expensive mitomycin C was used. (Equal effectiveness was assumed for these two agents.) Although the total costs were obviously lower, the incremental costs between the various strategies and the limited option none the less ranged from $1 800 000 to $3 600 000.

## Discussion

Approximately 2.6% to 9.6% of cancer patients present with metastatic carcinoma of unknown primary origin.[2,3] We compared the current practice of comprehensively searching for the primary site of the tumour with an alternative limited approach of identifying only the primary tumours for which relatively effective systemic therapy exists. We also examined the costs and outcomes of alternative therapeutic approaches if the primary site is not found.

Our study used two analyses. First, a costing of the alternative diagnostic strategies was undertaken. The incremental cost to the health care system of the comprehensive strategy was approximately $1768 per patient. This analysis was based on the rationale that although the comprehensive strategy gives more information it does not affect subsequent treatment decisions. Hence, the difference in cost between the two strategies is attributed solely to the additional cost of the comprehensive strategy.

The second analysis consisted of a cost-effectiveness evaluation of alternative diagnostic and therapeutic options. This approach assumes that a diagnostic strategy affects subsequent clinical management and that effectiveness (in terms of survival) may differ between the various diagnostic and therapeutic options. A decision tree was used to help define the inter-relations between the diagnostic and therapeutic strategies and to make the choices explicit. The decision tree and its associated probabilities represent the first step in formalizing many of the views currently expressed in the literature by Moertel[6] and others.

Our initial estimates indicated that the comprehensive diagnostic strategy is both more costly and possibly more effective than the limited approach. The relative magnitude of the cost differences depends primarily on the therapeutic strategy undertaken should the primary site not be found. The most costly strategy, comprehensive investigation combined with broad-spectrum chemotherapy when the site is not found, would cost approximately $7 850 000 more than the limited strategy and might result in an additional five patients' surviving 1 year after diagnosis.

The sensitivity analyses indicated that our initial results depended to a large extent on two assumptions: equal effectiveness of broad-spectrum chemotherapy and symptomatic care when the site was not found, and equal probabilities of 1-year survival with both the comprehensive and the limited searches, again when the site was not found. We based our initial estimates of survival on the best evidence currently available in the literature and clinical practice; however, the sensitivity of these results further emphasizes the need for rigorous clinical research in these areas.

Although we chose survival rates as the outcome of interest, we recognize that quality of life is an important consideration and that the value of survival may differ substantially depending on the diagnostic approach and treatment strategy employed. Moreover, patients and physicians may derive value from information that has little medical significance or no bearing on subsequent medical decisions. A logical direction for further research would therefore be to quantify the values associated with each outcome and adjust the outcomes accordingly. The implications of this omission from our study are not serious, however. We feel that the inherent disutilities associated with both the more lengthy and more invasive comprehensive diagnostic approach and with the side effects resulting from relatively ineffective therapy for untreatable cancers make the limited diagnostic approach even more attractive.

Given the frequent absence of reliable data and the imprecision of the data that are available, the contribution of research such as ours may understandably be questioned. None the less, the management of patients with carcinoma of unknown primary origin is a dilemma frequently faced by many physicians, and clinical decisions

must be made, even in the absence of definitive evidence. We have therefore attempted to work within the confines of existing data to formulate a systematic framework for the diagnosis and treatment of patients with carcinoma of unknown primary origin. Our analysis provides initial estimates of the cost-effectiveness of various strategies and identifies areas in which future research is needed. Furthermore, this framework can easily be modified to accommodate improvements in the diagnosis and treatment of this type of cancer.

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