CLINICAL REVIEW

The Utility of Follow-up Testing After Curative Cancer Therapy

A Critical Review and Economic Analysis

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OBJECTIVE: To review (1) basic principles of follow-up in patients who are in complete remission following curative therapy for cancer; (2) evaluate the available data on follow-up strategies for testicular cancer, Hodgkin's disease, non-Hodgkin's lymphoma, breast cancer, colorectal cancer, small cell and non-small cell lung cancer, and prostate cancer; and (3) analyze the cost of follow-up strategies

METHODS: The English language literature was reviewed utilizing MEDLINE headings for the specific malignancies and the text word "follow-up." Bibliographies of relevant articles also were reviewed. Emphasis was placed on prospective, randomized trials or large retrospective studies in which all patients who potentially could have been evaluated were accounted. The costs of various testing strategies were analyzed utilizing data from the Health Care Finance Administration.

DATA SYNTHESIS: Proper follow-up strategies should take into account patterns and time course of recurrence and should be obtained if detection of recurrence would allow meaningful therapeutic intervention. Testing also should be directed at early detection of malignant and nonmalignant complications known to be associated with the primary disease. Testicular cancer is a "model" malignancy in that sensitive tests for recurrence are available and early detection of recurrence allows for potentially curative therapy.

CONCLUSIONS: According to the currently available literature, repetitive follow-up laboratory and radiologic testing, except for nonseminomatous germ cell tumors, does not detect the vast majority of cancer relapses, nor does it result in a greater chance of cure or prolonged survival. The majority of recurrences at all disease sites will first be recognized as symptomatic changes in the patient's condition or alterations in the physical examination. A limited panel of blood tests and radiographic studies to detect recurrences, metachronous disease, and complications of therapy (malignant and nonmalignant), will suffice for most cancers. Though

data are limited, this more restrictive policy of follow-up testing does not appear to adversely impact patient quality of life and results in dramatic cost of savings to the health care system.

KEY WORDS: follow-up testing; cancer; testicular cancer; lymphoma; colon cancer.

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A great deal has been written about the utility of screening for cancer with great emphasis on cost-effectiveness.¹⁻³ Relatively little information exists on the value of follow-up testing of asymptomatic patients after potentially curative cancer therapy. This review will outline the general principles that should guide follow-up testing and then examine how these principles can be applied to testicular cancer, Hodgkin's disease and non-Hodgkin's lymphoma, and breast, colon, prostate, and lung cancers given currently available data. Economic analysis will demonstrate how this evidence-driven approach to follow-up testing can result in considerable savings without compromise of patient care. Testicular cancer will serve as a model to illustrate the rational application of follow-up testing. The lymphomas will be evaluated as they are among the most curable of malignancies. Breast, lung, colon, and prostate cancer are the most common solid tumors and are likely to be encountered by a wide range of practitioners. Together these seven malignancies constitute almost two thirds of cancer diagnoses in the United States.⁴

Four general principles should guide the selection of tests utilized to evaluate patients after potentially curative therapy of cancer:

1. The interval between examinations and duration of testing should be consistent with the time of maximal risk of recurrence and the natural history of the tumor.
2. The tests should be directed at the most likely sites of recurrence and should have a high predictive value, both positive and negative.
3. Therapy should be available that will result in cure, significant prolongation of life, or palliation of symptoms. The initiation of earlier ther-

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apy should improve the outcome compared with therapy given when the patient becomes symptomatic from the tumor.

4. The increased risk of second malignancy, both in the primary site and in other tissues that may have been exposed to the same carcinogens or in which there is epidemiologic evidence of increased risk, should also guide the ordering of tests. Malignant and nonmalignant complications of therapy must also be considered. Such testing should also be performed with a frequency and duration consistent with the nature of the risk and include only tests with high positive and negative predictive values.⁵

METHODS

The English language literature was reviewed utilizing MEDLINE headings for the specific malignancies and the text word "follow-up." Bibliographies of relevant articles also were reviewed. Emphasis was placed on prospective, randomized trials or large retrospective studies in which all patients who could have been potentially evaluated were accounted.

Recommendations for follow-up testing were graded according to the level of supporting evidence. The methodology of Cook et al. was adopted and simplified.⁶ Level 1 evidence is that in which at least one randomized trial is available supporting a particular strategy. Level 2 is based on retrospective studies in which the outcomes of all patients are reported. Level 3 is all other evidence and is assigned to tests for which there is conflicting level 1 or 2 evidence.

Economic analysis was performed for each of the malignancies in question utilizing national average allowed charges from 1995 Medicare Part B Extract Statistical System and are reported in 1995 U.S. dollars. These charges are illustrated in Table 1. Several simplifying assumptions are made. First, follow-up testing is only obtained during the periods of maximal risk of recurrence as defined in each section. Second, the rate of recurrence is assumed to be constant over this period. Third, no further surveillance testing after this period, beyond usual age-specific health maintenance testing, is performed. The total cost of follow-up is obtained by multiplying the number of patients at risk each year by the cost of follow-up for that year. The cost is then calculated from the sum of all the years of follow-up rounded to the nearest \$1 million. Cost per 1,000 patients is also provided and rounded to the nearest \$100,000. For breast, colon, lung, and prostate cancer, it is assumed that all patients with loco-regional disease can be rendered disease free. The number of patients at risk in the first year of follow-up is obtained by multiplying the number of patients with a particular diagnosis by the percentage with locoregional disease (in the case of breast, lung, prostate, and colorectal cancer) or by the percentage anticipated to achieve com-

Table 1. Allowed Charges Under Medicare Part B

	CPT-11 Codes*	U. S. Dollars
Laboratory		
Complete blood count with differential	85025	11
Erythrocyte sedimentation rate	85651	5
Total bilirubin	82250	6
Alkaline phosphatase	84075	7
Serum glutamic-oxadoacetic transaminoic	84450	7
α-fetoprotein	82105	23
Lactate dehydrogenase	83615	8
Human chorionic gonadotropin	84702	17
Carcinoembryonic antigen	82378	27
Prostate-specific antigen	84153	26
Fecal occult blood test	82270	4
Thyroid-stimulating hormone	84443	23
Radiologic		
Mammogram	76090	47
Bone scan	78306	189
Chest computerized tomography	71260	285
Chest x-ray	71020	18
Procedures		
Colonoscopy	45378	303
Outpatient visit (15 min)	99213	34

*CPT-11 indicates current procedural terminology.

plete remission (testicular cancer, Hodgkin's disease, and non-Hodgkin's lymphoma) (Table 2). For subsequent years, the relapsed patients in the preceding years are subtracted.

The yearly incidence and staging of the different cancers is derived from the Surveillance, Epidemiology and End Results (SEER) program data of the National Cancer Institute, Table 2.⁴ The relapse rates for the various malignancies are derived from SEER data for mortality as well as rates cited in clinical studies. Relapse is defined as recurrence after a primary therapy that has produced a remission. Furthermore, follow-up costs for those patients salvaged after relapse are not considered. Comparison is made between what is considered a "typical" evaluation based on published surveys or studies reporting results of follow-up and the recommendations presented in this article. Indirect costs and costs related to treatment of recurrence were not considered. This analysis is highly conservative and does not make adjustments for actual charges, inflation, or regional variation. It is most appropriately utilized as a method of determining the relative charges and potential savings rather than as actual dollar figures.

TESTICULAR CANCER

Nonseminomatous germ cell tumor (NSGCT), the most curable human tumor, may serve as a model for postcurative therapy surveillance. Series evaluating the question of observation alone versus retroperitoneal lymph node

Table 2. United States Incidence, Staging, and Relapse Rate of Malignancies Discussed

Malignancy	Incidence/Year (U.S.)	Local/Regional Disease, %	Relapse, %
Prostate	244,000	75	50
Lung	169,900	50	75
Colon/rectum	138,200	75	50
Breast	183,400	90	50
Nonseminomatous germ cell tumor	3,850	95*	15
Non-Hodgkin's lymphoma	28,000	85*	65
Hodgkin's disease	7,800	90*	35

*Approximate complete remission rate.

dissection (RPLND) in stage I disease (limited to the testicle) provide useful information regarding the ability of various tests to detect recurrence.⁷⁻¹⁴

Most recurrences will occur in the first 2 years (98.5%); therefore, surveillance should be most frequent and intensive during that time.¹⁵ Some groups advocate cessation of all studies at 5 years; however, a recently reported series of patients with relapses beyond 5 years has led some to advocate at least yearly follow-up for life.^{16,17} A reasonable follow-up schedule, based on the intervals utilized in published studies, would evaluate monthly tumor markers and examinations with bimonthly radiologic examinations in the first year. The frequency of visits should be decreased to every 2 months in the second year, every 3 months in the third year, and every 6 months in year 4 and 5, and annually thereafter.

Serum tumor markers such as β -human chorionic gonadotropin (β -HCG), lactate dehydrogenase (LDH), and α -fetoprotein, which are highly sensitive to the presence

of disease and carry prognostic significance, are available.¹⁸ Unfortunately, none of these markers are invariably elevated in the presence of disease. Markers are usually obtained at each follow-up visit. In patients who have undergone RPLND, relapse in the retroperitoneum is rare.¹⁹ The most likely site of recurrence is the chest, which may be asymptomatic, justifying the use of frequent imaging of the chest. In most centers this imaging has been with chest x-rays. Recent reports indicate that chest computed tomography (CT) is a more useful test than a chest x-ray. Gels et al. studied 154 patients with stage I disease who were observed without retroperitoneal lymph node dissection. Of 42 recurrences, 13 occurred in the chest. Only two of these were detected by chest x-ray, whereas all were detectable by CT.¹⁴ Though the CT was superior, the question of whether this earlier detection results in improved cure rates cannot be answered at this time. As Table 3 demonstrates, physical examination, tumor markers, and radiologic studies are complementary.

Table 3. Follow-up of Stage I Nonseminomatous Germ Cell Tumor

Abnormalities*												
Author/Year	Patients	Relapses	Site of Recurrence				Markers Only [‡]	CT/Chest				Markers + CT/ CXR
			Retroperitoneum	Chest	Both	Other [†]		Alone	CXR	H+P	CT+CXR	
Read, et al. ⁷ 1983	45	11	4	3	2	2	3	1	4	2	NS	NS [§]
Peckham, et al. ⁸ 1983	84	16	7	3	3	3	13	NS	NS	NS	NS	NS
Gelderman, et al. ⁹ 1987	54	11	5	2	2	3	1	NS	NS	1	4	5
Williams, et al. ¹⁰ 1987	147	37	14	10	5	8	8	7	0	0	5	9
Thompson, et al. ¹¹ 1988	36	12	4	5	0	3 [†]	4	3	2	3	0	NS
Dunn, et al. ¹³ 1991	72	9	5	2	1	1	NS	NS	NS	1	NS	3
Gels, et al. ¹⁴ 1995	154	42	27	4	9	2	8	16	0	1	0	17

*H+P indicates history and physical examination; CT, Computed tomography; CXR, chest x-ray; NS, not stated.

[†]Nodes or marker only relapses; one relapse in spleen only.

[‡] α -fetoprotein, β -HCG, LDH.

[§]Eight patients with borderline or elevated markers.

^{||}Three patients with increased markers and another study.

Systemic therapy for recurrent NSGCT is extremely effective with a 99% cure rate obtained for low-volume metastatic disease.²⁰ Because the results of therapy are dependent on the bulk of disease, an aggressive strategy to detect presymptomatic disease is justifiable despite an absence of rigorous prospective studies.

Although the acute and late toxicities of testicular cancer therapy have decreased as treatment has improved,²¹ significant long-term risks remain. Patients who received the chemotherapeutic agent etoposide appear to be at a small but increased risk of acute leukemia,²² as well as at a possible increased risk of atherosclerotic cardiovascular disease.²³ Despite these risks, there are no data to support routine blood counts or further testing beyond normally recommended lipid screening.

The cost of the follow-up plan as outlined in Table 4 is \$13 million (\$2.5 million/1,000 patients) for 5 years of follow-up. This cost is based on the utilization of chest x-ray as the method for screening for lung metastases. If the chest x-ray were to be replaced by CT scanning, the cost would be increased to \$34 million (\$9 million/1,000 patients).

LYMPHOMA

The lymphomas (Hodgkin's disease and intermediate grade non-Hodgkin's) share some of the features of testicular cancer. Both diseases respond to systemic treatment, cure rates depend greatly on disease burden, the time to recurrence is relatively brief, and salvage therapy (though not as effective as NSGCT) is available. Unlike testicular cancer, specific tumor markers for the lymphomas are not available.

Hodgkin's Disease

There is considerable literature detailing the patterns of relapse and long-term complications of therapy in Hodgkin's disease; however, there are few data on the utility of follow-up testing for asymptomatic individuals. Nevertheless, guidelines can be devised based on the criteria discussed above and available studies.

For all groups of treated patients (radiation therapy, chemotherapy, or combined modality therapy), the period of maximal risk of recurrence is in the first 4 to 5 years, and therefore this should be the period of maximal surveillance.²⁴ There are no prospective data on follow-up testing for any group, but it appears that every 3 months follow-up is common. Despite this frequency of follow-up, patients will frequently come for medical attention for symptomatic disease between visits. Radford followed 210 patients for up to 5 years with frequent office visits (every 2 months in the first year, 3 months in the second, 4 months in the third, biannually in years 4 and 5, and then annually). Of 37 relapses, 30 patients presented with symptomatic disease; 15 of these visits were initiated by the patient.²⁵

Recurrence of Hodgkin's disease tends to occur at sites of previous involvement.²⁶ There are few data regarding specific tests. In the Radford study two recurrences were detected by physical examination and only two cases were detected by chest x-ray. The utility and type of radiologic exams to be obtained in follow-up is unclear. Chest x-ray did not appear to be useful; however, the published studies do not evaluate the utility of this test in patients with previous disease in the chest. There are no data regarding CT scanning of areas of previous disease involvement. Gallium scanning for restaging after completion of induction therapy identifies a group of patients with a high likelihood of failure. King retrospectively evaluated 33 patients who had a restaging gallium scan within 4 weeks of completing treatment for advanced Hodgkin's disease. The 4-year freedom from relapse was 75% for patients with negative scans versus 8% for those with positive scans ($p < .001$).²⁷ Unfortunately, gallium scanning has not been studied as a long-term follow-up test.

The erythrocyte sedimentation rate (ESR) has demonstrated utility in initial follow-up. The European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group retrospectively evaluated 772 patients after therapy for stage I or II Hodgkin's disease. Patients with an elevated ESR after therapy had a 5 to 23-fold increased risk of relapse.²⁸ Though these data are extremely important in the early follow-up of patients with Hodgkin's disease, they do not provide conclusive evidence of the utility of this test in the long-term follow-up. Nevertheless, the test is inexpensive, easily available, and therefore can be recommended.

Effective salvage therapy is available for all groups of patients with Hodgkin's disease. The majority of low-stage patients relapsing after radiotherapy can be cured, and a fraction of those whose chemotherapy fails can be cured with reinduction of the same regimen (up to 35%), treatment with a non-cross-resistant regimen (5–15%), or bone marrow transplantation (40%).^{29,30}

Treated patients are at a significant long-term risk for both malignant and nonmalignant complications of therapy. Therapy-related leukemias, though occurring in only about 2% of patients, are the most lethal complication related to chemotherapy. This problem, if it occurs, will emerge within the first 11 years after therapy,³¹ and it occurs most frequently in patients treated with regimens containing nitrogen mustard or nitrosureas (e.g., mechlorethamine vincristine prednisone procarbazine), or in those who have received radiation as well as chemotherapy. The newer, and now standard, ABVD regimen (adriamycin, bleomycin, vinblastine, and DTIC) does not appear to increase the risk of hematologic malignancy.³²

Recently, a marked and rising risk of solid tumors, particularly lung and breast, in patients treated with radiotherapy has been noted.^{33,34} There does not appear to be a plateau in the occurrence of these cancers for at least 15–20 years. An increased risk of breast cancer was documented in a series of 885 patients, in which 25

women developed breast cancer versus an expected 6 patients. This risk is particularly marked in young women (age < 20, relative risk [RR] = 10 at 15 years after therapy) and has led to a recommendation of earlier screening mammography in this population.³⁵ The risk of thyroid cancer is also markedly elevated to 1.7% (RR = 15.6).³⁶

Nonmalignant complications of therapy are also common. Most frequent is the occurrence of thyroid disease (67% of 1,677 patients after 26 years of follow-up) after radiotherapy including hypothyroidism and Graves disease.³³ Hence, yearly evaluation of thyroid-stimulating hormone (TSH) is indicated. In summary, follow-up of asymptomatic individuals after treatment for Hodgkin's disease should consist of periodic physical examinations with laboratory testing limited to the ESR, as well as a TSH if the patient was irradiated. A complete blood count (CBC) in those who are at high risk of leukemia (e.g., those treated with MOPP or similar regimens) might also be considered. Mammography is indicated in female patients treated with radiation, though with a latency period of 10 to 15 years after treatment and the limitations of mammography in younger patients, it is unclear whether this procedure should be obtained earlier or more frequently than recommended for the general population. A chest x-ray should be considered in patients with previous chest disease, but there are insufficient data to recommend it routinely.

The cost of the strategy recommended in Table 4 is \$6 million for 5 years of follow-up (\$900,000/1,000 patients). This analysis assumes that all patients with stage I and II Hodgkin's disease, i.e., 60%, will receive radiation therapy as part of their treatment and require thyroid monitoring. In comparison, a more typical strategy, which includes routine laboratory testing (CBC, LDH, serum glutamic-oxaloacetic transaminase, alkaline phosphatase, total bilirubin) in addition to the evaluation proposed, is \$10 million (\$1.4 million/1,000 patients).

Non-Hodgkin's Lymphoma

Intermediate-grade non-Hodgkin's lymphoma is highly treatable and curable, with approximately 35% of all patients cured of their disease.³⁷ The major risk of relapse is within the first 4 to 5 years after therapy, with the proportion of patients surviving plateauing after that point.³⁷ In contrast to Hodgkin's disease, relapses occur frequently at previously uninvolved sites.³⁸ It is uncertain what tests beyond history and physical examination are useful. Weeks et al. retrospectively evaluated 139 patients with large cell non-Hodgkin's lymphoma in complete remission.³⁹ These patients were subjected to a variety of post-therapy studies including physical examination, serum chemistry tests, CBC, chest x-ray, gallium and CT scanning, ultrasound, and bone marrow biopsy. Visits and testing were done every 2 to 3 months. Despite this frequency of exams and testing, the vast majority of relapses were detected at unscheduled visits for symptomatic dis-

ease (32/35, 91%). Only a single test, LDH, was sensitive to preclinical relapse. There was a suggestion that gallium scanning, by virtue of high sensitivity for relapsed disease (90%), was also of value. Unfortunately, this test was not ordered frequently enough in that study. Front et al. evaluated the utility of gallium scanning immediately after therapy in 86 patients with non-Hodgkin's lymphoma. They found a positive predictive value of 73% and negative predictive value of 84% in this setting.⁴⁰ A similar study also found that gallium positivity was indicative of viable tumor.⁴¹ However, this still does not answer the question of the long-term utility of this test.

Of patients who have relapsed, approximately 20% to 30% may be salvaged with conventional or high-dose chemotherapy.^{42,43} Those most likely to respond are individuals relapsing more than 1 year after initial therapy and who remain sensitive to chemotherapy.

Second malignancies (Hodgkin's disease, acute myelogenous leukemia, bladder cancer, and melanoma), possibly as a consequence both of therapy and of the disease itself, are increased in frequency.^{44,45} The risk of secondary leukemia is related to the type of therapy and appears to be low with the CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) regimen.⁴⁶

Follow-up for patients who have undergone therapy for non-Hodgkin's lymphoma should occur at intervals of every 3 to 4 months during the first 4 years following therapy, though as noted above, relapses may occur between visit. With the possible exception of an LDH, routine serum chemistries and CBC are not indicated in non-Hodgkin's lymphoma. The utility of gallium scanning in the long term follow-up of non-Hodgkin's lymphoma remains to be established. A literature supported follow-up strategy would consist solely of physical examination and LDH. This approach would cost \$13 million for 5 years of follow-up (\$500,000/1,000 patients). In contrast, the more typical strategy, such as that reported by Weeks et al.,³⁹ would include CBC, chest x-ray with each visit, and at least one CT scan per year. The cost of this strategy would be \$42 million (\$1.8 million/1,000 patients).

BREAST CANCER

In contrast to the lymphomas, there is a large literature investigating the utility of follow-up studies in breast cancer patients. Two recently reported prospective trials provide important data in this area. Although most relapses occur in the first 3 years, breast cancer is very different from testicular cancer and the lymphomas in that patients are at continuous risk of recurrence for more than 20 years.⁴⁷ Common sites of recurrence are locoregionally (chest wall, axilla, and supraclavicular nodes), bone, chest, and liver. The vast majority of recurrences are detected at patient-initiated visits for symptoms. The experience of Winchester et al. is typical. Of 87 patients who relapsed after mastectomy, 79 (91%) presented with symptoms of recurrent disease (e.g., bone pain or visible

lesions), 5 were discovered by physical examination, and only 3 were discovered by screening radiologic or laboratory studies.⁴⁸ A large, retrospective series from the Eastern Cooperative Oncology Group found that 74% of recurrences were detected either symptomatically or by routine physical examination.⁴⁹

Several other retrospective studies focusing on various types of surveillance testing have failed to document efficacy. The utility of routine chest x-rays was evaluated in 1,697 breast cancer patients. Of 523 relapses, only 39 were identified solely by chest x-ray.⁵⁰ Radionuclide bone scans also have not been found to be of value in asymptomatic patients with normal serum chemistry values.⁵¹ Two randomized, controlled studies indicate that bone scans are of no utility in asymptomatic patients regardless of serum chemistry values.^{52,53}

The only useful radiologic study for the detection of asymptomatic disease is mammography, mostly for the detection of new primary cancer sites in the contralateral breast. The risk of metachronous disease (i.e., disease occurring after discovery of the primary site) in the contralateral breast is approximately 4% in the first 5 years after initial diagnosis.⁵⁴ Senofsky et al. retrospectively reviewed two groups of patients with early breast cancer. The first group of 500 consecutive patients was diagnosed between 1969 and 1975 and the second group of 557 patients was diagnosed between 1977 and 1984. The latter group was monitored with mammography as well as physical examination. There was a marked decline in the stage at presentation of new primary sites discovered in the contralateral breast for the second group with locally advanced (stage III) or metastatic disease (stage IV) declining from 35.1% to 7.4%.⁵⁵ Similar results have been obtained by others.⁵⁶

Despite this preponderance of evidence demonstrating the lack of utility of most routine tests, including bone scans, major textbooks⁵⁷ as well as some reviews and editorials⁵⁸ continue to argue for a policy of extensive follow-up testing. Two recently reported studies provide definitive data in this area.^{52,53} Both were prospective, randomized, phase III trials that evaluated different strategies of routine follow-up. In both studies, patients with locoregional breast cancer were randomized between strategies of intensive follow-up consisting of frequent radiologic testing versus only physical examination and yearly mammography with further studies performed only for symptoms. Patients were treated in a similar manner, both adjuvantly and at relapse. For the 2,500 patients randomized in the two studies, compliance with the prescribed regimens was excellent. No survival differences were detected between patients followed with either surveillance strategy in either study with a median follow-up of 5 years.

In one of the studies, quality of life was prospectively and serially evaluated.⁵¹ Utilizing a validated questionnaire administered at 6, 12, 24, and 60 months, no differences were found between the intensively and conservatively followed groups in terms of emotional well-being,

body image, social function, satisfaction with care, or overall health and quality-of-life measures. The authors concluded that intensive surveillance neither reassured patients nor caused undue anxiety.

Some studies have reported increased incidences of colon and gynecologic cancers in patients with a history of treated breast cancer.⁵⁹ Chemotherapy has been associated with an increased risk of myelodysplasia and leukemia, particularly in patients who received irradiation.⁶⁰ This risk has been decreased by using cyclophosphamide rather than melphalan.⁵⁷ In patients undergoing long-term (i.e., 5 year) therapy with tamoxifen, a small increase in endometrial cancer has been noted.⁶¹ However, the value of screening for gynecologic and colorectal cancers beyond standard guidelines for the regular population is not established.

In summary, on the basis of the limited surveillance arms of the two randomized trials cited above, a policy of follow-up visits every 3 to 4 months in the first 5 years after treatment, decreasing to one to two times per year thereafter, and annual mammography of remaining breast tissue without other testing is most consistent with available data.

The strategy proposed in Table 4, which would restrict testing to physical examination and yearly mammography, would cost \$113 million for 5 years (\$700,000/1,000 patients). In comparison, the inclusion of routine CBC, serum chemistry values with each visit, semiannual chest x-rays, and yearly bone scans escalates this 5-year cost to \$376 million (\$2.3 million/1,000 patients). Schapira and Urban, comparing the same "minimalist policy" with a somewhat more extensive workup and adjusting for actual hospital charge data, found an *annual* difference of \$636 million (1990 dollars).⁶²

COLORECTAL CANCER

The current standard of practice in the follow-up of colorectal cancer patients is frequent serologic and radiologic follow-up, despite a paucity of evidence supporting such a strategy.⁶³ The natural history of colon cancer differs from breast cancer in that most recurrences occur within 3 years with a plateau in survival thereafter. Though rectal cancer has an increased risk of local relapse in comparison to colon cancer, the diseases will be considered together as they have been frequently combined in follow-up studies.

The risk of recurrence is closely related to stage with approximately 10% of patients with stage A cancer (tumor confined to mucosa), 30% of those with stage B (tumor penetrating into muscle), and 60% of those with stage C (nodal involvement) relapsing in most series.⁶⁴ The outlook for stage C patients has been improved with the use of adjuvant chemotherapy, reducing the risk of relapse to 40%.⁶⁵ Similarly, the outlook for patients with rectal cancer (stage B, C) has improved with the use of adjuvant chemoradiation.⁶⁶

There are, at this time, no fully published randomized, controlled studies of follow-up strategies for colon cancer, and one must therefore rely on retrospective data. Testing can be divided into two types, tests designed to evaluate local recurrence or second primary cancers (fecal occult blood test [FOBT], colonoscopy) and those designed to detect metastatic disease (chest x-ray, biochemical tests, and the carcinoembryonic antigen [CEA]).

Buhler et al. followed 188 patients who underwent curative resection and later underwent colonoscopy.⁶⁷ Locally recurrent cancer was found in 20 patients, and only the 9 who were asymptomatic at the time of the procedure were potentially resectable. The authors argue that regular endoscopy would increase the number of potentially curative salvage procedures. However, others have found the incidence of such local, asymptomatic, potentially curable lesions to be quite small.⁶⁸ Thus, available data do not clearly support the utilization of colonoscopy for detecting asymptomatic local recurrence. Colonoscopy may have a more important role in the detection of a second primary cancer.

Evaluation for asymptomatic recurrence, either locally or metastatic, does not appear to be fruitful with current technology. Radiographic studies (chest x-ray, CT, and radionuclide studies) for the detection of potentially curable isolated pulmonary or liver metastases are rarely beneficial. Biochemical surveillance (e.g., by liver function tests) has also not improved outcome.⁶⁹ Mucosal disruption resulting in a positive FOBT is unusual. The experience of Safi and Beyer is typical. Of 1,045 patients followed after curative resection, 15 (1.4%) had isolated pulmonary metastasis, of which 7 (0.7%) were resected, and only 2 (0.2%) were long-term survivors.⁷⁰ Seventeen studies performed over the past 15 years using a variety of aggressive follow-up schedules and strategies individually and in the aggregate failed to demonstrate that frequent testing is advantageous. Of 1,475 patients with recurrences, only 109 (7.4%) were alive and free of disease for more than 1 year.⁷⁰⁻⁸⁶

The role of CEA merits special discussion. CEA is an oncofetal antigen whose level is frequently elevated in patients with primary and metastatic colon cancer,⁸⁷ and a CEA test is commonly ordered as a follow-up in colorectal cancer. Despite a large volume of literature evaluating CEA, only a few studies present sufficient data to evaluate its usefulness in detecting recurrences resulting in improvement in outcome. A recent study of 311 patients with 98 recurrences who were followed with physical examination, CBC, CEA, liver function tests, and FOBT (at a minimum) demonstrated that an elevated CEA level was the first indication of recurrence in the majority of patients (50% of all patients and 80% of those with liver metastasis).⁸⁶ Despite this finding, Moertel et al. have reported a large retrospective series that failed to demonstrate an improvement in survival in patients who were aggressively monitored with CEA levels compared with those who were not.⁸³ Of 1,216 patients resected for colon

cancer, 1,017 had frequent CEA levels drawn at the discretion of their primary physicians compared with 199 patients who were not subjected to this monitoring. There was no difference in outcome among those who underwent salvage surgery between the two groups.

False elevations of CEA occur frequently during therapy with 5-fluorouracil (21% of patients receiving adjuvant therapy had CEA > 5 mg/dL), now a common feature of management for stage B and C disease.^{65,83} This report suffers from its retrospective nature and variabilities in screening and evaluation of CEA. Preliminary results of a large prospective, randomized, controlled trial (CRC/NIH CEA Second Look Trial) have been presented.⁸⁸ In this study 1,417 patients were randomized between aggressive management (including second look laparotomy) compared with observation if an elevated CEA level was detected. The study was terminated following an interim analysis that failed to detect any survival advantage for the aggressively treated group. In contrast, a meta-analysis of retrospective studies found a 9.1% improvement (95% confidence interval +2.2% to +16.9%) in 5-year survival in patients followed with CEA versus those not followed with CEA.⁸⁹ Therefore, while the CEA may satisfy the requirement for a follow-up test to be sensitive for recurrence of disease, its ability to improve outcome is uncertain. The full reporting of the CRC/NIH trial should settle this issue.

As noted above, there is a small possibility of long-term survival if a single metastatic lesion is found and resected.⁹⁰ Also, if local recurrences at the site of anastomosis are found, resection may be curative.⁹⁰ Systemic disease is incurable, though current chemotherapy may provide palliation and a modest prolongation in survival.^{91,92}

The occurrence of metachronous primary cancers as well as adenomas (approximately 1.5-3.0% of patients) argues for regular endoscopy (at 1 year after diagnosis and every 3 years thereafter).⁹³ Recent data demonstrate that endoscopy and polypectomy can prevent colorectal cancer.^{94,95}

In conclusion, the potential benefit of close surveillance in high-risk patients (stage B, C) is limited. Once again, most recurrences are discovered as a result of symptoms, and even those discovered by monitoring are usually not amenable to cure. The low risk of relapse in patients with stage A disease means that even an effective program would have very little benefit. A reasonable strategy would be to follow stage A, B₁ patients with a colonoscopy in the first year after diagnosis and then every 3 years if negative. For stage B₂ and C patients, periodic physical examinations and colonoscopy as indicated in Table 4 should be obtained. At this time the evidence for obtaining periodic CEA values is uncertain. The 5-year cost of this follow-up program including CEA is \$119 million (\$1.1 million/1,000 patients). (This analysis subjects patients with Stage A and B₁ disease to the same intensity of follow-up as stage B₂ and C.) If CEA is eliminated, the cost decreases to \$90 million (\$900,000/1,000 patients).

In contrast, a follow-up strategy that includes CBC, liver function tests, and FOBT at each follow-up exam, chest x-ray twice a year, and annual colonoscopy is \$251 million (\$2.4 million/1,000 patients). A similar analysis found comparable relative savings.⁹⁶

PROSTATE CANCER

The management of prostate cancer is extremely controversial. The approach to early-stage disease varies from radical surgery to radiation therapy to observation.⁹⁷ Patients with localized prostate cancer treated with either surgery or radiation are at risk of relapse for more than 10 years.^{98,99} Follow-up testing of patients treated with curative intent, either with radiation therapy or surgery, has included physical examination, bone scans, prostatic acid phosphatase, and more recently the prostate specific antigen (PSA).

The prostatic acid phosphatase lacks sensitivity and specificity for the presence of metastatic disease and has been replaced by the serum PSA.¹⁰⁰ A rising PSA level is frequently a harbinger of relapse, predating symptomatic disease by months to years. Following surgery the PSA level should drop to female levels (<0.4 ng/mL, monoclonal assay) within the first month. Persistence of a PSA level above female levels or a rising PSA after achieving female levels is an indicator of either residual disease or relapse. Lightner et al. evaluated 63 patients who had undergone radical prostatectomy and were later found to have an elevated PSA. Six patients were found to have local or systemic recurrence after evaluation with physical examination, bone scan or CT scanning. Among the remaining 57 men, biopsies of the anastomotic site revealed tumor in 24.¹⁰¹ This study demonstrates the utility of PSA in detecting recurrent disease. Studies have also documented the frequent occurrence of an elevated PSA level in men who have not had clinical recurrence despite an extended period of follow-up. Twenty-nine (46%) of 63 patients reported by Lightner et al. fell into this category despite a mean follow-up of 43 months. Frazier et al. reported a similar series in which 11 patients with an elevated PSA had no evidence of failure despite a minimum follow-up of more than 36 months.¹⁰² Conversely, it is extremely unusual for a patient to have recurrent disease in the absence of an elevated PSA.^{103,104}

Similar studies have been performed with patients who have been treated with radiotherapy. In this setting the PSA may not reach female levels because of residual prostate tissue. Most studies have found that a gradual normalization of PSA occurs over a 6-month period following radiotherapy. If the PSA remains in the normal range, patients have not relapsed. As with the postsurgical patients, elevations of the PSA after normalization following radiotherapy indicate a high likelihood of relapse. Kaplan evaluated 117 patients with serial PSA tests before and after radiotherapy.¹⁰⁴ Forty-four patients experienced an increasing PSA after therapy, of whom 30 (68%) relapsed

with a median time to relapse of 156 days from the occurrence of an elevation. Only four patients had clinical relapse without a change in PSA, one of whom had a persistently elevated level and the other three had evidence of only local recurrence.

It is not clear whether a knowledge of recurrence is useful in determining the timing of further treatment. If disease is locoregional to the prostate bed (i.e., residual postsurgery or radiation therapy), there is a possibility that further local therapy may be curative. Several small studies have evaluated radiation therapy in patients with detectable PSA either immediately postoperatively or in the follow-up period. Results vary, but it appears that a third to a half of these patients can obtain biochemical remissions (i.e., undetectable PSA) with radiation.¹⁰⁵⁻¹⁰⁸ In one series, salvage surgery (with or without androgen deprivation) in the setting of localized radiation failure also appeared useful with 22 of 34 patients rendered disease free (clinically and biochemically) after a mean follow-up of 53 months.¹⁰⁹

If disease is systemic, there is conflicting evidence regarding the utility of early (i.e., presymptomatic) androgen deprivation.¹¹⁰⁻¹¹³ The toxicities of early androgen ablation include impotence, fatigue, muscle wasting, and vasomotor instability. Unfortunately, all of the series described above were observational. Given the large fraction of patients with an elevated PSA in the absence of clinical disease and the significant toxicities of therapies for recurrent disease, the value of salvage therapy is not clearly established. Therefore, the utility of following PSA levels to monitor for recurrence remains uncertain.

Metastasis to bone is the most common site of systemic relapse, and thus bone scans have been a routine part of the evaluation and follow-up of prostate cancer for decades. Several recent studies, however, indicate that bone scans should be abandoned as a routine follow-up test in asymptomatic patients with a normal PSA. Freitas et al. prospectively studied 107 patients with PSA and bone scan who had undergone definitive therapy for prostate cancer (radiotherapy or surgery). They found that a PSA less than 8 ng/mL excluded the possibility of a positive scan with a negative predictive value of 98.5%.¹¹⁴ Virtually identical results were obtained by Teris et al. in a follow-up of 118 men.¹¹⁵

A typical follow-up strategy consisting of physical examination, CBC, and PSA, every 6 months for 2 years, then annually, and bone scan annually would cost \$339 million (\$1.4 million/1,000 patients) to follow for 10 years. In contrast, the approach recommended in Table 4, which eliminates bone scans, chest x-rays, and CBC, reduces the cost to \$94 million (\$400,000/1,000 patients).

LUNG CANCER

Small cell lung cancer and non-small cell lung cancer (NSCLC) are both potentially curable in patients with lo-

calized disease. However, the majority of patients with either of these diseases will relapse.^{4,116}

Small Cell Lung Cancer

Most relapses of small cell lung cancer occur within 3 years of initial therapy, though another one third of patients surviving beyond that point will also relapse.¹¹⁷ Relapses may occur either locally or systemically.⁹⁶ A single retrospective study addresses the utility of follow-up testing. Perez et al. reviewed 115 complete responders to chemotherapy with or without radiotherapy (58 with limited and 57 with extensive stage disease). All patients ultimately relapsed. Recurrences were detected by history in 71%, physical examination in 10%, and chest x-ray in 13%. Only 6% were discovered by serum chemistry values; 59% of patients became symptomatic between regular visits, which were every 4 months for 1 year, then every 6 months.¹¹⁸

Curative therapy is not available for relapses, though palliation and possibly a modest increase in longevity may be achieved with salvage therapy.¹¹⁹ Thus, early detection of relapse is of questionable benefit.

Second cancers of the upper aerodigestive tract occur frequently in patients cured of small cell, most notably NSCLC. Sagman et al. reported a relative risk of 6.83 for the development of NSCLC, and similar findings were reported by Heyne.^{120,121} Given the potential curability of NSCLC and head and neck cancers in early stages, there is potential benefit for early detection. Aggressive screening (with sputum cytology and chest x-ray) of high-risk patients (older male smokers) for initial lung cancer was able to detect cancers at an earlier stage though this did not translate into improved survival.¹²²

Non-Small Cell Lung Cancer

Non-small cell lung cancer is the most common cause of cancer death in the United States. Surgical cure rates for stage I and II cancers are between 30% and 70%.¹²³ Most recurrences occur within the first 3 years postoperatively, and relapse may be local, systemic, or both.^{124,125} The known patterns of relapse are not encouraging. The Ludwig Lung Cancer Study Group reviewed the patterns of failure in three prospective therapeutic trials.⁸⁶ Of 426 patients with clearly documented failure, only 26% failed locally, the site most amenable to retreatment.

The typical approach to follow-up after surgery includes quarterly physical examination with chest x-rays, blood counts, and blood chemistry values. One study demonstrated the potential utility of gallium scanning, but it has not been replicated.¹²⁶ Two retrospective studies address the utility of follow-up testing in NSCLC. Virgo et al. studied 182 patients with resected disease. Patients were divided into those who were intensively followed compared with those who were nonintensively followed as defined by the frequency and extent of clinic visits for ra-

diologic and laboratory studies. Despite the retrospective nature of this study and the absence of true randomization, the groups were well balanced. There was no difference in survival or other outcomes between the two groups.¹²⁷ Walsh studied 358 patients and found that detection of recurrence in asymptomatic patients did not improve outcome when controlled for disease-free interval. They recommend a follow-up strategy of physical examination and chest x-ray every 6 months for 1 year followed by yearly examination and chest x-ray.¹²⁸

As in the case of small cell lung cancer, the value of early detection of relapse is not established for NSCLC. The results of retreatment with either surgery or radiation for local recurrence reveal that a minority of patients will experience long-term benefit. Curran et al. described a series of 37 patients with postresection locoregional recurrence treated with radiotherapy and obtained a 22% two-year survival, equivalent to that of newly diagnosed stage III patients.¹²⁹ Gabler and Liebig reoperated on 17 patients with recurrent disease and had six long-term survivors.¹³⁰ Although patients with systemic disease and good performance status probably benefit from cisplatin-based chemotherapy, no curative potential has yet been demonstrated.^{131,132} Patients are at high risk for the occurrence of second aerodigestive tract malignancies as well as other lung cancers.¹³³

Overall, despite the potential benefit for the detection of early-stage malignancies elsewhere in the aerodigestive tract and possibly for the aggressive management of locoregional relapse, there is little justification for routine testing beyond periodic physical examination and chest x-ray. Controlled clinical trials of follow-up strategies for both small cell and NSCLC similar to those done for breast cancer are clearly needed.

For both types of lung cancer, the cost of the recommended follow-up (Table 4) for 5 years is \$20 million (\$230,000/1,000 patients). A more typical evaluation would include blood chemistry values and chest x-ray with each office visit and an annual chest CT scan. Such an evaluation would cost \$113 million (\$1.3 million/1,000 patients).

DISCUSSION

In this review and economic analysis, we have examined follow-up strategies for the most common and treatable malignancies. With the exception of testicular cancer, the value of aggressive routine follow-up testing, characterized by frequent radiologic and biochemical testing, is questionable. Despite a lack of demonstrated efficacy, such testing occurs frequently. Although we recognize that many medical interventions lack the conclusive evidence provided by randomized clinical trials, we believe that such practices should at least be supported by the weight of other types of evidence or be eliminated. Table 4 summarizes follow-up strategies and provides levels of ev-

Table 4. Summary of Recommendations for Follow-up Testing for Asymptomatic Patients After Curative Cancer Therapy*

Cancer	Follow-up Year	History and Physical Exam	Serum Chemistries	Complete Blood Count	Serologic Markers	Chest X-ray	Other
Nonseminomatous germ cell tumor			No (2)	No (2)	α -fetoprotein, β HCG, LDH (2)	Yes (2) [†]	(CT abdomen) [‡]
	1	q 1 mo			q 1 mo	q 1 mo	
	2	2 mo			2 mo	2 mo	
	3	3 mo			3 mo	3 mo	
	4-5	6 mo			6 mo	6 mo	
	≥ 6	1 yr			1 yr	1 yr	
Non-Hodgkin's lymphoma (intermediate or high grade)			LDH (2)	No (2)	No (2)	No (2)	(? Gallium scan (3)), annually
	1	q 3 mo	q 3 mo				
	2	3 mo	3 mo				
	3	4 mo	4 mo				
	4	4 mo	4 mo				
	>5	6-12 mo	6-12 mo				
Hodgkin's			No (2)	No (2) [¶]	No (2)	(? Yes (3))	TSH (2) [§] q 1 yr
	1	q 3 mo				q 3 mo	(mammography (3)) q 1 yr
	2	3 mo				3 mo	ESR (2) with each office visit.
	3	4 mo				4 mo	(? Gallium scan (3)) [#]
	4	4 mo				4 mo	
	>5	6-12 mo				6-12 mo	
Breast			No (1)	No (1)	No (2)	No (2)	Mammography (1)
	1	q 3 mo					q 1 yr
	2	4 mo					q 1 yr
	3	4-6 mo					q 1 yr
	4	4-6 mo					q 1 yr
	>5	1 yr					q 1 yr
Colon			No (2)	No (2)	? CEA (3)	No (2)	Colonoscopy (2)
	1	q 3 mo			q 3 mo		
	2	4 mo			4 mo		
	3	6 mo			6 mo		
	4	1 yr			4-6 mo		
	>5	1 yr			1 yr		Once within first year, then q 3 yr thereafter
Prostate			No (2)	No (2)	? PSA (2)	No (2)	No (2)
	1	q 6 mo			q 6 mo		
	2	6 mo			6 mo		
	>3	1 yr			1 yr		
Lung			No (2)	No (2)	No (2)	Yes (2)	No (2)
	1	q 6 mo				q 6 mo	
	2	1 yr				1 yr	
	>3	1 yr				1 yr	

*Numbers in parenthesis indicate level of evidence supporting a recommendation (see text). Studies in parenthesis are not considered in economic analysis. β HCG indicates human chorionic gonadotrophin; LDH, lactate dehydrogenase; CT, computed tomography; TSH, thyroid stimulating hormone; ESR, erythrocyte sedimentation rate; CEA, carcinoembryonic antigen; PSA, prostate specific antigen.

[†]CT of the chest may be superior.

[‡]If patient has not undergone retroperitoneal lymph node dissection.

[§]Thyroid function tests are indicated for patients who underwent treatment with neck irradiation.

^{||}In women who have undergone mantle radiotherapy.

[¶]If the patient received MOPP (or similar regimen), or combined modality therapy, a CBC should be considered.

[#]Utility for gallium scanning ESR, has been demonstrated in early follow-up (i.e., immediately after therapy resulting in complete remission) but not in extended follow-up.

idence supporting each test. It is clear that many tests are in a "gray zone" at this time.

The economic analysis in this review is similar in methodology to that of others.^{62,96} Differences in the absolute cost savings for breast cancer between our study and that of Schapira and Urban are explained by the markedly different costs they utilize for the various tests and procedures.⁶² Though it is not clearly stated in their article, they apparently utilized their institutional costs. We have utilized the national average figures from the 1995 Medicare Part B extract statistical system which are more

generalizable. Our results are therefore similar to those of Virgo et al. who employed the 1992 database in their analysis of colon cancer.⁹⁶ Differences between this study and Virgo's are attributable to our removal of relapsed patients from the cost analysis and our omission of a conversion factor to translate Medicare-allowed costs to actual hospital charge data. In several of the studies cited, the more aggressive evaluation involved considerably more testing than we included in our analysis,^{62,96,126} which emphasizes the very conservative nature of potential cost savings in this review.

At a time of increased scrutiny of medical testing and de facto medical rationing, restriction of follow-up in asymptomatic patients to tests that have demonstrated clear benefit in terms of palliation or survival is an area in which medical cost containment can be achieved without compromising the quality of care. The elimination of unnecessary testing would also decrease the risk of further physical and psychological harm from the inevitable occurrence of false-positive results. Such a follow-up policy places a premium on traditional medical skills, the ability to take a history and perform a physical examination. In addition, patient education must be emphasized as symptoms will be the harbinger of relapse in most patients.

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