Computed Tomography Screening and Lung Cancer Outcomes

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LUNG CANCER ACCOUNTS FOR 20% of cancer deaths in Italy and 25% of cancer deaths in the United States, and 6% of all deaths in both countries.[1,2] Screening individuals at high risk for lung cancer might reduce these statistics based on the premise that most cases of lung cancer that will cause death can be detected through routine screening while they are still localized and potentially curable. However, prior randomized studies of lung cancer screening with chest x-ray have not supported this premise. Rather, chest x-ray was effective at identifying many additional small tumors in the lung that could be removed, but their discovery and removal did not reduce the likelihood that individuals would be diagnosed with new cases of advanced lung cancer, or would die of lung cancer.[3-7] These findings led to speculation that the additional small cancers that were being found through screening may be indolent, relative to lung cancer that is typically encountered in a clinical setting.[8,9]

Today there is renewed enthusiasm for lung cancer screening with computed tomography (CT) because it is more sensitive for the detection of very small nodules.[10,11] Yet, CT screening de-

Context Current and former smokers are currently being screened for lung cancer with computed tomography (CT), although there are limited data on the effect screening has on lung cancer outcomes. Randomized controlled trials assessing CT screening are currently under way.

Objective To assess whether screening may increase the frequency of lung cancer diagnosis and lung cancer resection or may reduce the risk of a diagnosis of advanced lung cancer or death from lung cancer.

Design, Setting, and Participants Longitudinal analysis of 3246 asymptomatic current or former smokers screened for lung cancer beginning in 1998 either at 1 of 2 academic medical centers in the United States or an academic medical center in Italy with follow-up for a median of 3.9 years.

Intervention Annual CT scans with comprehensive evaluation and treatment of detected nodules.

Main Outcome Measures Comparison of predicted with observed number of new lung cancer cases, lung cancer resections, advanced lung cancer cases, and deaths from lung cancer.

Results There were 144 individuals diagnosed with lung cancer compared with 44.5 expected cases (relative risk [RR], 3.2; 95% confidence interval [CI], 2.7-3.8; $P<.001$). There were 109 individuals who had a lung resection compared with 10.9 expected cases (RR, 10.0; 95% CI, 8.2-11.9; $P<.001$). There was no evidence of a decline in the number of diagnoses of advanced lung cancers (42 individuals compared with 33.4 expected cases) or deaths from lung cancer (38 deaths due to lung cancer observed and 38.8 expected; RR, 1.0; 95% CI, 0.7-1.3; $P=.90$).

Conclusions Screening for lung cancer with low-dose CT may increase the rate of lung cancer diagnosis and treatment, but may not meaningfully reduce the risk of advanced lung cancer or death from lung cancer. Until more conclusive data are available, asymptomatic individuals should not be screened outside of clinical research studies that have a reasonable likelihood of further clarifying the potential benefits and risks.

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pends on the same unproven premise as chest x-ray screening.

We studied the effect of CT screening on individuals enrolled in 1 of 3 single-arm studies of screening by comparing the frequency of lung cancer cases, lung cancer resection, advanced lung cancer cases, and deaths from lung cancer occurring in these studies with what would have occurred in the absence of screening, as determined from a set of validated prediction models.[12-15] We aimed to pro-

duce preliminary estimates of the impact of widespread CT screening on these lung cancer outcomes.

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METHODS

Individuals were enrolled in 1 of 3 studies conducted at the Istituto Tumori in Milan, Italy, the Mayo Clinic in Rochester, Minn, and the Moffitt Cancer Center in Tampa, Fla.[16-20] Each study recruited individuals with a smoking history and no prior history or symptoms suggestive of lung cancer through advertisements, direct mail, and local physician outreach. The Istituto Tumori study is ongoing, the Mayo Clinic study offered an initial and 3 subsequent annual CT scans, and the Moffitt study offered an initial and 4 subsequent annual CT scans. In these studies, when noncalcified nodules were detected, they were evaluated using a systematic approach of follow-up imaging and biopsy.[16,17]

Prediction Models

The frequency of lung cancer events occurring among the study participants was compared with benchmarks that were determined using 2 models developed to estimate an individual's level of risk of either being diagnosed with lung cancer or dying of lung cancer. Both models have been extensively described and validated in prior studies.[12-15] The models were designed to apply to high-risk individuals, whose risk factor values fall within the following ranges: age 50 to 80 years, smoked for between 25 and 60 years, averaged between 10 and 60 cigarettes per day, and if quit, had quit within the past 20 years. These limits led us to exclude 58 of the 1035 individuals from the Istituto Tumori study, 81 of 1520 individuals from the Mayo Clinic study, and 321 of 1151 individuals from the Moffitt study.

Modifications of Prediction Models

The probabilities of advanced lung cancer diagnosis and lung cancer surgery were based on the estimated probability of lung cancer diagnosis from our model multiplied by the conditional probability of these events among age- and sex-matched individuals diagnosed with lung cancer in the National Cancer Institute's Surveillance, Epidemiology, and End Results can-

cer registry database for 1993 through 1998. Estimates for the Moffitt study were also adjusted to compensate for an enriched prevalence of obstructive lung disease (due to a requirement that participants have obstructive lung disease) in the first cohort (enrolled between December 11, 1998, and January 4, 2001; n=376), and subsequent dilution of the prevalence of obstructive lung disease (resulting from late entry of individuals without obstructive lung disease who were not eligible for the first cohort) in the second cohort (enrolled between January 5, 2001, and August 13, 2003; n=458). The estimated risk of each individual was multiplied by the aggregate change in the population risk resulting from the alteration in prevalence of obstructive lung disease based on the following prevalences for obstructive lung disease: 97% for cohort 1 and 25% for cohort 2. The expected prevalence in the absence of the additional entry criterion was 46%, as estimated for the 163 individuals who were newly recruited to the second cohort. The relative risk (RR) estimates for the impact of obstructive lung disease on lung cancer incidence (2.80) and lung cancer death (2.02) were taken from the literature, the latter being an average of the additional risks conferred by differing levels of obstruction, weighted by the proportion of individuals with those differing levels of obstruction in the first cohort.[21,22] The end result of these adjustments was a small increase in the expected number of events.

Outcomes

We evaluated the number of individuals diagnosed with lung cancer (first diagnoses of non–small cell or small cell lung cancer), the number of first surgical resections of lung cancer, the number of individuals whose first lung cancer diagnosis was of advanced stage (stage III or IV non–small cell lung cancer or any stage of small cell lung cancer), and the number of individuals who died from lung cancer. For the Istituto Tumori study, dates and cause of death were ascertained through medical record review and the Lombardy Region cancer registry and death records, and clinician investigators coded cause of death. For the Mayo Clinic

and Moffitt studies, dates and cause of death were coded according to the National Death Index assignment of cause of death to parallel other studies of lung cancer screening.[8] Individuals whose vital status could not be reliably checked through public data sources were eliminated from the mortality analyses, as was the case for 1 individual enrolled in the Istituto Tumori study who resided outside of the Lombardy region of Italy, and 7 and 22 individuals enrolled in the Mayo Clinic and Moffitt studies, respectively, who did not provide Social Security numbers at the time of study enrollment.

Clinical End Points

The date of the first CT screen is the baseline for all of our analyses. The timing of lung cancer diagnoses corresponds to either the date of lung cancer in the diagnostic pathology report or the date of death for individuals who died from lung cancer without a known antecedent diagnosis. This approach to ascertaining the date of cancer diagnosis parallels the manner in which epidemiological and clinical data are collected, and thus is appropriate for the comparisons presented herein. An alternative would be to back-date the date of diagnosis to the date of the first scan on which the cancer was theoretically visible (eg, prevalence or incidence scan). Follow-up times for diagnostic and treatment end points for each individual extend to the point that the individual was diagnosed with lung cancer, or underwent surgery for lung cancer, or alternatively was lost to follow-up or died. Few individuals were lost to follow-up during the first years of the studies (89% follow-up through 2 years, 71% follow-up through 3 years), but the median follow-up was 3.9 years and only 33% were followed up past 4 years.

There is a potential that our results are biased if the probability that an individual is lost to follow-up is correlated with the likelihood that he/she experienced one of the study events. For instance, if individuals with symptoms of late-stage cancer are more likely to remain in clinical follow-up than individuals who feel healthy, such a bias would produce results that down-

play the effect of CT screening on preventing advanced cancers, while the alternative would exaggerate the effect of CT screening on preventing advanced diagnosis. Given this potential source of bias, additional analyses are presented that reflect how many events would have been estimated had all individuals been followed up to the time of their observed event, or otherwise followed up to the maximum time possible, which was set to be the last date of observed follow-up for any individual in the study. These alternative analyses increase the number of predicted events without increasing the number of observed events, so they represent the most conservative estimate of the extent to which CT screening may increase the likelihood of lung cancer diagnosis, and lung cancer surgery, as well as the most optimistic projection of the extent to which CT may reduce the frequency of advanced cancer diagnosis.

Mortality and Survival End Points

For the Istituto Tumori study, the censoring date was the date of death from a cause other than lung cancer, or the date of last confirmation of vital status; for the Moffitt and Mayo Clinic studies, the censoring date was the earlier of either the date of death from a cause other than lung cancer or December 31, 2004, the most recent date through which National Death Index data linked to death certificate information were complete. Our original analytic plan was to examine all deaths from lung cancer beginning at the commencement of screening but there was strong evidence for a healthy volunteer bias in the 3 studies. There was only 1 death from lung cancer occurring in the first year across all studies (compared with 9.5 deaths anticipated in the absence of screening). Because it is plausible that there was a large reduction in the first year due to the requirement that all study individuals be asymptomatic at the time of enrollment in the studies, and not plausible that CT screening reduced deaths immediately, the mortality end point was evaluated commencing 1 year after the first CT scan through death due to lung cancer or a censoring event. How the results would have appeared had the first year's events been

considered is also reported. The date of tissue diagnosis served as the start time for the survival analyses.

Statistical Analysis

The numbers of observed O events were compared with the numbers expected E at the end of available follow-up time using the formula $(O-E)^2/E$, which produces a χ^2 statistic with 1 degree of freedom. The results are indistinguishable from those obtained from a more computationally intensive approach to calculate the variance of E.[13] The 95% confidence intervals (CIs) assume a Poisson distribution. The survival estimates are based on the Kaplan-Meier method. All P values are 2-sided. $P<.05$ was considered statistically significant. Analyses were performed using Stata version 9.0 (StataCorp, College Station, Tex).

The study was approved by the institutional review boards of the 3 study sites where the screening was performed and written informed consent was obtained. The institutional review board at Memorial Sloan-Kettering Cancer Center acknowledged the authority of these institutions to authorize this research. Only the investigators at Memorial Sloan-Kettering Cancer Center had access to data from all 3 sites, which had been deidentified.

RESULTS
Characteristics of Studies

The Mayo Clinic study contributed both the largest number of individuals and the greatest amount of follow-up time, followed by the Istituto Tumori study (**TABLE 1**). The lung cancer mortality rate overall was 3.5 lung cancer deaths per 1000 person-years; the 5.6 lung cancer deaths per 1000 person-years in the Moffitt study is most likely due to the additional prevalence of obstructive lung disease. The lung cancer mortality rates in the Istituto Tumori and Mayo Clinic cohorts (2.7 and 3.1 per 1000 person-years, respectively) are similar to the rates in prior well-known studies of lung cancer screening with chest x-ray (3.0 and 3.2 per 1000 person-years in the 2 arms

of the original Mayo Clinic study; 2.6 and 3.6 per 1000 person-years in the 2 arms of a study of chest x-ray screening performed in Czechoslovakia; and 2.7 per 1000 person-years in the Memorial Sloan-Kettering study).[7-9,23]

Frequency of Lung Cancer Diagnosis and Lung Cancer Resection

Individuals in all 3 studies were diagnosed with lung cancer in far greater numbers than would have occurred in the absence of screening (**FIGURE 1**A, B, C and **TABLE 2**). For the Istituto Tumori study, the observed frequency was 36 compared with an expected frequency of 11.3; Mayo Clinic, 66 vs 19.5; and Moffitt, 42 vs 13.7 ($P<.001$ for each). The number of lung cancer surgeries performed exceeded the number expected in the absence of screening to an even greater extent for the Istituto Tumori study (33 vs 2.7); Mayo Clinic (48 vs 4.8); and Moffitt (28 vs 3.4) ($P<.001$ for each; Figure 1D, E, F and Table 2). Combining data from the 3 studies, there were 144 cases of lung cancer diagnosed, whereas 44.5 cases were expected, which resulted in an RR of lung cancer diagnosis of 3.2 (95% CI, 2.7-3.8; $P<.001$; **FIGURE 2**A). A total of 109 lung cancer surgeries were performed compared with 10.9 cases expected, which resulted in an RR of lung cancer surgery of 10.0 (95% CI, 8.2-11.9; $P<.001$; Figure 2B). If follow-up time is included for those patients who were lost to follow-up for unknown reasons, the number of observed lung cancer cases is 2.3 times the number predicted (144 vs 62.2 predicted; $P<.001$) and the number of lung cancer surgeries performed is 7.2 times the number predicted (109 vs 15.2 predicted; $P<.001$).

Number of Advanced Lung Cancers and Deaths Due to Lung Cancer

Early detection via CT screening did not appear to reduce the risk of advanced lung cancer diagnoses (Figure 1G, H, I, Figure 2C, and Table 2). Combined, there were 42 cases of advanced lung cancer, while the model predicted 33.4

(P=.14). If we include the follow-up times of patients lost to follow-up for unknown reasons, providing an upper bound of possible benefit, the number of observed cases of advanced lung cancer is less than the number predicted by 18% (42 observed vs 51.2 predicted; P=.18).

There was no evidence that CT screening reduced the risk of death due to lung cancer in any of the studies individually or combined (Figure 1J, K, L, Figure 2D, and Table 2). Loss to follow-up is unlikely to have biased this outcome, which was assessed using a standardized follow-up time. Combined, there were 38 deaths due to lung cancer after the first year of screening and the model predicted 38.8 deaths (RR, 1.0; 95% CI, 0.7-1.3; P=.90). If we had included the first year of mortality data

in this analysis (Table 2), CT screening would have appeared to reduce lung cancer mortality by 20%, although this reduction would not have been statistically significant (RR, 0.8; 95% CI, 0.55-1.06; P=.18).

Relationship Between Initial Lung Cancer Diagnosis and Death Due to Lung Cancer

Shown in TABLE 3 are the lung cancers detected during the course of the study, the number of individuals who died from lung cancer after 1 year or more of study participation who had each type of lung cancer diagnosis, and the 2-year probability of overall survival for those individuals diagnosed with lung cancer. As in other studies of CT screening, the preponderance of lung cancers (96 [67%]

of 144) were of early stage (ie, stage I or stage II), and the outcomes for these individuals were quite good—only 12 (13%) of the individuals with early stage non–small cell lung cancer died from lung cancer during the study. Instead, the majority of individuals who died from lung cancer, despite participation in annual screening, did not have their cancer detected when it was in an early stage and likely to be curable: 13 (34%) of those who died from lung cancer were initially diagnosed with stage III or stage IV non–small cell lung cancer, 7 (18%) were diagnosed with small cell lung cancer, and 6 (16%) had no documented diagnosis of lung cancer prior to their death from lung cancer.

Reported in Table 3 are also the 2-year overall survival probabilities for

Table 1. Characteristics of Studies Included in Analysis of Computed Tomography Screening for Lung Cancer*

	Total (N = 3246)	Istituto Tumori (n = 977)	Mayo Clinic (n = 1439)	Moffitt Cancer Center (n = 830)
Age, mean (SD), y	60.1 (6.4)	58.4 (5.4)	60.0 (6.3)	62.2 (7.0)
Sex, No. (%)				
Male	1917 (59)	693 (71)	737 (51)	487 (59)
Female	1329 (41)	284 (29)	702 (49)	343 (41)
Smoking history				
Years of smoking, mean (SD)	39.1 (7.2)	38.0 (6.4)	39.2 (7.2)	40.4 (8.0)
Cigarettes smoked per day, mean (SD)	27.1 (10.2)	25.2 (10.0)	26.7 (9.9)	30.1 (10.3)
Quit at study entry, No. (%)	1043 (32)	121 (12)	551 (38)	371 (45)
Years since quitting for those who had quit, mean (SD)	7.1 (5.0)	7.3 (6.0)	5.1 (3.2)	10.0 (5.5)
Clinical end point†				
Follow-up to diagnostic outcomes				
Person-years	10 736	3482	5199	2055
Median, y	3.9	3.9	4.0	2.1
Diagnosed with lung cancer				
No. of persons	144	36	66	42
Rate per 1000 person-years	13.9	10.3	12.7	20.4
Diagnosed with advanced lung cancer				
No. of persons	42	11	18	13
Rate per 1000 person-years	3.9	3.6	3.5	6.3
Follow-up to surgical outcomes				
Person-years	10 738	3484	5200	2055
Median, y	3.9	3.9	4.0	2.1
Lung cancer resection				
No. of persons	109	33	48	28
Rate per 1000 person-years	10.2	9.5	9.2	13.6
Mortality end point	(N = 3210)	(n = 976)	(n = 1432)	(n = 802)
Follow-up from 1 year to death or censoring				
Person-years	10 942	2592	6217	2133
Median, y	3.7	3.0	4.4	2.2
Lung cancer deaths				
No. of deaths	38	7	19	12
Rate per 1000 person-years	3.5	2.7	3.1	5.6

*The entry dates for the studies are as follows: Istituto Tumori (September 9, 2000, through July 13, 2001), Mayo Clinic (January 18, 1999, through December 17, 1999), and the Moffitt Cancer Center (December 11, 1998, through August 13, 2003).
†First diagnosis of lung cancer and first surgery.

Figure 1. Results for Studies of Lung Cancer Screening With Computed Tomography
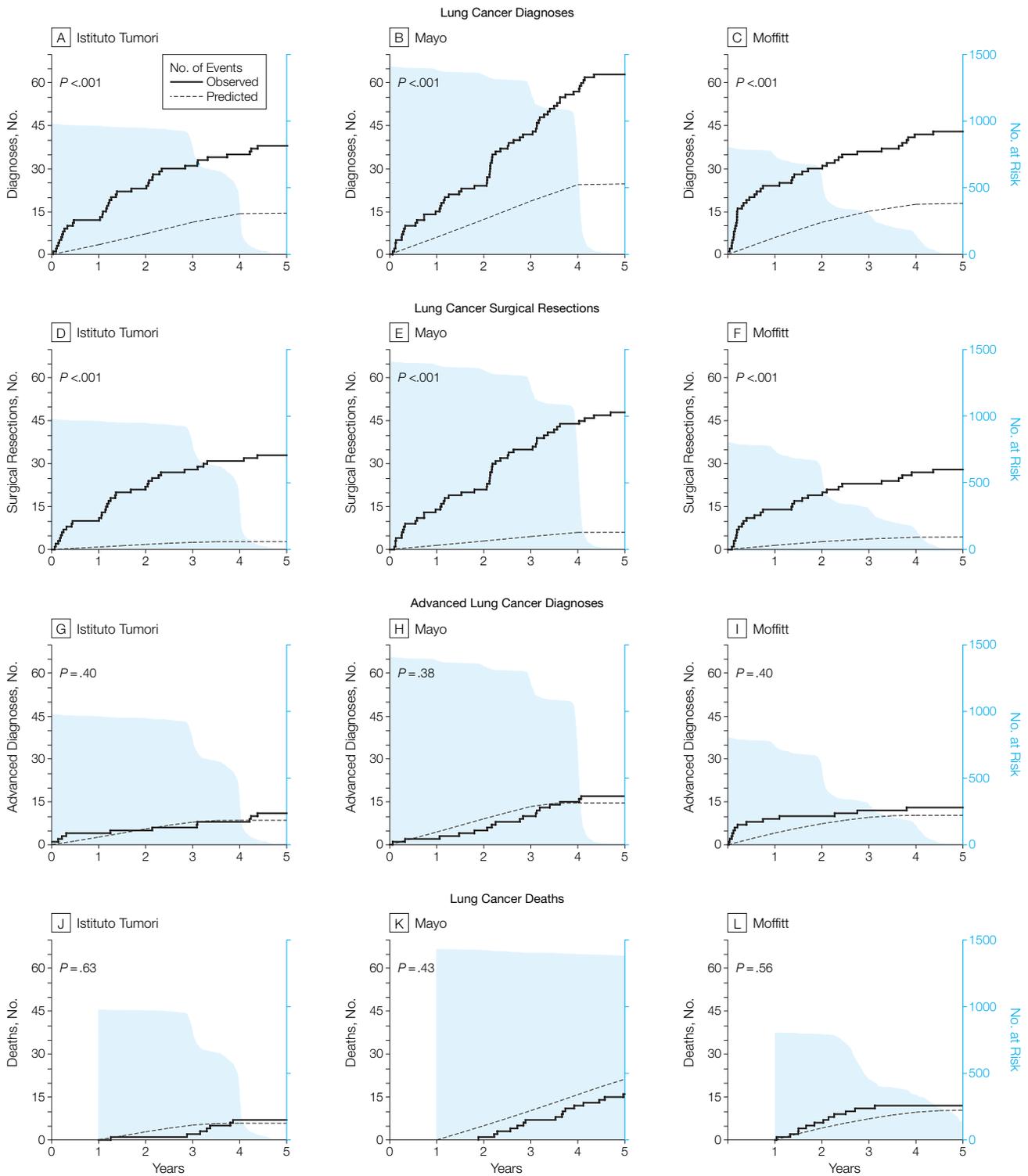
Conducted at the Istituto Tumori (Milan, Italy), the Mayo Clinic (Rochester, Minn), and the Moffitt Cancer Center (Tampa, Fla). The left axis shows the actual and predicted numbers of individuals with different lung cancer outcomes. The right axis shows the number at risk (blue tinted area). *P* values are for the difference between the observed and the predicted number of events over the course of the study.

each group of individuals by initial diagnosis. For instance, individuals diagnosed with stage I to stage II and stage III to stage IV non–small cell lung cancer had 2-year overall survival rates of 90% and 47%, respectively, superior to the published survival rates of 86% (stage IA) to 56% (stage IIB) in the first case, and 40% (stage IIIA) to 5% (stage IV) in the second case.[24] The 4-year lung cancer–specific survival of the 81 individuals in our studies diagnosed with clinical stage I lung cancer and undergoing surgery was 94% (95% CI, 85%-97%), matching outcomes reported in another recent study of CT screening.[25]

COMMENT

Previous studies of chest x-ray screening for lung cancer produced 2 intriguing results. Screening increased the rate of detection of small resectable lung cancers and thus the frequency of lung surgery.

However, screening did not reduce the risk of either advanced lung cancer diagnosis or death from lung cancer.[7] In our study of CT screening, we observed a similar pattern. When individuals are screened for lung cancer with CT, the likelihood that they are diagnosed with lung cancer is increased more than 3-fold, and the likelihood that they undergo a thoracic resection for lung cancer is increased 10-fold. However, as for chest x-ray screening, there appears to be neither a meaningful reduction in the number of advanced cancers being diagnosed nor a reduction in the number of individuals who die of lung cancer. These findings, because they are thematically consistent with the findings of several randomized studies of lung cancer screening with chest x-ray, should raise doubts about the premise underpinning CT screening for lung cancer, and also raise concerns about its potential harms if pursued on a wide scale.

To generate our findings, we used a comparative approach similar to that used in evaluations of other cancer screening tests. Cytological cervical cancer screening was established through comparisons of the incidence and mortality rates between populations in which cervical cytology screening was common compared with populations in which it was uncommon.[26-28] Colonoscopy screening for colon cancer is widely recommended based on comparisons of colon cancer rates among individuals screened with colonoscopy compared with those not screened.[29-31] Screening children for neuroblastoma is not recommended due to the absence of a difference in advanced cases and deaths due to neuroblastoma between screened and unscreened populations.[32,33]

There are 2 differences between our analyses and these other comparative studies. First, these other studies were large

Table 2. Frequency of Predicted and Observed Events

| Time, y	Lung Cancer Diagnoses, No.		Lung Cancer Surgical Resections, No.		Advanced Lung Cancer Diagnoses, No.		Lung Cancer Deaths, No.	
	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed
Istituto Tumori								
1	3.49	11	0.85	10	2.64	4	2.17	0
2	3.79	10	0.92	10	2.87	1	2.83	1
3	3.12	8	0.75	7	2.36	1	2.35	0
4	0.86	4	0.21	4	0.65	2	0.64	4
5	0.01	3	0	2	0.01	3	0.01	2
6	0	0	0	0	0	0	0	0
Total	11.27	36	2.73	33	8.53	11	7.99*	7*
Mayo Clinic								
1	5.93	15	1.44	14	4.44	2	3.89	0
2	6.14	9	1.50	7	4.60	2	4.96	0
3	5.74	18	1.41	14	4.30	4	5.28	3
4	1.69	15	0.41	9	1.27	6	5.60	4
5	0.03	6	0.01	4	0.02	3	5.38	7
6	0	3	0	0	0	1	1.58	5
Total	19.52	66	4.77	48	14.63	18	26.68*	19*
Moffitt Cancer Center								
1	5.43	18	1.33	11	4.06	8	3.44	1
2	4.35	7	1.07	6	3.26	2	4.05	4
3	2.99	8	0.73	6	2.24	1	3.14	6
4	0.95	3	0.23	1	0.71	1	2.30	2
5	0.01	6	0	4	0.01	1	0.66	0
6	0	0	0	0	0	0	0.01	0
Total	13.73	42	3.37	28	10.28	13	13.59*	13*

*Totals incorporate information from the first year of each study but first-year mortality data were not included in the primary analysis.

and definitive, while ours is small and preliminary. Second, rates of cancer events were compared between unscreened and screened populations in these other studies, while in our analyses the comparator was generated by prediction models that used individual risk factor information to estimate individual-level risk. So the validity of our comparisons hinges on our models, which in prior analyses have been shown to accurately predict the frequency of lung cancer events occurring among individuals enrolled in other screening and prevention studies.[12-15]

A possible explanation for the association of screening and an increase in the frequency of lung cancer diagnosis more than 3-fold is that many of the early lung cancers found through screening would not have progressed rapidly to a point of clinical detection. As such, if left unattended, they would have been unlikely to account for a meaningful share of all deaths occurring from lung cancer among the screened individuals.[34-36] An alternative perspective is that the additional cancers found at screening would have progressed if left untreated to cause clinically significant disease, and ultimately death in a substantial proportion of cases.[37-39] If there were a reduction in lung cancer mortality observed over a longer period of follow-up, such a finding would support this latter explanation.

Our data more strongly support the former explanation because of 2 findings. (1) The number of excess cases diagnosed each year continues to exceed the number predicted. An initial rise followed by a return to the baseline incidence rate would be more consistent with a 1-time discovery of a large number of cancers that would have soon appeared sporadically had screening not been performed. This persistent elevation of lung cancer incidence suggests that there is a pool of small nodules being found by CT screening that either have reduced metastatic potential, or have a much slower growth rate and longer natural history than that of the clinically detected lung cancers on which current knowledge of this disease is based. (2) There was no decline in the number of advanced cancers being detected in the studies. Had there been, this too would

Figure 2. Combined Results for the Studies of Lung Cancer Screening With Computed Tomography
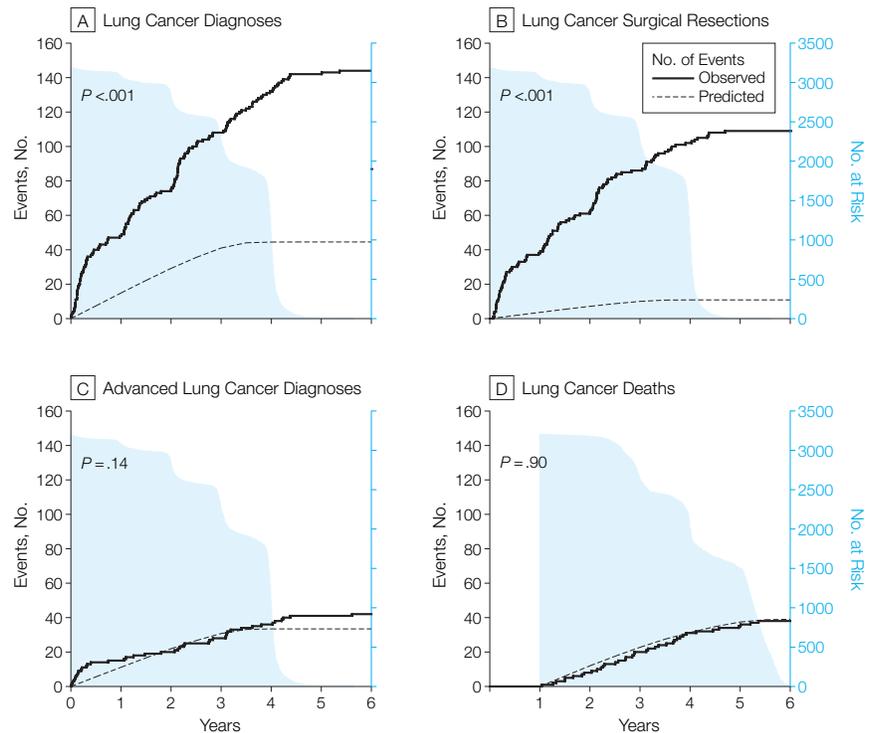
Conducted at the Istituto Tumori (Milan, Italy), the Mayo Clinic (Rochester, Minn), and the Moffitt Cancer Center (Tampa, Fla). The left axis shows the actual and predicted numbers of individuals with different lung cancer outcomes. The right axis shows the number at risk (blue tinted area). *P* values are for the difference between the observed and the predicted number of events over the course of the study.

have constituted evidence that the additional cancers found through screening would have soon progressed had they not been detected. Even with our most conservative estimate, 9 fewer cases of advanced lung cancer than anticipated were observed over the entire study period across all 3 studies, which is less than one tenth the number of excess cases of lung cancer detected by screening, totaling 99.

Our finding of a 10-fold increase in lung cancer surgeries resulting from screening underscores one of the potential public health consequences of CT screening. If the majority of excess early cancers found through screening are unlikely to progress rapidly to a point where they cause clinically significant disease or death, then the thoracic surgeries performed to remove them may be insufficiently beneficial to justify the resulting morbidities. Despite some studies that have demonstrated excellent outcomes

when lung cancer resections are performed in high-volume hospitals by thoracic surgeons, excellent outcomes are not uniform.[38,39] Rather, the postoperative mortality rate following resection of lung cancer in the United States averages 5%, and the frequency of serious complications ranges from 20% to 44%.[40-43] We did not examine the additional morbidities that result from diagnostic procedures or biopsies performed in response to an abnormal CT result, but other investigators have reported that up to 12% of people who are screened for lung cancer with CT undergo invasive biopsies that ultimately reveal 1 or more benign processes.[44] Thus, these biopsies and the other diagnostic procedures that are performed in response to findings on a screening CT constitute another potential downstream harm that could result from widespread CT screening.

Table 3. Lung Cancers and Lung Cancer Deaths

Lung Cancer Diagnosis	Istituto Tumori	Mayo Clinic	Moffitt Cancer Center	Total
No. of cases	36	66	42	144
No. of deaths due to lung cancer	7	19	12	38
2-Year survival, % (95% CI)*				77 (68-84)
Non–small cell				
Stage I/II				
No. of cases	25	44	27	96
No. of deaths	2	8	2	12
2-Year survival, % (95% CI)*				90 (81-94)
Stage III/IV				
No. of cases	9	9	9	27
No. of deaths	4	4	5†	13
2-Year survival, % (95% CI)*				47 (26-64)
Small cell				
No. of cases	2	9	4	15
No. of deaths	1	3	3	7
2-Year survival, % (95% CI)*				50 (21-74)
Diagnosis not captured in study				
No. of cases	0	4	2	6
No. of deaths	0	4	2	6

Abbreviation: CI, confidence interval.
*Survival analysis included the death due to lung cancer that occurred within the first year of the study but does not include the 6 individuals who were diagnosed with lung cancer by death certificate.
†One individual died of lung cancer within the first year of the study. Consistent with the primary analysis, the diagnosis is reported but the death is not.

Our findings that CT screening is not associated with a reduction in the chance that a person will develop advanced lung cancer or die from lung cancer are important negative results that should influence how screening is viewed up until that time when more rigorous data are available from randomized trials. Our findings also emphasize the potentially confusing nature of survival analyses in screening studies. The individuals in our study with early lung cancer had excellent lung cancer–specific survival, equivalent to that reported by the International Early Lung Cancer Action Project.[25] However, as our study illustrates, excellent survival of a few individuals does not necessarily equate to a benefit overall.

The mechanism responsible for the disconnect between the excellent lung cancer–specific survival observed among the few individuals with early stage cancer found by screening and the unchanged lung cancer mortality seen in the group as a whole is illustrated in Table 3. Few of the individuals who died from lung cancer in our study also belonged to the group who had their lung cancers discovered at an early stage. Instead, despite routine screening, most of the lung cancers that were ultimately fatal were not detected until an advanced stage, or until they caused death. So, although excellent survival of individuals with early stage lung cancer is a necessary condition for CT screening to be beneficial, it is not a sufficient condition. Computed tomography screening must also intercept at an early stage those cancers that will later progress to cause clinical disease and death, and in our study, CT screening did not intercept these cancers. Had it, then the number of deaths from lung cancer would have been lower than the number that we expected. In other words, our results raise further doubts about the premise of lung cancer screening, suggesting that it may be difficult to detect at an early stage a meaningful proportion of the lung cancers that cause clinically significant disease and death, even when using a sensitive technology such as CT.

These findings must be viewed in consideration of our study's limitations. A larger sample size may have allowed us to detect a benefit of screening; our 95% CIs actually allow for a reduction in lung cancer mortality as large as 30%, which would constitute a potentially important public health benefit. Also, a longer period of follow-up, or a longer period of screening, may have allowed us to detect a benefit of screening. The design of the National Lung Screening Trial of CT is germane to this latter concern because the duration of screening and length of follow-up roughly match those in our study. In the National Lung Screening Trial, individuals will be screened 3 times (at baseline and at 2 annual follow-up appointments). All 3 of our studies included at least this many screening evaluations. The National Lung Screening Trial is then powered to detect a 50% reduction in lung cancer mortality within about 2 years of follow-up, and a 20% reduction in mortality within 6 years of the commencement of screening.[45] In our study, the median amount of follow-up from the initial CT evaluation to the mortality end point was nearly 5 years.

Despite the paucity of evidence supporting lung cancer screening, and no clear delineation of the harms that may result from excess diagnoses, additional diagnostic procedures, and additional treatment, screening is being offered widely, and claims that screening saves lives and should be available to all are widespread.[25,46,47] Legislation has also been introduced that would require Medicare to cover lung cancer screening.[48] A more prudent course would be to await the findings of the National Lung Screening Trial and several trials that are being conducted and planned in Europe. It would also be wise to explore other approaches to lung cancer prevention and early detection based on modalities other than regular imaging. Until then, CT screening for lung cancer should be considered an experimental procedure, based on an uncorroborated premise.

REFERENCES

1. Jemal A, Clegg LX, Ward E, et al. Annual report to the nation on the status of cancer, 1975-2001, with a special feature regarding survival. *Cancer.* 2004;101:3-27.
2. World Health Organization. *Numbers and Rates of Registered Deaths: Italy, 2001.* Geneva, Switzerland: World Health Organization; 2002.
3. Fontana R, Sanderson DR, Woolner LB, Taylor WF, Miller WE, Muhm JR. Lung cancer screening: the Mayo program. *J Occup Med.* 1986;28:746-750.
4. Kubik A, Polak J. Lung cancer detection: results of a randomized prospective study in Czechoslovakia. *Cancer.* 1986;57:2427-2437.
5. Levin ML, Tockman MS, Frost JK, Ball WC Jr. Lung cancer mortality in males screened by chest X-ray and cytologic sputum examination: a preliminary report. *Recent Results Cancer Res.* 1982;82:138-146.
6. Stitik FP, Tockman MS. Radiographic screening in the early detection of lung cancer. *Radiol Clin North Am.* 1978;16:347-366.
7. Bach PB, Kelley MJ, Tate RC, McCrory DC. Screening for lung cancer: a review of the current literature. *Chest.* 2003;123(suppl):72S-82S.
8. Marcus PM, Bergstralh EJ, Fagerstrom RM, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. *J Natl Cancer Inst.* 2000;92:1308-1316.
9. Kubik AK, Parkin DM, Zatloukal P. Czech Study on Lung Cancer Screening: post-trial follow-up of lung cancer deaths up to year 15 since enrollment. *Cancer.* 2000;89(suppl):2363-2368.
10. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early lung cancer action project: a summary of the findings on baseline screening. *Oncologist.* 1901;6:147-152.
11. Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet.* 1998;351:1242-1245.
12. Bach PB, Kattan MW, Thornquist MD, et al. Variations in lung cancer risk among smokers. *J Natl Cancer Inst.* 2003;95:470-478.
13. Bach PB, Elkin EB, Pastorino U, et al. Benchmarking lung cancer mortality rates in current and former smokers. *Chest.* 2004;126:1742-1749.
14. Bach PB, Begg CB. Further validation of lung cancer mortality model [published online March 18, 2005]. *Chest.* http://www.chestjournal.org/cgi/eletters/126/6/1742. Accessibility verified February 7, 2007.
15. Cronin K, Gail MH, Zou Z, Bach PB, Virtamo J, Albanes D. Validation of a model of lung cancer risk prediction among smokers. *J Natl Cancer Inst.* 2006;98:637-640.
16. Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. *Lancet.* 2003;362:593-597.
17. Swensen SJ, Jett JR, Sloan JA, et al. Screening for lung cancer with low-dose spiral computed tomography. *Am J Respir Crit Care Med.* 2002;165:508-513.
18. Swensen SJ, Jett JR, Hartman TE, et al. Lung cancer screening with CT: Mayo Clinic experience. *Radiology.* 2003;226:756-761.
19. Zhukov TA, Johanson RA, Cantor AB, Clark RA, Tockman MS. Discovery of distinct protein profiles specific for lung tumors and pre-malignant lung lesions by SELDI mass spectrometry. *Lung Cancer.* 2003;40:267-279.
20. Tockman MS, Hazelton T, Coppage L, et al. Lung cancer screening with helical CT: evidence for a stage shift. Presented at: 10th International Congress on Lung Cancer; August 10-14, 2003; Vancouver, British Columbia.
21. Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data From the First National Health and Nutrition Examination Survey follow-up. *Arch Intern Med.* 2003;163:1475-1480.
22. Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Relation of ventilatory impairment and of chronic mucus hypersecretion to mortality from obstructive lung disease and from all causes. *Thorax.* 1990;45:579-585.
23. Melamed MR. Lung cancer screening results in the National Cancer Institute New York study. *Cancer.* 2000;89(suppl):2356-2362.
24. Mountain CF. Revisions in the international system for staging lung cancer. *Chest.* 1997;111:1710-1717.
25. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med.* 2006;355:1763-1771.
26. Gibson L, Spiegelhalter DJ, Camilleri-Ferranti C, Day NE. Trends in invasive cervical cancer incidence in East Anglia from 1971-1993. *J Med Screen.* 1997;4:44-48.
27. Kjellgren O. Mass screening in Sweden for cancer of the uterine cervix: effect on incidence and mortality. *Gynecol Obstet Invest.* 1986;22:57-63.
28. Hakama M, Chamberlain J, Day NE, Miller AB, Prorok PC. Evaluation of screening programs for gynecological cancers. *Br J Cancer.* 1985;52:669-673.
29. Winawer SJ, Zauber AG, Ho MN, et al; The National Polyp Study Workgroup. Prevention of colorectal cancer by colonoscopic polypectomy. *N Engl J Med.* 1993;329:1977-1981.
30. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G; Veterans Affairs Cooperative Study Group 380. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. *N Engl J Med.* 2000;343:162-168.
31. Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer: Telemark Polyp Study I. *Scand J Gastroenterol.* 1999;34:414-420.
32. Woods WG, Gao RN, Shuster JJ, et al. Screening of infants and mortality due to neuroblastoma. *N Engl J Med.* 2002;346:1041-1046.
33. Schilling FH, Spix C, Berthold F, et al. Neuroblastoma screening at one year of age. *N Engl J Med.* 2002;346:1047-1053.
34. Black WC. Overdiagnosis: an underrecognized cause of confusion and harm in cancer screening. *J Natl Cancer Inst.* 2000;92:1280-1282.
35. Dammas S, Patz EF Jr, Goodman PC. Identification of small lung nodules at autopsy: implications for lung cancer screening and overdiagnosis bias. *Lung Cancer.* 2001;33:11-16.
36. Lindell RM, Hartman TE, Swensen SJ, et al. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. *Radiology.* 2007;242:555-562.
37. Henschke CI, Yankelevitz DF, Naidich DP, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. *Radiology.* 2004;231:164-168.
38. Yankelevitz DF, Reeves AP, Kostis WJ, Zhao B, Henschke CI. Small pulmonary nodules: volumetrically determined growth rates based on CT evaluation. *Radiology.* 2000;217:251-256.
39. Yankelevitz DF, Kostis WJ, Henschke CI, et al. Overdiagnosis in chest radiographic screening for lung carcinoma: frequency. *Cancer.* 2003;97:1271-1275.
40. Silvestri GA, Handy J, Lackland D, Corley E, Reed CE. Specialists achieve better outcomes than generalists for lung cancer surgery. *Chest.* 1998;114:675-680.
41. Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med.* 2001;345:181-188.
42. Harpole DH Jr, DeCamp MM Jr, Daley J, et al. Prognostic models of thirty-day mortality and morbidity after major pulmonary resection. *J Thorac Cardiovasc Surg.* 1999;117:969-979.
43. Stéphan F, Boucheseiche S, Hollande J, et al. Pulmonary complications following lung resection: a comprehensive analysis of incidence and possible risk factors. *Chest.* 2000;118:1263-1270.
44. Pinsky PF, Marcus PM, Kramer BS, et al. Diagnostic procedures after a positive spiral computed tomography lung carcinoma screen. *Cancer.* 2005;103:157-163.
45. Goldberg KB. *NCI Lung Cancer Screening Trial: The Cancer Letter.* Washington, DC: National Cancer Institute; 2002.
46. Lee TH, Brennan TA. Direct-to-consumer marketing of high-technology screening tests. *N Engl J Med.* 2002;346:529-531.
47. Focus on lung cancer: screening and early detection. Lungcancer.org Web site. http://www.lungcancer.org/health_care/focus_on_lc/screening/screening.htm. Accessibility verified January 31, 2007.
48. Medicare Lung Cancer Screening Benefit Act of 2006, HR 5514. http://thomas.loc.gov. Accessibility verified January 31, 2007.

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1. International Campaign to Ban Landmines. *Landmine Monitor Report 2005: Toward a Mine-Free World.* Ottawa, Ontario: Mine Action Canada; 2005.
2. Bilukha OO, Brennan M, Woodruff B. Death and injury from landmines and unexploded ordnance in Afghanistan. *JAMA.* 2003;290(5):650-653.
3. Bilukha OO, Brennan M. Injuries and deaths caused by unexploded ordnance in Afghanistan: review of surveillance data, 1997-2002. *BMJ.* 2005;330(7483):127-128.
4. Geneva International Centre for Humanitarian Demining. Information Management System for Mine Action. http://www.gichd.ch/1225.0.html. Accessed May 7, 2007.
5. World Health Organization. *Guidance for Surveillance of Injuries Due to Landmines and Unexploded Ordnance.* Geneva, Switzerland: World Health Organization; 2000.
6. Bilukha OO, Tsitsaev Z, Ibragimov R, Anderson M, Brennan M, Murtazaeva E. Epidemiology of injuries and deaths from landmines and unexploded ordnance in Chechnya, 1994 through 2005. *JAMA.* 2006;296(5):516-518.

CORRECTIONS

Incorrect Figure Legend: In the Medical News & Perspectives article entitled "JCAHO Tweaks Emergency Departments' Pneumonia Treatment Standards" published in the April 25, 2007, issue of *JAMA* (2007;297[16]:1758-1759), the figure legend was incorrect. On page 1758, the figure legend should be "An emergency department radiograph shows normal lungs, but a subsequent computed tomography scan reveals a right lower lobe consolidation (arrowhead) consistent with pneumonia."

Allocation of Lung Cancer Deaths by Year: In the Original Contribution entitled "Computed Tomography Screening and Lung Cancer Outcomes" published in the March 7, 2007, issue of *JAMA* (2007;297[9]:953-961), some lung cancer deaths were allocated to the incorrect year of occurrence in Table 2. On page 958, in Table 2, last column, the numbers of observed lung cancer deaths for the Istituto Tumori should be 0 for 1 year, 1 for 2 years, 1 for 3 years, 5 for 4 years, 0 for 5 years, and 0 for 6 years. The respective numbers of observed lung cancer deaths for the Mayo Clinic are 0, 1, 6, 5, 4, and 3; and the numbers are 1, 6, 5, 1, 0, and 0 for the Moffitt Cancer Center.

> It is impossible to convey to you the picture of human misery continually before my eye. . . . While I amputate one man's thigh, there lay at one time thirteen, all beseeching to be taken next. . . . It was a strange thing to feel my clothes stiff with blood, and my arms powerless with the exertion of using the knife! . . . The view of the field, the gallant sorties, the charges, the individual instances of enterprise and valour recalled to me the sense the world has of victory and Waterloo. But this is transient. A gloomy uncomfortable view of human nature is the inevitable consequence of looking upon the whole as I did—as I was forced to do.
>
> —Sir Charles Bell (1774-1842)