

Review of Thoracic Surgical Oncology

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Editor's note: I am happy to acknowledge that TGH has assumed a co-sponsorship role starting with this month's edition of the Review.

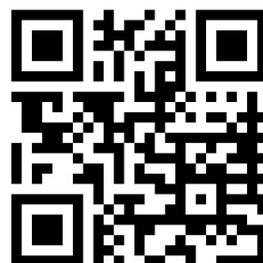
Lung cancer

NCIC BR.19 reports no benefit for adjuvant Iressa

Clin Oncol. 2013 Sep 20;31(27):3320-6. Gefitinib versus placebo in completely resected non-small-cell lung cancer: results of the NCIC CTG BR19 study. [Goss GD](#), [O'Callaghan C](#), [Lorimer I](#), [Tsao MS](#), [Masters GA](#), [Jett J](#), [Edelman MJ](#), [Lilenbaum R](#), [Choy H](#), [Khuri F](#), [Pisters K](#), [Gandara D](#), [Kernstine K](#), [Butts C](#), [Noble J](#), [Hensing TA](#), [Rowland K](#), [Schiller J](#), [Ding K](#), [Shepherd FA](#). **PURPOSE:** Survival of patients with completely resected non-small-cell lung cancer (NSCLC) is unsatisfactory, and in 2002, the benefit of adjuvant chemotherapy was not established. This phase III study assessed the impact of postoperative adjuvant gefitinib on overall survival (OS). **PATIENTS AND METHODS:** Patients with completely resected (stage IB, II, or IIIA) NSCLC stratified by stage, histology, sex, postoperative radiotherapy, and chemotherapy were randomly assigned (1:1) to receive gefitinib 250 mg per day or placebo for 2 years. Study end points were OS, disease-free survival (DFS), and toxicity. **RESULTS:** As a result of early closure, 503 of 1,242 planned patients were randomly assigned (251 to gefitinib and 252 to placebo). Baseline factors were balanced between the arms. With a median of 4.7 years of follow-up (range, 0.1 to 6.3 years), there was no difference in OS (hazard ratio [HR], 1.24; 95% CI, 0.94 to 1.64; $P = .14$) or DFS (HR, 1.22; 95% CI, 0.93 to 1.61; $P = .15$) between the arms. Exploratory analyses demonstrated no DFS (HR, 1.28; 95% CI, 0.92 to 1.76; $P = .14$) or OS benefit (HR, 1.24; 95% CI, 0.90 to 1.71; $P = .18$) from gefitinib for 344 patients with epidermal growth factor receptor (EGFR) wild-type tumors. Similarly, there was no DFS (HR, 1.84; 95% CI, 0.44 to 7.73; $P = .395$) or OS benefit (HR, 3.16; 95% CI, 0.61 to 16.45; $P = .15$) from gefitinib for the 15 patients with EGFR mutation-positive tumors. Adverse events were those expected with an EGFR inhibitor. Serious adverse events occurred in $\leq 5\%$ of patients, except infection, fatigue, and pain. One patient in each arm had fatal pneumonitis. **CONCLUSION:** Although the trial closed prematurely and definitive statements regarding the efficacy of adjuvant gefitinib cannot be made, these results indicate that it is unlikely to be of benefit

Editors's commentary: While results for this trial have killed Iressa as an option for adjuvant treatment, it should be noted that only 15 of the 503 pts enrolled were shown to have EGFR mutation and there was no difference noted between the 7 pts with it and the 8 pts without it. Of note, pts with KRAS mutation fared worse with Iressa.

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Almost a quarter of all NSCLC in NLST were overdiagnosis

JAMA Intern Med. 2013 Dec 9. Overdiagnosis in Low-Dose Computed Tomography Screening for Lung Cancer. [Patz EF Jr](#), [Pinsky P](#), [Gatsonis C](#), [Sicks JD](#), [Kramer BS](#), [Tammemägi MC](#), [Chiles C](#), [Black WC](#), [Aberle DR](#); for the NLST Overdiagnosis Manuscript Writing Team. IMPORTANCE Screening for lung cancer has the potential to reduce mortality, but in addition to detecting aggressive tumors, screening will also detect indolent tumors that otherwise may not cause clinical symptoms. These overdiagnosis cases represent an important potential harm of screening because they incur additional cost, anxiety, and morbidity associated with cancer treatment. OBJECTIVE To estimate overdiagnosis in the National Lung Screening Trial (NLST). DESIGN, SETTING, AND PARTICIPANTS We used data from the NLST, a randomized trial comparing screening using low-dose computed tomography (LDCT) vs chest radiography (CXR) among 53 452 persons at high risk for lung cancer observed for 6.4 years, to estimate the excess number of lung cancers in the LDCT arm of the NLST compared with the CXR arm. MAIN OUTCOMES AND MEASURES We calculated 2 measures of overdiagnosis: the probability that a lung cancer detected by screening with LDCT is an overdiagnosis (PS), defined as the excess lung cancers detected by LDCT divided by all lung cancers detected by screening in the LDCT arm; and the number of cases that were considered overdiagnosis relative to the number of persons needed to screen to prevent 1 death from lung cancer. RESULTS During follow-up, 1089 lung cancers were reported in the LDCT arm and 969 in the CXR arm of the NLST. The probability is 18.5% (95% CI, 5.4%-30.6%) that any lung cancer detected by screening with LDCT was an overdiagnosis, 22.5% (95% CI, 9.7%-34.3%) that a non-small cell lung cancer detected by LDCT was an overdiagnosis, and 78.9% (95% CI, 62.2%-93.5%) that a bronchioalveolar lung cancer detected by LDCT was an overdiagnosis. The number of cases of overdiagnosis found among the 320 participants who would need to be screened in the NLST to prevent 1 death from lung cancer was 1.38. CONCLUSIONS AND RELEVANCE More than 18% of all lung cancers detected by LDCT in the NLST seem to be indolent, and overdiagnosis should be considered when describing the risks of LDCT screening for lung cancer.

Editor's commentary: This is one of the many follow-on publications to come out of the National Lung Screening Trial (NLST) and I think one of the most important. The authors were able to determine the rate of overdiagnosis (lung cancers discovered by screening that would have never become apparent had the patient not undergone screening) by comparing rates of incidence and mortality between the CXR vs. CT groups. 22.5% of all NSCLC were considered overdiagnosis in the CT screened group, the majority of which were "BAC" now known as in situ carcinomas or minimally invasive carcinomas. In fact, 78.9% of "BAC" tumors were considered overdiagnosis. The authors state that as a population continues to undergo yearly screening, that the rate of overdiagnosis drops to much lower percentages as these non-fatal tumors are removed from the screened population.

This paper brings many importance issues surrounding CT screening for lung cancer to the forefront: firstly is the concept of "indolent" lung cancer. Biopsy proven NSCLC has always been considered an urgent problem, but this concept will have to undergo revision in light of this new information. Small BACs and minimally invasive adenocarcinomas have long been known to almost never metastasize, and there are many publications showing that they can be treated with less than lobectomy. The problem is knowing beforehand which of these tumors harbor more invasive elements and which can be safely left alone. It will take years of effort to safely make recommendations about classification of NSCLC into an "indolent" subset.

The second major issue raised by this report is economic. Overdiagnosed tumors will severely limit the cost-effectiveness of widespread screening since, by definition, over one out of five tumors discovered at screening will not have had to be removed. So in economic terms, the first 45% of cancers discovered by screening will be an economic wash, since the savings lost to the first 22.5% of overdiagnosed tumors will have to be captured by the next 22.5% of "real" tumors (more to be technical, since not every tumor discovered by screening will be cured by surgery). Another way of expressing this concept is that for every one life saved from lung cancer by screening, 1.38 cases of overdiagnosis will be encountered. Add overdiagnosis to the already hard to balance cost-effectiveness equation for lung cancer screening, and it's hard to imagine a less than disastrous effect on cancer line budgets.

Patterns of recurrence in esophageal cancer defined

J Thorac Oncol. 2013 Dec;8(12):1558-62. Esophageal cancer recurrence patterns and implications for surveillance. [Lou E](#), [Sima CS](#), [Adusumilli PS](#), [Bains MS](#), [Sarkaria JS](#), [Rusch VW](#), [Rizk NP](#). **INTRODUCTION:** After definitive treatment of esophageal cancer, patients are at high risk for recurrence. Consistent follow-up is important for detection and treatment of recurrence. The optimal surveillance regimen remains undefined. We investigated posttreatment recurrence patterns and methods of detection in survivors of esophageal cancer. **METHODS:** We retrospectively studied a cohort of patients who had undergone surgical resection for esophageal cancer at our institution between 1996 and 2010. Routine computed tomography scan and upper endoscopy were performed for surveillance. **RESULTS:** In total, 1147 patients with resected esophageal adenocarcinoma or squamous cell carcinoma were included (median follow-up, 46 months). Of these, 723 patients (63%) had received neoadjuvant therapy before surgery. During follow-up, there were 595 deaths (52%) and 435 recurrences (38%) (distant [55%], locoregional [28%], or both [17%]). Half of recurrences were detected as a result of symptoms (n = 217), 45% by routine chest and abdominal computed tomography scan (n = 194), and 1% by surveillance upper endoscopy (n = 6). The recurrence rate decreased from 27 per 100 person-years in posttreatment year 1 to 4 per 100 person-years in year 6. In the first 2 years, the rate of recurrence was higher among patients who had received neoadjuvant therapy (35 per 100 person-years) than among those who had not (14 per 100 person-years) (p < 0.001). **CONCLUSIONS:** The incidence of recurrence is high after esophagectomy for cancer. Surveillance endoscopy has limited value for detection of asymptomatic local recurrence. The yield from follow-up scans diminishes significantly after the sixth year; surveillance scans after that point are likely unnecessary

Editor's commentary: This is a useful report from Memorial Sloan-Kettering which looked at recurrence patterns following surgery for esophageal cancer. As expected, rates of recurrence were highest in the period immediately following surgery. About half of recurrences were symptomatic and half were discovered on imaging. Of note, patients who received neoadjuvant chemoradiation followed by esophagectomy were especially prone to early distant and local recurrence. Endoscopy only identified 1% of recurrence and should not be done routinely. Follow up past six years is probably not necessary.

Lung cancer adjuvant chemotherapy

Lymphovascular invasion shown (again) to be predictive of worse outcome in resected NSCLC

Ann Thorac Surg. 2014 Jan 11. pii: S0003-4975(13)02491-0. Lymphovascular Invasion as a Prognostic Indicator in Stage I Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. [Mollberg NM](#)¹, [Bennette C](#)², [Howell E](#)³, [Backhus L](#)³, [Devine B](#)², [Ferguson MK](#)⁴. **BACKGROUND:** Lymphovascular invasion (LVI) is considered a high-risk pathologic feature in resected non-small cell carcinoma (NSCLC). The ability to stratify stage I patients into risk groups may permit refinement of adjuvant treatment recommendations. We performed a systematic review and meta-analysis to evaluate whether the presence of LVI is associated with disease outcome in stage I NSCLC patients. **METHODS:** A systematic search of the literature was performed (1990 to December 2012 in MEDLINE/EMBASE). Two reviewers independently assessed the quality of the articles and extracted data. Pooled hazard ratios (HRs) and 95% confidence intervals (CI) were estimated with a random effects model. Two end points were independently analyzed: recurrence-free survival (RFS) and overall survival (OS). We analyzed unadjusted and adjusted effect estimates, resulting in four separate meta-analyses. **RESULTS:** We identified 20 published studies that reported the comparative survival of stage I patients with and without LVI. The unadjusted pooled effect of LVI was significantly associated with worse RFS (HR, 3.63; 95% CI, 1.62 to 8.14) and OS (HR, 2.38; 95% CI, 1.72 to 3.30). Adjusting for potential confounders yielded similar results, with RFS (HR, 2.52; 95% CI, 1.73 to 3.65) and OS (HR, 1.81; 95% CI, 1.53 to 2.14) both significantly worse for patients exhibiting LVI. **CONCLUSIONS:** The present study indicates that LVI is a strong prognostic indicator for poor outcome for patients with surgically managed stage I lung cancer. Future prospective lung cancer trials with well-defined methods for evaluating LVI are necessary to validate these results.

Editor's commentary: In thinking about risk stratification for surgically resected patients, I think it is important to remember that there already exists a lot of information about who is at higher risk of recurrence and therefore may benefit from adjuvant chemotherapy. (What we are talking about here is Stage I tumors since patients in Stages II and III will already be deemed candidates for adjuvant chemotherapy.) LVI is clearly an important predictor and should be available from any path report. Tumor size (which is formally incorporated into staging), Large Cell histology, and hilar location (independent of nodal involvement) are all available from standard reports. There will be an increasing pressure to adopt proprietary assays in the future but whether these will add to the information already available, **AND** show an improvement in prognosis with adjuvant treatment remains to be seen.

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