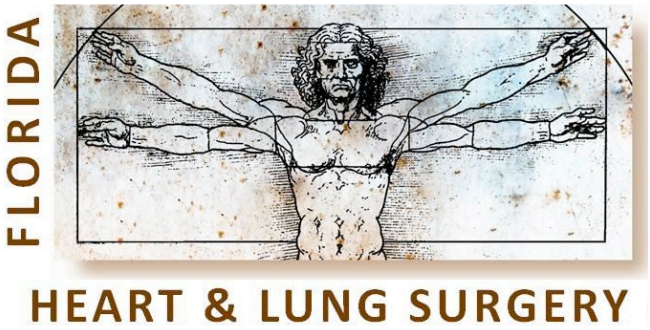
Review of Thoracic Surgical Oncology



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Tumor genomics

New England Journal report details extensive intra-tumor genomic heterogeneity

N Engl J Med. 2012 Mar 8;366(10):883-92. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, Martinez P, Matthews N, Stewart A, Tarpey P, Varela I, Phillimore B, Begum S, McDonald NQ, Butler A, Jones D, Raine K, Latimer C, Santos CR, Nohadani M, Eklund AC, Spencer-Dene B, Clark G, Pickering L, Stamp G, Gore M, Szallasi Z, Downward J, Futreal PA, Swanton C. Cancer Research UK London Research Institute, London, United Kingdom. Abstract BACKGROUND: Intratumor heterogeneity may foster tumor evolution and adaptation and hinder personalized-medicine strategies that depend on results from single tumor-biopsy samples. METHODS: To examine intratumor heterogeneity, we performed exome sequencing, chromosome aberration analysis, and ploidy profiling on multiple spatially separated samples obtained from primary renal carcinomas and associated metastatic sites. We characterized the consequences of intratumor heterogeneity using immunohistochemical analysis, mutation functional analysis, and profiling of messenger RNA expression. RESULTS: Phylogenetic reconstruction revealed branched evolutionary tumor growth, with 63 to 69% of all somatic mutations not detectable across every tumor region. Intratumor heterogeneity was observed for a mutation within an autoinhibitory domain of the mammalian target of rapamycin (mTOR) kinase, correlating with S6 and 4EBP phosphorylation in vivo and constitutive activation of mTOR kinase activity in vitro. Mutational intratumor heterogeneity was seen for multiple tumor-suppressor genes converging on loss of function; SETD2, PTEN, and KDM5C underwent multiple distinct and spatially separated inactivating mutations within a single tumor, suggesting convergent phenotypic evolution. Gene-expression signatures of good and poor prognosis were detected in different regions of the same tumor. Allelic composition and ploidy profiling analysis revealed extensive intratumor heterogeneity, with 26 of 30 tumor samples from four tumors harboring divergent allelic-imbalance profiles and with ploidy heterogeneity in two of four tumors. CONCLUSIONS: Intratumor heterogeneity can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples and may present major challenges to personalized-medicine and biomarker development. Intratumor heterogeneity, associated with heterogeneous protein function, may foster tumor adaptation and therapeutic failure through Darwinian selection. (Funded by the Medical Research Council and others.).

Editor's commentary: This is a fascinating and detailed description of genomic heterogeneity within primary tumor tissue and associated metastatic deposits. The authors found up to 60% heterogeneity among somatic mutations. The implications for biopsy directed genomic testing is obvious and go a long way in explaining the limitations of targeted treatments. The report also gives a plausible rationale for the curious practice of resecting primary tumors of the kidney even in the face of metastatic disease: resecting the primary removes the source of ongoing evolution of clones capable of metastatic potential.

This study also explains the limited utility of large biorepositories of tumor tissue since single samples of such tissue are likely not to be representative of the heterogeneity described in this report. Of note, the report is based on only four patients all with the same tumor type, renal cell carcinoma, and the general applicability of these findings to other tumor types remains to be seen.

NSCLC

No survival benefit in elderly N2 IIIA patients who get XRT following resection

Cancer. 2012 Feb 13. doi: 10.1002/cncr.26585. Postoperative radiotherapy for elderly patients with stage III lung cancer. Wisnivesky JP, Halm EA, Bonomi M, Smith C, Mhango G, Bagiella E.Division of General Internal Medicine, Mount Sinai School of Medicine, New York, New York; Division of Pulmonary, Critical Care, and Sleep Medicin e, Mount Sinai School of Medicine, New York, New York. juan.wisnivesky@mssm.edu. BACKGROUND: The potential role of postoperative radiation therapy (PORT) for patients who have completely resected, stage III nonsmall cell lung cancer (NSCLC) with N2 disease remains controversial. By using population-based data, the authors of this report compared the survival of a concurrent cohort of elderly patients who had N2 disease treated with and without PORT. METHODS: By using the Surveillance, Epidemiology, and End Results (SEER) registry linked to Medicare records, 1307 patients were identified who had stage III NSCLC with N2 lymph node involvement diagnosed between 1992 and 2005. Propensity scoring methods and instrumental variable analysis were used to compare the survival of patients who did and did not receive PORT after controlling for selection bias. RESULTS: Overall, 710 patients (54%) received PORT. Propensity score analysis indicated that PORT was not associated with improved survival in patients with N2 disease (hazard ratio [HR], 1.11; 95% confidence interval [CI], 0.97-1.27). Analyses that were limited to patients who did or did not receive chemotherapy, who received intermediate-complexity or high-complexity radiotherapy planning, or adjusted for time trends produced similar results. The instrumental variable estimator for the absolute improvement in 1-year and 3-year survival with PORT was -0.04 (95% CI, -0.15 to 0.08) and -0.08 (95% CI, -0.24 to 0.15), respectively. CONCLUSIONS: The current data suggested that PORT is not associated with improved survival for elderly patients with N2 disease. These findings have important clinical implications, because SEER data indicate that a large percentage of elderly patients currently receive PORT despite the lack of definitive evidence about its effectiveness. The potential effectiveness of PORT should be evaluated further in randomized controlled trials.

Editor's commentary: It has always surprised me how often patients are offered postoperative XRT in N2 disease despite the relative paucity of evidence for survival benefit. This report, derived from the SEER database, confirms that in the study population of elderly patients, there is no demonstrable survival benefit. In my opinion, postoperative XRT for IIIA N2 patients who are fully resected should only be offered for recurrent disease and not routinely used in an adjuvant fashion.

NSCLC

Sleeve lobectomy or angioplastic resections are an independent risk for decreased long term survival

Ann Thorac Surg. 2012 Feb;93(2):389-96. Local extension at the hilum region is associated with worse long-term survival in stage I non-small cell lung cancers. Chen C, Bao F, Zheng H, Zhou YM, Bao MW, Xie HK, Jiang GN, Ding JA, Gao W. Department of General Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China. BACKGROUND: The prognostic significance of hilar structures invasion, which remains undefined for non-small cell lung cancer (NSCLC), may have potential application for cancer staging. Tumor extension along the bronchus and pulmonary vessels was examined for survival significance. METHODS: In all, 213 pathologically proved central-type stage I NSCLC cases were enrolled. Four study groups were assigned based on the extent of resections: standard lobectomy (group L, n=32), bronchoplastic procedures (group B, n=94), standard lobectomy combined with pulmonary angioplasty (group A, n=48), and bronchial sleeve resection combined with pulmonary artery angioplasty (group BA, n=39). Univariate and multivariate analysis were performed by the Kaplan-Meier method and the Cox regression model. RESULTS: There were 2 postoperative deaths (pulmonary embolism and serious pulmonary infection). Complications were noted in 39 patients (18.3%). Among these patients, the overall 5-year survival rate was 60.2%±0.05%, with a median survival time of 75.0±7.5 months. The 5-year survival rates of subgroups were 79.5%, 59.7%, 59.0%, and 47.9%, respectively for groups L, B, A, and BA. Univariate analysis indicated tumor size, bronchial invasion, arterial involvement, and type of operation as closely associated with long-term survival. Multivariate analysis indicated that type of operation and tumor size were the most prominent prognostic factors of 5-year survival. CONCLUSIONS: Proximal tumor extension into bronchus, invasions into extrapericardial pulmonary vessels, and tumor size were the most important risk factors for 5-year survival with central-type stage I NSCLC. Tumor extension in the hilum was highly related to prognosis and might provide pertinent information to accurately define a tumor ("T") subclass.

Editor's commentary: This report adds to the growing number of poor prognostic features in resected lung cancer independent of traditional tumor and nodal staging. It is not surprising when one considers the invasiveness of these tumors, even at relatively small sizes. I would add the necessity for bronch- or angioplastic resection to other independent poor risk factors like large cell neuroendocrine histology, lymphovascular invasion, extracapsular lymph node involvement, and pleural involvement when weighing the addition of adjuvant treatment.

Robotic vs. laparoscopic resections compared

J Clin Oncol. 2012 Mar 10;30(8):783-91. Epub 2012 Jan 30. Comparative effectiveness of robotic versus laparoscopic hysterectomy for endometrial cancer. Wright JD, Burke WM, Wilde ET, Lewin SN, Charles AS, Kim JH, Goldman N, Neugut AI, Herzog TJ, Hershman DL. Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, 161 Fort Washington Ave, 8th Floor, New York, NY 10032; jw2459@columbia.edu. PURPOSE Use of robotics in oncologic surgery is increasing; however, reports of safety and efficacy are from highly experienced surgeons and centers. We performed a population-based analysis to compare laparoscopic hysterectomy and robotic hysterectomy for endometrial cancer. PATIENTS AND METHODS The Perspective database was used to identify women who underwent a minimally invasive hysterectomy for endometrial cancer from 2008 to 2010. Morbidity, mortality, and cost were evaluated using multivariable logistic and linear regression models. Results We identified 2,464 women, including 1,027 (41.7%) who underwent laparoscopic hysterectomy and 1,437 (58.3%) who underwent robotic hysterectomy. Women treated at larger hospitals, nonteaching hospitals, and centers outside of the northeast were more likely to undergo a robotic hysterectomy procedure, whereas black women, those without insurance, and women in rural areas were less likely to undergo a robotic hysterectomy procedure (P < .05 for all). The overall complication rate was 9.8% for laparoscopic hysterectomy versus 8.1% for robotic hysterectomy (P = .13). The adjusted odds ratio (OR) for any morbidity for robotic hysterectomy was 0.76 (95% CI, 0.56 to 1.03). After adjusting for patient, surgeon, and hospital characteristics, there were no significant differences in the rates of intraoperative complications (OR, 0.68; 95% CI, 0.42 to 1.08), surgical site complications (OR, 1.49; 95% CI, 0.81 to 2.73), medical complications (OR, 0.64; 95% CI, 0.40 to 1.01), or prolonged hospitalization (OR, 0.85; 95% CI, 0.64 to 1.14) between the procedures. The mean cost for robotic hysterectomy was $10,618 versus $8,996 for laparoscopic hysterectomy (P < .001). In a multivariable model, robotic hysterectomy was significantly more costly ($1,291; 95% CI, $985 to $1,597). CONCLUSION Despite claims of decreased complications with robotic hysterectomy, we found similar morbidity but increased cost compared with laparoscopic hysterectomy. Comparative long-term efficacy data are needed to justify its widespread use.

Editor's commentary: This is one of several reports directly comparing robotic vs. laparoscopic resection. This is an area of interest to me as I have found robotic techniques to be helpful in my practice and for my patients. In this report, the authors compare hysterectomy by the two techniques and found little difference. This is similar to recent reports comparing robotic vs. laparoscopic prostatectomy. In fact, most of the literature comparing robotics to minimally invasive techniques show similar results whether comparing hysterectomy, prostatectomy or lung resection: there are little differences in outcomes and a small increase in costs associated with the use of the robotic platform.

The accompanying editorial gives an excellent rationale for continuing the development of robotics. Firstly, while minimally invasive scope-based resection (laparoscopy and thoracoscopy) give better results than open procedures, adoption by surgeons has been slow and robotics promises to greatly expand the total number of patients who may benefit from minimally invasive techniques. Secondly, robotic technology is in its infancy; the technology will continue to evolve and improve over time. Costs will continue to go down, particularly as competitors to the Intuitive daVinci system emerge. Finally, it is too early in the development of robotics, in my opinion, to call for the type of comparative trials that would potentially stall future improvements in the technology.

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