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A novel role for the cell cycle regulator polo-like kinase 4 in cell migration and invasion. Francis S.W. Zih,^{*†‡} Carla O. Rosario,^{*§} Alexandra George,^{*} James W. Dennis,^{*§¶} Carol J. Swallow.^{*†‡§} From the ^{*}Samuel Lunenfeld Research Institute, Mount Sinai Hospital, the [†]Institute of Medical Science, and the Departments of [‡]Surgical Oncology, [§]Laboratory Medicine and Pathobiology and [¶]Molecular Genetics, University of Toronto, Toronto, Ont.

Introduction: Our laboratory has shown that in patients with colorectal cancer, polo-like kinase 4 (Plk4) expression is increased modestly in primary tumours and markedly in liver metastases. We recently found that haploid levels of Plk4 are associated with defective cytokinesis, which is related to lack of appropriate actin filament rearrangement resulting from failure to activate RhoA in mitotic cells (Rosario et al., *PNAS*, in press). We hypothesized that Plk4 increases the motility of interphase cells via Rho GTPase activation, enhancing migration and invasion, and thereby metastatic capacity. **Methods:** Both Plk4^{+/-} and Plk4^{-/-} murine embryonic fibroblasts (MEFs) were compared via an expression array (Illumina) and via spreading, scratch wound and transwell migration assays. Migration of DLD-1 colorectal cancer cells was measured using the Real-time Cell Analyzer system (Roche) comparing cells transfected with FLAG-tagged Plk4 to FLAG alone. **Results:** On array analysis, expression of genes that decrease cell migration was higher in Plk4^{+/-} MEFs, suggesting that Plk4 may enhance cell motility. Also, Plk4^{+/-} MEFs showed impaired spreading with fewer cell protrusions ($p = 0.003$). Furthermore, Plk4^{+/-} MEFs showed reduced wound healing along with failure to realign microtubule organizing centres in a scratch wound assay ($p = 0.025$) and a defect in directional migration ($p = 0.004$). DLD-1 cells transfected with Plk4 demonstrated a higher migration rate than cells transfected with FLAG alone. **Conclusion:** These results indicate that Plk4, which was previously recognized as a cell cycle regulator required for centriole duplication, also facilitates cell migration and invasion. Increased expression of Plk4 may contribute to metastatic potential in cancer cells. Future studies will directly test the effect of Plk4 on metastasis formation in vivo.

Long-term outcomes of patients with cutaneous melanoma managed with sentinel node biopsy performed after versus concurrent with wide local excision. Eran Sharon,^{*} Wey Liang Leong,^{*†} Kengo Asai,[†] Aliyah Kanji,[†] Lindsay Jacks,[‡] Alexandra Easson,^{*†} Michael Reedijk,^{*†} Danny Ghazarian,^{‡§} David R. McCreedy.^{*†} From the Departments of ^{*}Surgical Oncology, [†]General

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Introduction: The status of sentinel node biopsy (SNB) is an important prognostic indicator for long-term outcomes in cutaneous melanoma. Concurrent SNB is preferred over SNB after wide local excision (WLE) because of the theoretical risks of altering lymphatic drainage after WLE. We compared outcomes between the 2 groups. **Methods:** Of 855 SNB patients seen between July 1996 and December 2005, 47 were excluded because of inaccurate data and recurrent disease. Of 807 eligible patients, 231 were referred to us after WLE (group 1), whereas 576 patients had SNB concurrent with WLE (group 2). We compared clinicopathologic variables using standard statistical analyses. Multivariate analysis was used to determine the independent association between survival/recurrence risk and groups. **Results:** Group 1 tumours were thicker (2.58 v. 2.35 mm, $p = 0.04$) and more ulcerated (35% v. 28%, $p = 0.05$). Both groups were similar in median follow-ups (6.2 v. 5.3 yr), technical success rates (100% v. 98%), the number of sentinel node retrieved (2.6 v. 2.7, $p = 0.61$), SNB positive rates (27% v. 22%, $p = 0.14$) and false-negative rates (4% v. 2%, $p = 0.27$). After adjusting for tumour factors, group 1 had a marginally poorer recurrence-free survival ($p = 0.09$) but was similar in overall survival ($p = 0.27$). **Conclusion:** In cutaneous melanoma, it is preferred to perform SNB concurrent with WLE. We observed a marginally higher risk of recurrence ($p = 0.09$) when SNB was performed after WLE. However, in patients who already had WLE, SNB was technically feasible with a similar positive SNB rate and overall survival.

Sentinel node frozen section: Should it be done? Mohammad H. Jamal, Jonathan Rayment, Suhail Doi, Ari Megueditchian, Sarkis Meterissian. From the McGill University Health Centre, Montréal, Que.

Introduction: The reported sensitivity of intraoperative sentinel lymph node biopsy frozen section (SLNFS) varies in the literature. The aim of this study was to examine the sensitivity and accuracy of SLNFS along with factors predictive of a positive result. **Methods:** We performed a retrospective review of all patients who underwent SLNFS for a T1–T3 N0 breast cancer at a single institution between 2005 and 2007. The χ^2 statistic and Fisher exact test were used to determine significance in differences between groups for categorical variables. Binomial logistic regression was used for multivariate analysis. **Results:** In all, 176 patients underwent SLNFS, giving a total of 376 sentinel nodes. On final pathologic analysis, 56 of 176 (31.8%) patients

had sentinel nodes that were positive for metastatic carcinoma. Of these 56 patients, 32 were identified on intraoperative SLNFS, for an intraoperative sensitivity of 57.1%. All (120/120) patients with truly negative sentinel node test results were correctly identified on intraoperative SLNFS (100% specificity). Overall, frozen section analysis correctly identified the metastatic status of 152 of 176 patients (86% accuracy). Only lymphovascular invasion (OR 12.1, 95% CI 4.74–31.1) and a larger primary tumour size (OR 1.76, 95% CI 1.09–2.85) were independent predictors of a positive intraoperative SLNFS result. Nodes that contained micrometastases (< 2 mm) were 17.2 times more likely to be categorized as falsely negative on intraoperative analysis than those with metastatic lesions larger than 2 mm (OR 17.2, 95% CI 3.86–76.6). Of the clinicopathologic factors analyzed in the present study, the presence of lymphovascular invasion (OR 8.47, 95% CI 3.12–23.0), multifocality (OR 2.60, 95% CI 1.05–6.46) and primary tumour size (OR 1.69, 95% CI 1.05–2.74) were all independent predictors of a positive final SLNB result. **Conclusion:** We identified factors predictive of intraoperative and final sentinel lymph node positivity. SLNFS is effective in eliminating the need for a second surgical procedure in the majority of patients.

Can clinicians abstract data? A population-based audit of cancer staging in the central-south region of Ontario. Kelly N. Vogt,^{*†} Angela Coates,[‡] Gemma Lee,[§] Eric Holowaty,[§] Marko Simunovic.^{*‡} From the ^{*}Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, the [†]Department of Surgery, University of Western Ontario, London, the [‡]Department of Surgery, McMaster University, Hamilton, and [§]Cancer Care Ontario, Toronto, Ont.

Introduction: Traditionally, the Ontario Cancer Registry (OCR) collected TNM staging data only for patients seen at regional cancer centres. Stage was recorded by the treating oncologist. We assessed the quality (completeness and accuracy) of this practice and the feasibility of data abstractors performing population-based cancer staging. **Methods:** The OCR provided a random sample of 277 breast, 276 colorectal and 215 lung cancer cases from the central-south region of Ontario (population 1.2 million) in 2004, an area served by the Juravinski Cancer Centre (JCC). Clinician experts acted as gold standards for data abstractor training and interrater reliability testing. Oncologist staging at the JCC was tested using the Pearson χ^2 for completeness and Krippendorff α for accuracy. **Results:** Abstractors staged 755 of 804 (93.9%) cases; 475 (59.1%) of 804 patients were assessed at the JCC. For breast, colorectal and lung cancer cases, oncologist staging was done for 81.4%, 80.7% and 63.7%, respectively, whereas abstractor staging was done for 99.1%, 93.3% and 94.1%, respectively. The difference in overall completeness was 76.0% and 96.2% ($p < 0.001$). For the 352 JCC patients staged by both oncologists and abstractors, there was disagreement in 36 (10.2%) cases. Krippendorff α showed good statistical agreement (0.86). **Conclusion:** Trained abstractors staged 93.9% of cancer cases in a population-based sample. Compared with JCC oncologists, abstractors had superior staging completeness and similar accuracy. The OCR is implementing an abstractor model for provincial cancer staging. Databases that rely on clinician entry should consider ongoing evaluation for data completeness and accuracy.

Utility of preoperative imaging in evaluating declining rates of colorectal liver metastases over time. Simon Yang,^{*} Sermsak Hongjinda,^{*} Sherif S Hanna,^{*} Steven Gallinger,[†] Alice C. Wei,[†] Alex Kiss,[‡] Calvin H.L. Law.^{*} From the ^{*}Division of General Surgery, Sunnybrook Health Sciences Centre, the [†]Ontario Division of General Surgery, University Health Network, University of Toronto, and the [‡]Institute for Clinical Evaluative Sciences, Toronto, Ont.

Introduction: Reports on the sensitivity and accuracy of contrast-enhanced helical computed tomography (HCT) in the preoperative evaluation of colorectal liver metastases (CLM) have been conflicting. Few studies have controlled and reported the time interval between HCT and eventual surgery. We propose that the utility of HCT is affected by the time between imaging and surgery. **Methods:** A multi-institutional retrospective review of consecutive patients who underwent hepatic resection for CLM from January 1999 to September 2004 was conducted. Data regarding lesion characteristics and resectability were extracted from radiology reports, operative findings, histopathologic data and follow-up visits. HCT studies were evaluated for their sensitivity for detecting CLM and ability to predict resectability. **Results:** We identified 217 consecutive patients who received hepatic resection for CLM. The overall sensitivity of HCT for detection of CLM was 83%. Prolonged time between imaging and surgery was a negative predictor of HCT sensitivity in univariate and multivariate analyses ($p < 0.0001$). In predicting resectability, preoperative HCT was accurate 77% of the time. The time to surgery was negatively correlated with HCT prediction accuracy in univariate and multivariate analysis ($p < 0.0001$). **Conclusion:** The utility of HCT as a preoperative tool to evaluate CLM declines over time until surgery is performed. This may explain conflicting reports of HCT accuracy in the current literature. Inaccuracies as a result of a delay between imaging and surgery are preventable and can lead to unnecessary surgery.

Adoption of surgical innovations: factors influencing the use of sentinel lymph node biopsy for breast cancer. F.C. Wright,^{*} A.R. Gagliardi,[†] B.J. Wells,^{*} N. Fraser,^{*} M.L. Quan.[‡] From the ^{*}Department of Surgery, Sunnybrook Health Sciences Centre, the [†]Toronto General Research Institute, University Health Network, University of Toronto, Toronto, Ont., and the [‡]Department of Surgery, Foothills Medical Centre, University of Calgary, Calgary, Alta.

Introduction: Sentinel lymph node biopsy (SLNB) has been unevenly adopted into practice. In this qualitative study we explored individual, institutional and policy factors that may have influenced SLNB adoption. **Methods:** Qualitative methods were used to examine factors influencing SLNB adoption. Grounded theory guided data collection and analysis. Semistructured interviews were based on Roger's diffusion of innovation theory. Purposive and snowball sampling was used to identify participants. Semistructured telephone interviews were conducted with urban, rural, academic and community health care providers and administrators to ensure all perspectives and motivations were explored. Two individuals independently analyzed the data and achieved

consensus on emerging themes. **Results:** In all, 43 interviews were completed with 21 surgeons, 5 pathologists, 7 nuclear medicine physicians and 10 administrators. Generated themes included awareness of SLNB with the exception of some administrators, the acknowledged advantage of SLNB, SLNB compatibility with beliefs regarding axillary staging, acknowledgement that SLNB was a complex innovation to adopt, extensive trialing of SLNB before adoption by early adopters, observable benefits with SLNB, acknowledgement that hospital-level administrative support enabled adoption, desire for a provincial policy supporting SLNB, requirement of a local high-volume breast surgery champion who communicated extensively with the team to facilitate local adoption and the need for credentialing of SLNB to ensure quality. **Conclusion:** Sentinel lymph node biopsy is a complex innovation to adopt. Successful adoption was assisted by a high-volume breast cancer surgical champion and administrative support. Important factors identified by this study could be used to enhance adoption of SLNB and possibly other surgical innovations.

Usefulness of preoperative axillary ultrasound in breast cancer patients. *Jonathan Cools-Lartigue,* Nora Trabulsi,* Alison Sinclair,† Ari Meguerditchian,* Benoit Mesurrolle,‡ Rebecca Fuhrer,† Sarkis Meterissian.** From the *Department of Surgery, McGill University Health Centre, the †Department of Epidemiology, Biostatistics and Occupational Health, McGill University, and the ‡Department of Diagnostic Radiology, McGill University Health Centre, Montréal, Que.

Introduction: Axillary lymph node status is the most important prognostic factor in early stage breast cancer. Sentinel lymph node biopsy is used to determine the need for axillary node dissection. Axillary ultrasound is increasingly used to determine nodal status before surgery. The purpose of this study was to determine the sensitivity, specificity and accuracy of axillary ultrasound in breast cancer patients. **Methods:** A consecutive series (2005–2007) of patients with early-stage breast cancer who underwent surgery and staging was reviewed. Axillary ultrasound findings were assessed (normal, suspicious/abnormal, enlarged, multiple). Lymph node status was recorded for all nodes following axillary dissection. The data were cross-tabulated, and test characteristics were calculated. **Results:** Of 354 patients (mean age 57.8 yr), 68% (242) had invasive ductal cancer, 63% (224) and 48% (170) were estrogen- and progesterone-receptor positive, respectively, 8% (30) were HER-2/neu positive and 46% (164) were axillary node positive. Ultrasound results were normal in 216 patients (61%), suspicious/abnormal in 78 (22%), enlarged in 43 (12%) and multiple in 17 (4.8%). The sensitivity and specificity were 62% (95% CI 54.8–69.7) and 81% (95% CI 75.5–86.6). The positive and negative predictive values were 74% (95% CI 66.6–81.2) and 71% (95% CI 65.3–77.3). Accuracy was 72% (95% CI 67.3–78.9) and improved with the number of positive nodes (≥ 3 v. < 3 , $p < 0.0001$) and size of metastasis (> 2 mm v. ≤ 2 mm, $p < 0.0001$). **Conclusion:** Axillary ultrasound had an accuracy of 70% or greater in this series. It is easily performed and may prevent unnecessary sentinel node dissection.

Breast lesion of uncertain malignant potential: a challenge for surgeons. *Nancy Deslauriers,* Michel-Pierre Dufresne,† E. Yves Leclerc,‡ Pierre Dubé,‡ Lucas Sidéris,‡ Guy Leblanc.‡*

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Introduction: The need for surgical resection of breast lesions of uncertain malignant potential diagnosed at core biopsy is not well established. The aim of our study was to determine the incidence of these lesions on core biopsy and to find the rate of upgrade at surgery and during follow-up. **Methods:** All breast biopsies at our hospital were prospectively collected from November 1999 to December 2008. We reviewed the records of all patients diagnosed with lobular carcinoma in situ (LCIS), atypical lobular neoplasia (ALH), atypical ductal hyperplasia (ADH) and radial scar during that period. **Results:** Among 9325 breast biopsies done during that period, there were 20 patients with LCIS (0.2%), 36 with ALH (0.4%), 60 with radial scars (0.6%) and 110 with ADH (1.2%). For lobular neoplasia, 85% of LCIS patients had surgical excision with an upgrade rate of 29% (5/17). On follow-up, no patient developed a breast cancer at the biopsy site. Of the patients with ALH, 28% had surgical resection, with only 1 patient presenting an upgrade. For radial scars, 58% had surgical resection with an upgrade rate of 3 of 35 (8%). In all 3 patients with an upgrade, the biopsy was done on a hypoechoic lesion. No patient with a radial scar visible on mammogram only presented an upgrade, and no patient at follow-up developed a cancer at the biopsy site. For patients with ADH, 53 of 110 (48%) had a surgical excision with an upgrade rate of 9 of 53 (18.9%). Nine patients of the 49 who did not undergo a surgical excision developed a cancer at the biopsy site during follow-up (18%). Finally, 51% of the patient who did not have surgery had to be rebiopsied. **Conclusion:** The important rate of upgrade in LCIS and ADH mandates a surgical excision when these lesions are found on biopsy results. The low rate of upgrade in radial scar and ALH could allow these cases to be observed.

Predicting local recurrence following breast conserving therapy for early stage breast cancer: the significance of a narrow (≤ 2 mm) surgical resection margin. *G. Groot, H. Rees, P. Pahwa, S. Kanagaratnam, M. Kinloch.* From the Department of Surgery, University of Saskatchewan, Saskatoon, Sask.

Introduction: Whereas survival following breast conserving therapy (BCT) has been demonstrated in 8 randomized controlled studies to be equivalent to mastectomy in early stage breast cancer (stages I and II), there is an increased risk of local recurrence (LR). Controversy continues over the extent of surgical resection margin required to minimize the risk of LR. This study explores whether or not a narrow (≤ 2 mm) resection margin affects LR. **Methods:** All patients registered at the Saskatoon Cancer Centre between Jan. 1, 1991, and Dec. 31, 2000, who had a diagnosis of early stage invasive duct carcinoma treated with BCT were examined. All charts and pathology reports were reviewed. A central pathology review was carried out for all cases where the pathologic resection margin was unclear in the original pathology report. Other factors known or thought to affect LR (age, radiation boost, grade, extensive ductal carcinoma in situ, estrogen/progesterone receptor status) were considered in the statistical analysis. **Results:** Among the 200 narrow margin cases, 19 local recurrences were detected (9.5%), whereas 52 local

recurrences were detected in the 491 wide margin cases (10.6%). This difference was not statistically significant. **Conclusion:** A narrow (≤ 2 mm) resection margin does not result in an increase in local recurrence compared with a surgical resection margin > 2 mm in breast conserving therapy for early stage ductal carcinoma and does not warrant re-excision.

Impact of elective central compartment lymph node dissection in differentiated thyroid cancer on survival.
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Introduction: The battle of thyroid cancer is thought to be lost in the central compartment. The present study assessed whether elective central compartment lymph node dissection (CLND) impacts disease-specific survival in differentiated thyroid cancer. **Methods:** In all, 1501 consecutive patients with differentiated thyroid cancer were identified as a population-based cohort at the Manitoba Cancer Registry (1970–2005) with a median follow-up of 12 years. Outcomes of these patients in terms of overall, disease-specific and disease-free survival were calculated using the Kaplan–Meier method, and intergroup comparisons were made by the log rank test. The Cox proportional hazards model was used for multivariate analysis. **Results:** Mean age at diagnosis was 46.2 (SD 17.4) years, and 77.2% of the patients were female. Overall, 83.8% had papillary carcinoma and 75.4% had stage I disease; 1205 patients were node negative and 16.4% had CLND; 4.1% of patients recurred in the central compartment of the neck and 2.2% in the lateral compartment of the neck; 37.2% of the central compartment neck failures occurred after central compartment lymph node dissection; however, there was no significant survival difference between those who had CLND and those who did not. On multivariate analysis, age at diagnosis, grade of tumour, metastatic disease and completeness of resection were the only factors that significantly influenced disease-specific survival. **Conclusion:** Elective CLND did not provide any significant survival advantage over wait and watch central compartment lymph node exploration.

The effect of surgical stress and hypercoagulability on experimental colorectal cancer metastases.
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Introduction: Surgical resection is a mainstay of therapy for patients with localized solid malignancies. Many patients still develop metastatic recurrences, the mechanisms of which are not completely understood. We hypothesized that surgical stress promotes the development of metastases. The goal of this study was to characterize the interactions between postoperative hypercoagulability and the increase in metastases seen after surgery. **Methods:** BalbC mice were injected with CT-26LacZ colon cancer cells intravenously, and a partial hepatectomy was performed to induce surgical stress. The control group received intravenous CT-26LacZ cells only. Mice were euthanized on day 8, and their lungs were stained with Xgal to visualize the tumours. A cohort of mice was also treated with perioperative tinzaparin, a low-molecular-weight heparin (LMWH). The role of fibrin clots was also studied. **Results:** Surgical stress resulted in a dramatic increase in the metastatic deposits seen in the lungs of mice that underwent surgery compared with the controls. Administration of heparin resulted in a significant decrease in the metastatic deposits seen on day 3 and day 8. At 4 hours, increased fibrin was associated with CT-26 cells in the surgical stress group, and the effect was abrogated by LMWH. Hematoxylin and eosin staining confirmed these findings. **Conclusion:** Surgical stress facilitates metastases, and treatment with LMWH abrogates this effect. Fibrin clots are associated with tumour cells more significantly in mice subjected to surgical stress, and LMWH reduces this effect. Thus, perioperative anticoagulation can attenuate enhancement of metastases following surgery in a murine model.