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Development of Guidelines for the Surgical Treatment of Gastric Cancer in BC

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DR. TREVOR HAMILTON

It is estimated that 4,100 people in Canada will be diagnosed with gastric cancer in 2019, and 420 of them will be in BC[1]. Although we have seen a declining incidence of gastric cancer over the past few decades, it still remains a highly lethal disease with a 5-year survival rate of 28% in Canada[1].

A recent review of gastric cancer patients treated at BC Cancer with curative intent strategy identified a number of factors concerning for poor survival outcomes. In particular, surgical margins on pathologic assessment were positive in 16% of cases; adequate lymph node harvest was achieved in only 35% of cases; the majority of cases were performed at hospitals doing one or fewer cases per year; and only 15% of patients received pre-operative therapy (chemotherapy or radiation)[2,3].

The Surgical Standards Working Group was established to develop evidence-based guidelines for the surgical treatment of all stages of gastric cancer. The aim was to enhance the quality of surgical care, and ultimately improve outcomes for gastric cancer patients. A systematic review of the current literature was performed with outcome measures for recommendations including survival, recurrence, morbidity and mortality. Evidence was rated for quality based on established techniques. Recommendations were then qualified as strong or weak based on available quality of evidence in the literature. The recommendations were also peer reviewed for content prior to consensus.

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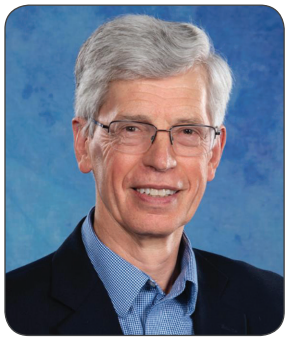
The guideline[4] consists of nine recommendations and is endorsed by the BC Cancer Gastrointestinal Tumour Group. The recommendations cover numerous aspects of care for gastric cancer patients ranging from pre-operative working/staging, surgical margins, nodal harvest, operative approach, metastatic disease, multi-modality treatments, hospital facilities and case-volume.

In addition to developing recommendations for gastric cancer treatment, the guidelines also identify a number of quality indicators for monitoring and evaluation to provide feedback to healthcare providers and develop strategies to improve outcomes for gastric cancer patients in the future.

**The guideline recommendations and article references are located in the newsletter insert.*

Electronic Synoptic Pathology Reporting: How Can Pathologists Help Surgeons Improve Patient Care?

DR NICK VAN DER WESTHUIZEN
CHAIR, BC ELECTRONIC SYNOPTIC PATHOLOGY REPORTING COMMITTEE



DR. NICK VAN DER WESTHUIZEN

The great majority of cancers are diagnosed by pathologists working in collaboration with surgeons and other clinicians. As pathology reporting becomes more complex, the need for complete, concise and clear reports becomes increasingly important. A clear and thorough report of pathological findings informs clinicians and aids in treatment decisions that lead to better patient outcomes.

Synoptic pathology reporting software creates a standardized pathology report that guarantees all mandatory diagnostic, prognostic and therapeutic fields are included. Between 2014 and 2017, British Columbia embarked on a three-year project to implement mTuitive's xPert Synoptic Pathology Reporting Software in all 23 pathology sites.

No matter where the surgery was performed, when the xPert synoptic pathology reporting tool is used the surgeon and oncologist will get a standardized complete pathology report enabling the necessary treatment decisions. Tumour details are also transmitted in real-time as discrete data elements to BC's Central Data Repository. Data can then be analyzed for quality metrics including analysis at the pathologist, surgeon, institutional, regional and provincial level. In addition, data is electronically transmitted to the BC Cancer Registry providing up to date cancer registry data.

In the next phase of the project (2017-2020), with funding from the Canadian Partnership Against Cancer (CPAC), our goal is to maximize data impact through knowledge mobilization to allow for continuous quality improvement.

Using the principles outlined below we have the ability to report key quality indicators to pathologists and surgeons, thus helping drive improvements in cancer care.

1. CLINICAL LEADERS are trusted members of physician communities with a desire to drive system-level change Clinical leaders engage physicians in the feedback reporting process and facilitate group consensus building.

2. FEEDBACK REPORTS provide clinicians with a summary of relevant clinical measures associated with the care they delivered over a specified period of time. Effective feedback reports are easy to use and drive physicians toward meaningful conversations to improve patient care and outcomes.

3. COMMUNITIES OF PRACTICE are knowledge sharing and social connection models used to solve problems, share ideas or knowledge, or collaborate to generate new knowledge. Communities of practice are positive collaborative spaces that can be built on existing groups and operate best with the support of the institution.

USING PHYSICIAN LEVEL FEEDBACK REPORTS & COMMUNITIES OF PRACTICE TO IMPROVE QUALITY - CPAC NOV 2017

We are grateful to our pathology checklist champions and surgeons (Clinical Leaders) who identified key pathological, clinical and prognostic indicators for each of the five major cancer sites. These indicators were used to create two new dashboards: the Pathologist Dashboard and the Surgeon Dashboard (Feedback Reports) that will provide feedback reports to individual pathologists and surgeons in a culture of trust by ensuring privacy and confidentiality.

We hope that by reflecting on your individual data and discussing with your peers, it will foster further discussion among communities of practice around the meaning of the data. The feedback loop would be completed when communities of practice make recommendations to the clinical leaders about systemic improvements/changes that can be made.

For any feedback or questions you can reach Dr. Westhuizen at *nicholas.westhuizen@viha.ca*

Highlights from the Fall Update 2019: Management of Not So Rare Cancers

DR. TREVOR HAMILTON
CHAIR, 2019 FALL UPDATE PLANNING COMMITTEE
CHAIR, GI SURGICAL TUMOUR GROUP, BC CANCER SURGERY NETWORK

The annual BC Cancer Surgery Network Fall Update was held on October 5, 2019 and was attended by residents and surgeons from across the province. This year the topic was "Management of Not So Rare Cancers" and included a number of topics including gastric cancer, cutaneous malignancies and soft tissue tumours.

Hereditary Testing for Gastric Cancer

We started the day with visiting speaker, Dr. Savtaj Brar, Surgical Oncologist from Mount Sinai Hospital in Toronto who discussed the evaluation of gastric cancer patients for potential genetic testing. He discussed Hereditary Diffuse Gastric Cancer (HDGC) and CDH-1 gene mutation and reviewed the current indications for genetic testing for CDH-1 gene mutation, as well as potentially adopting more liberal criteria, as many CDH-1 families do not meet current testing criteria. Patients with known CDH-1 mutations should be considered for prophylactic total gastrectomy after age 20. If endoscopic surveillance is performed, annual gastroscopy screening with the Cambridge protocol is recommended. Dr. Brar gave an overview of the newly discovered Gastric Adenocarcinoma and Proximal Polyposis Syndrome (GAPPS) associated with APC gene mutation and recognition of the phenotype. He also reviewed evaluation and surveillance recommendations in Lynch syndrome, SMAD4 and STK11 gene mutations.

CDH-1 Testing Criteria (at least one of the following)

- Two cases of diffuse gastric cancer in one family, at any age
- Diffuse gastric cancer at age < 40
- Personal or family history of diffuse gastric cancer and lobular breast cancer, one age < 50

Endoscopic Evaluation of Gastric Cancer

Next, Dr. Eric Lam, Gastroenterologist from St. Paul's Hospital in Vancouver, discussed the pathophysiology of gastric cancer development, different pathologic classifications of gastric cancer, and the Borrmann classification of the gross appearance of advanced gastric cancers. For obtaining adequate tissue diagnosis, multiple biopsies are necessary (8 minimum) and the edges of an ulcer should be targeted.

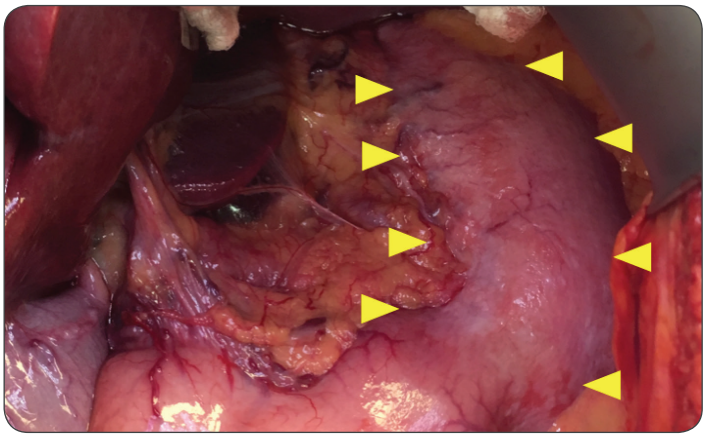
Symptoms that warrant investigation with gastroscopy include new onset dyspepsia, anemia, or weight loss. General population screening is not endorsed; however, certain populations may be warranted including family history of gastric cancer, patient from high-prevalence area, chronic dyspepsia, intestinal metaplasia (proximal to antrum), dysplasia, and atrophic gastritis. He reviewed different types of gastric polyps (fundic, adenoma, hyperplastic, inflammatory) and the morphological features and management strategies. He also outlined the key features in an endoscopy report including accurate descriptions, location, Paris classification, size estimation, and photo/video documentation.

Tips for detecting premalignant lesions:

- Use Paris Classification
- Accurately report size and location
- High index of suspicion for small lesions in the setting of chronic gastritis, atrophic gastritis and intestinal metaplasia
- Biopsy any suspicious areas

Diagnostic Workup of Gastric Cancer

Dr. Trevor Hamilton, Surgical Oncologist from Vancouver General Hospital, reviewed the diagnostic workup of gastric cancer. He emphasized the importance of the endoscopic assessment, as location is critical to surgical management strategies. In addition, he reviewed specific endoscopic features and tips for the recognition of infiltrative "linitus plastica" type tumours that can sometimes be difficult to diagnose histologically.



Linitus Plastica

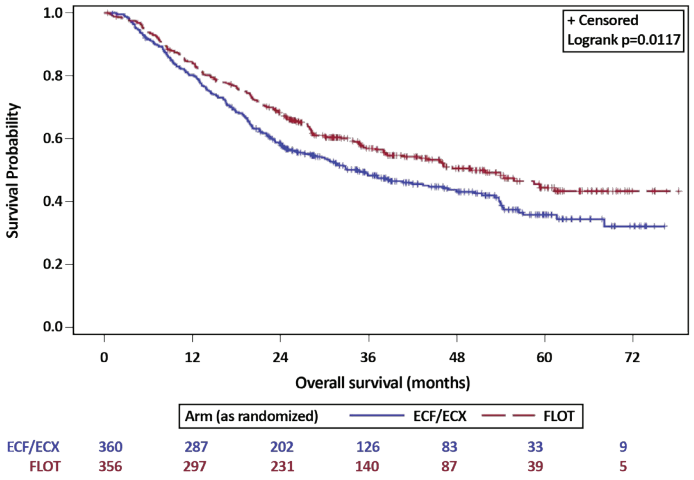
Specific features on cross-sectional imaging that can assist in surgical planning or in diagnosing metastatic disease were

reviewed. CT/PET scans are not routinely recommended in the staging of gastric cancer due to low detection rate in diffuse and mucinous tumours. Endoscopic ultrasound (EUS) was recommended for earlier stage tumours (T1 and T2), indeterminate lymph nodes on imaging, and to assist in expediting multi-modality treatment. Diagnostic laparoscopy is recommended for ≥T2 and/or node positive gastric cancers prior to initiation of treatment.

Considerations for Neoadjuvant Chemothearpy for Gastric Cancer

Dr. Howard Lim, Medical Oncologist from BC Cancer Vancouver Centre, reviewed the existing evidence for neoadjuvant and peri-operative chemotherapy strategies in gastric cancer. He discussed the current standard for peri-operative chemotherapy (FLOT) in BC for advanced gastric cancer based on a recent randomized clinical trial. The recently published CRITICS trial comparing peri-operative chemotherapy to neoadjuvant chemotherapy with adjuvant chemoradiotherapy showed no improvement in survival.

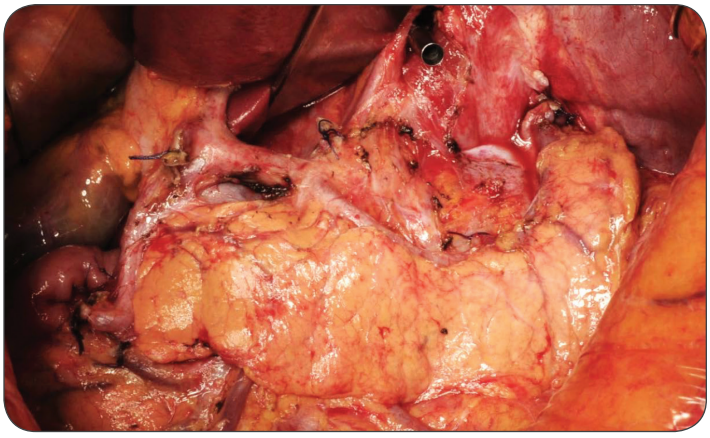
He also reviewed ongoing trials including the TOPGEAR trial and ARTIST 2 trial evaluating different multi-modal management strategies. The CLASSIC trial demonstrated a potential role for adjuvant chemotherapy in advanced gastric cancer treated with D2 resections. Future directions for chemotherapy strategies may be dictated by histologic classification (as intestinal type tumours have higher rates of chemotherapy response) or genetic analysis (microsatellite unstable tumours may see less benefit from traditional chemotherapy).



FLOT Overall Survival

Surgical Approach for Gastric Cancer

Our last talk of the morning was on the Surgical Approach for Gastric Cancer and was delivered by our visiting speaker, Dr. Savtaj Brar. He discussed the variation in outcomes in East vs. West, as well as in different regions in Ontario. The treatment of early gastric cancer (T1N0) may involve endoscopic or surgical resection but does not require chemotherapy or radiotherapy. The treatment of advanced gastric cancer involves staging laparoscopy, multi-modal perioperative therapy, and gastrectomy with D2 lymphadenectomy. Surgeons should strive for R0 resection with generous gross margins (4-6 cm), preoperative chemotherapy, intraoperative frozen section evaluation, and intraoperative endoscopy (laparoscopic cases). Consider roux-en-y reconstruction if <25% of stomach remains.



D2 lymphadenectomy

Circular vs. linear reconstruction techniques after total gastrectomy were reviewed as well as functional outcomes with jejunal pouch. Dr. Brar also reviewed recommendations for extent of lymphadenectomy (D1 vs. D2) and the current literature. A minimum of 16 lymph nodes harvested is recommended for adequate staging and many studies have shown improved survival associated with more extensive nodal harvest.

Laparoscopic gastrectomy techniques were reviewed and recent trials have shown no difference in survival in early stage disease; long-term oncologic outcomes for advanced gastric cancer are still unknown. Robotic gastrectomy has shown no difference in outcomes compared to laparoscopic gastrectomy but has increased cost and longer operative time. Surgery has a limited role in metastatic gastric cancer where systemic therapy or best supportive care is usually recommended. Non-curative gastrectomy has no survival benefit and non-surgical interventions may be beneficial in palliative situations. Peritoneal cytology positive patients that convert to negative cytology after chemotherapy have improved survival. Management of these patients is controversial and is evolving.

Lymph Node Dissection for Melanoma

We were fortunate to have Dr. McKinnon return to the Fall

Update to provide an update on melanoma, which has seen undergoing changes in the staging system, and treatment options.

There has been a change in indications for sentinel lymph node biopsy (SLNB) based upon the AJCC staging system. Although prognosis in melanoma worsens with tumour depth, it is important to know that 70% of new diagnosis are T1 lesions, and 29% of melanoma deaths are in patients with a Breslow depth of less than 1mm. There appears to be some separation in survival between patients with a Breslow thickness of 0.80 mm prompting a division of Stage I melanoma into T1a (<0.80 mm) and T1b (>0.80 mm or ulcerated), having implications for consideration of SLNB where the NCCN guidelines recommend discussing and considering SLNB in those with:

Breslow depth > 0.80 mm or less than 0.80 mm with ulceration

It is important to note that mitotic figures are no longer a component of the AJCC staging system, and in particular are no longer an indication for SLNB.

Discussion then occurred regarding previous melanoma SLNB trials. In the MSLT-I trial while the survival benefit of removal of occult lymph node positive sentinel lymph nodes is up for debate, there are other advantages to SLNB. First, there are now adjuvant immunotherapy trials in melanoma showing a survival benefit in those found with lymph node positive disease. Second, that identification lymph nodal disease with a SLNB will prevent these patients from developing palpable node disease and requiring a full lymphadenectomy, which has a much higher morbidity than SLNB. With reference to MSLT-II, there is no survival benefit to performing the completion lymph node dissection, as only 20% will have residual disease found.

Furthermore, in those that recur, only a small percentage recur in isolation in the lymph nodes, thus suggesting very few patients benefit from this procedure, even with a pathologically positive SLN. He also stressed that patients with extranodal extension of disease in the SLN's were not included in the trials, and this small subset generally should undergo a completion lymph node dissection along with those with clinically positive disease.

Patients with pathologically involved SLN's do require ongoing clinical follow-up for regional recurrence, with clinical and ultrasound surveillance:

- every four months for the first two years
- every six months for years three to five
- annual clinical exam only for years six to ten

Recommendations:

Sentinel Lymph Node Biopsy in melanoma:

- should be discussed in those with T1b lesions
- is prognostic
- stratifies patients for effective adjuvant therapy
- can be performed with minimal morbidity
- usually is therapeutic in the lymph node basin involved

Completion Lymph Node Dissection:

- rarely needed and is no longer mandatory
- clinical followup of nodal basin mandatory in those not having CLND
- therapeutic lymph node dissections should still be done

Targeted Therapy for Melanoma

Next, we had Dr. Corey Metcalfe presenting the topic of immunotherapy, which has changed the treatment landscape for patients with melanoma.

There are two general classes of treatment options currently for melanoma:

1. Checkpoint inhibitors
    a. CTLA-4 Inhibitors (Ipilimimumab)
    b. PD-1 inhibitors (Nivolumab and Pembrolizumab)

2. Targeted therapy (MAPK Pathway)
    a. BRAF (Dabrafenib and Vemurafamib)
    b. MEK (Trametinib)

The Checkpoint inhibitors work by binding to receptors on the T-cell that prevent T cell stimulation, in effect allowing the T cells to respond. A landmark study in 2010 in the NEJM found that Ipilimumab improved survival in patients with metastatic melanoma.

Eventually in 2017, this approach was taken to the adjuvant setting with Checkmate 238 which randomized patients to Nivolumab vs Ipilimumab, finding an improved recurrence-free survival with Nivolumab. They also noted a markedly reduced number of adverse events with Nivolumab as well.

In 2018, Pembrolizumab was compared with placebo in the adjuvant setting in Keynote-54. This revealed approximately a 15% improvement in recurrence free survival at 1 year.

Approximately 50% of melanomas have a BRAF mutation, which is also amendable to a targeted approach. COMBI-AD

was published in 2017 utilizing Dabrafenib and Trametinib vs placebo which showed a 20% decrease in relapse-free survival at three years, showing this to be an effective option as well.

Currently adjuvant Nivolumab and Pembrolizumab are available in BC in the adjuvant setting, but BRAF is not available at this time.

There was discussion during this presentation and in the subsequent case studies of also using immunotherapy in the neoadjuvant setting where Ipi + Nivo has been combined for use in BRAF wild-type patients with remarkable responses found, but with high toxicity. Targeted therapy is also very effective in the neoadjuvant setting for surgically non-respectable disease.

In summary there are a number of exciting new developments that have impacted the surgical management of melanoma. Adjuvant treatment shows promise for patients and has increased the importance of the sentinel lymph node in patients with non-metastatic melanoma. Furthermore, neoadjuvant treatment is also expanding the indications for surgery as well, providing hope to all patients with melanoma.

Desmoid Fibromatosis

In the afternoon, Dr. Andrea MacNeill, Surgical Oncologist at Vancouver General Hospital, reviewed the current treatment strategies for desmoid fibromatosis. She emphasized the shift towards non-operative management in recent years due to significant functional/cosmetic implications with surgery, propensity to recur not clearly related to margin status, young patients with benign diagnosis, and significant rates of spontaneous regression. Prognostic features associated with progression include young age (<37 years), size (>7 cm), and extra-abdominal site. Specific tumour genetic mutations in B-catenin (S45F) may indicate more aggressive biologic behaviour as well as response to imatinib. Dr. MacNeill outlined a specific watch-and-wait strategy based on progression and symptoms. Medical therapies include hormonal treatments, NSAIDs, traditional chemotherapy, and targeted therapy. A recent randomized control trial demonstrated a significantly improved progression-free survival in desmoid fibromatosis treated with sorafenib vs. placebo. Radiation therapy can be considered for borderline/unresectable disease that is symptomatic and/or progression. Other local therapies including cryotherapy are showing some promising results.

Watchful waiting strategy:

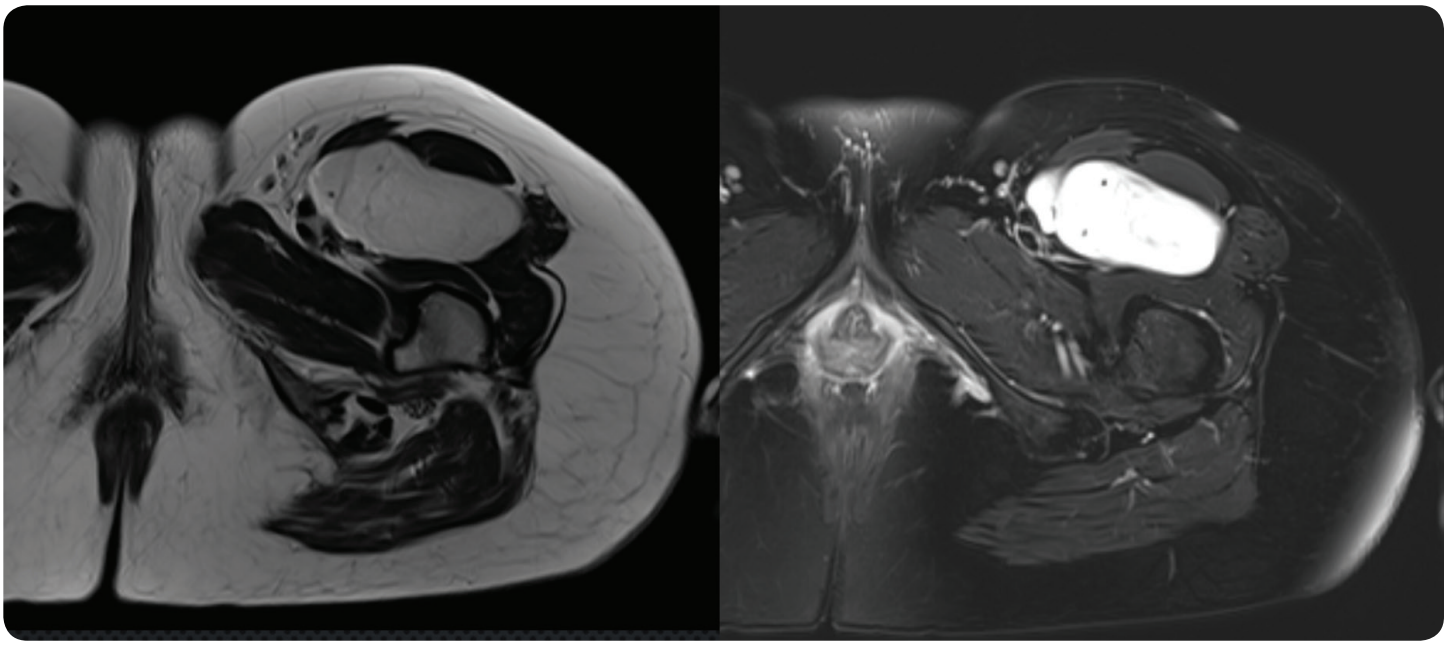
- MRI q3mo x 1 yr, then q6mo until 5 yr, annually thereafter
- Dimensional changes reported according to RECIST criteria
- MRI T2 signal intensity may be better reflection of biologic behaviour
- Progression defined as increase on 3 successive scans, unless urgent intervention required
- Assess symptoms/functional limitations at each time point
- Initiate treatment on clear progression or disability

Management of Extremity Lipomatous Tumours

For our final talk of the day, Dr. Paul Clarkson, Orthopedic Oncology Surgeon at Vancouver General Hospital, reviewed the management of extremity lipomatous tumours. He outlined the features and typical presentations of a number of different benign lipomatous tumours. He reviewed the different types of liposarcoma with typical presentations and radiologic features.

Most superficial lipomatous tumours are benign. Deep tumours are more likely to be a sarcoma if they are >5 cm, inter-muscular, growth over last 12-24 months, and do not have typical fat signal on all MRI sequences. Consider simple excision for small (<5 cm) superficial lesions; rapidly growing/fungating lesions need a biopsy; lesions >8 cm should have an MRI. Deep, small, asymptomatic, intra-muscular lesions can likely be observed with serial imaging.

FROM LEFT TO RIGHT: DR. TREVOR HAMILTON, DR. SAVTAJ BRAR, DR. GREG MCKINNON & DR. CHRIS BALISKI



LIPOMATOUS TUMOUR

Flat Epithelial Atypia Identified on Core Needle Biopsy Does Not Require Excision

DR. CLAIRE LIU, BC CANCER SURGERY NETWORK 2019 TRAVEL AWARD RECIPIENT

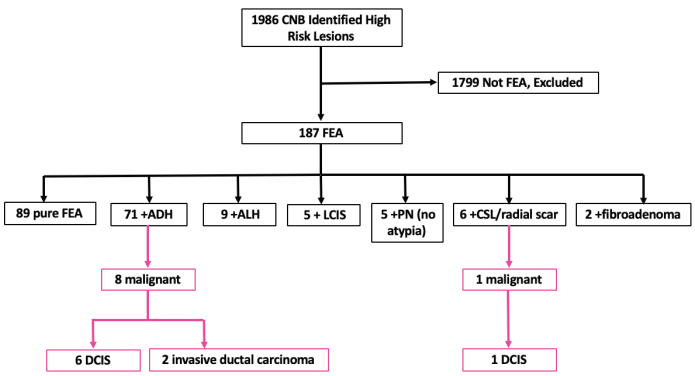
DR. CLAIRE LIU

The management of Flat Epithelial Atypia (FEA) of the breast identified on core needle biopsy (CNB) has evolved and routine surgical excision of FEA is being questioned. However, it is recognized that CNB may undersample an area of abnormality and miss an underlying malignancy. The purpose of this study was to evaluate the upstage rates of CNB diagnosed FEA from diagnostic centres across Metro Vancouver, to identify factors predictive of malignancy, and to identify a group of patients at low risk of malignancy.

Patients having excision of FEA at Mount St. Joseph Hospital between 2013 and 2017 were identified from a prospectively maintained database. The primary endpoint was the frequency at which malignancy was identified after complete surgical excision. The association of clinical, radiologic, and histologic characteristics as risk factors for upstaging to cancer were also evaluated.

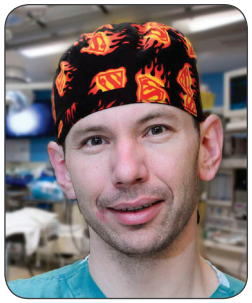
We found that of the 187 FEA cases, 89 were pure FEA lesions while the remaining had another concurrent high-risk lesion in the biopsy. In total, nine patients were upstaged to malignancy, where eight cases had concurrent Atypical Ductal Hyperplasia (ADH) and one had concurrent complex sclerosing lesion (CSL). This gave an overall upstage rate of 4.8%. It is of note that no cases of pure FEA lesions upstaged, and the presence of ADH and CSL in the CNB were the only factors found to predict upstage to malignancy.

In conclusion, the upstage of pure FEA lesions to malignancy at our centre is 0%. Therefore, we now recommend that pure FEA with radiology and pathology concordance does not require surgical excision and can instead be followed with serial imaging. Additionally, patients with FEA in association with other high-risk lesions, should be managed as per indicated for the other high-risk lesion, as FEA does not confer independent risk of malignancy. Having said this, due to the high upstage rates demonstrated in this study as well as previous studies from our centre, ADH lesions in particular should be excised.



BC Cancer Surgery Network News

Update from Dr. Carl Brown, BC Cancer Surgery Provincial Leader



DR. CARL BROWN

Our BC Cancer Surgery team have been working hard to develop a strategy to support high quality cancer surgery throughout British Columbia. As part of this effort, we have a plan to curate and deliver cancer surgery quality metric feedback to hospitals and clinicians to help identify opportunities for improvement.

On November 23, 2019, over 50 cancer surgeons representing every health region in BC met in Vancouver and contributed their time and expertise to this effort. The day started with an overview of our current understanding of cancer surgery performance across the province, proposed strategies to enhance cancer surgery timeliness/quality and challenges to achieving these goals. Colleen McGahan, BC Cancer Surgery lead data scientist, walked the group through available data sources that might inform cancer surgery quality, as well as limitations inherent to each. Dr. Nick van der Westhuizen shared details regarding the implementation and current status of synoptic pathology reporting in BC, an impressive initiative whereby critical pathology elements informing cancer surgery quality are being collected and will be reported to clinicians.

Once the surgeons in attendance were apprised of these data sources, they met with the members of their respective Surgical Tumour Groups (representing Neurology, ENT, Thyroid, Breast, Thoracic, Gastric, Hepatobiliary, Colorectal, Gynecology, Urology and Sarcoma) to identify and prioritize possible quality metrics for tumours managed by surgery. The conversations within each group were impressive high level discussions about best patient care focused on current established standards. After lively discussion, each group presented their ideal quality metrics to the entire group for feedback.

Beyond the impressive work accomplished during the day to move us a step closer to cancer surgery quality metrics, there was a real sense of camaraderie developed through the sharing of expertise and experiences by the surgeons. We hope that the success of this event will lead to an annual meeting of cancer surgeons, with expanded opportunities to attend and contribute in the future.

DR. BROWN WITH THE 12 SURGICAL TUMOUR GROUP CHAIRS

BC CANCER SURGERY NETWORK NEWSLETTER

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VISIT THE SURGERY NETWORK WEBSITE:
www.bccancer.bc.ca/surgerynetwork

The BC Cancer Surgery Network exists to promote and advance quality cancer surgery throughout the province, enable the integration of quality surgical oncology services into the formal cancer care system, and ensure that patients have the best possible outcomes through consistent access to high quality multidisciplinary care. To enhance appropriate, equitable and timely access to surgical services for cancer patients as close to home as possible, the Network supports communication and sharing of knowledge between subspecialty and community surgeons, their respective hospitals and BC Cancer.