BC Cancer Agency
CARE & RESEARCH
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# BC Surgical Oncology Network

Newsletter
www.bccancer.bc.ca/son
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## *In This Issue...*



## UPDATED SURVEILLANCE GUIDELINES FOR PATIENTS WITH STAGE II & III COLORECTAL CANCER

*By: Lyly H. Lê, MD CM, FRCP(C), Medical Oncologist, BC Cancer Agency-Fraser Valley Centre*

The BCCA GI Tumour Group has recently updated the surveillance guidelines for patients treated curatively with stage II and III colon and rectal cancer. The changes came about as a result of updated guidelines published by the American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO).

The changes reflect the results of three recent meta-analyses that look at the available evidence for the various investigations frequently done in surveillance. There are four major elements of surveillance once patients have completed their adjuvant therapy with their oncologist. They are: History & Physical, Endoscopy, Carcinoembryonic Antigen (CEA) tumour marker, and Diagnostic Imaging.

The following table summarizes the updated guidelines (with changes in bold) and the rationale for the changes:

*References available on request*

| | | |
|---|---|---|
| History & Physical | Every 3 months x 3 years, then **every 6 months for an additional 2 years.** | Meta-analyses suggest more intense surveillance is beneficial. |
| Endoscopy | Colonoscopy – prior to surgery or within the first 12 months post-op and then every 3 – 6 years.<br><br>**Patients with genetic syndromes should follow the American Gastroenterological Association guidelines.**<br><br>Flexible sigmoidoscopy – should be done frequently in patients with rectosigmoid tumours **who have not had radiotherapy**. | Patients with Hereditary Non-Polyposis Colon Cancer and other syndromes benefit from more stringent screening for second primaries and other cancers.<br><br>The previous guidelines specified frequency of flexible sigmoidoscopy in all patients with rectal cancers; however this is not recommended in all guidelines and does not reflect current practice. |
| CEA tumour marker | With every follow up visit in patients who are candidates for resection of solitary metastases. | |
| Imaging | **Liver imaging every 6 months x 3 years then annually x 2 years in patients who are candidates for resection of solitary metastases.**<br><br>**Chest X-ray every 6 – 12 months x 5 years in patients with rectal primaries.** | Recent trials have found that either CT or ultrasound can be effective in the early detection of resectable solitary metastases.<br><br>Patients with rectal cancer are at higher risk of lung metastases. |

Complete guidelines will be posted soon on the BC Cancer Agency Website (www.bccancer.bc.ca) under Cancer Management Guidelines.

# ARE WE PERFORMING TOTAL MESORECTAL EXCISION (TME) IN BC? AN EDITORIAL

By: Terry Phang

Colorectal Surgical Tumour Group Chair

We identified a problem with high local recurrence rates for rectal cancer in BC in a 1996 outcomes review. The recurrence rate for stage 3 rectal cancer in BC was 27%, much higher than the 4.3% local recurrence for stage 3 rectal cancer treated using preoperative radiation and TME in the 2001 Dutch trial [N Engl J Med 2001; 345: 638-646]. As a strategy to decrease local recurrence, we held educational workshops in 2002 and 2003 with aims to:

1. Standardize preoperative imaging and recommendations for preoperative adjuvant radiation for stage 2 and 3 rectal cancer.
2. Standardize rectal cancer surgery as TME, with teaching on the technical details of TME.
3. Standardize pathology reporting of the TME specimen especially regarding reporting of the quality of the TME specimen and assessment of the radial margin.

After the educational workshops we began to collect data on rectal cancer cases in order to provide feedback to surgeons and pathologists regarding their adherence to the recommended rectal cancer management protocols and their resulting outcomes.

In this editorial, I wish to provide feedback on technical aspects of rectal cancer surgery performed in BC in the year after the workshops, October 2003 to September 2004. At this time, we do not have a complete data set from individual surgeons and hospitals. We do have data from 411 rectal cancer cases referred to the BC Cancer Agency (BCCA) for adjuvant therapy. We anticipate that the 411 cases represent the majority of rectal cancer cases in BC during this time period.

From the BCCA charts, only 31% had mention that TME was the procedure used for surgical excision of the rectal cancer. Presumably TME is being performed at a much higher rate and further effort must be made to educate surgeons and pathologists to report on the technique of rectal cancer excision. Further to reporting that TME was the surgical technique, the TME specimen should be assessed for completeness of excision of the mesorectum with grossly clear radial margins as indicated by the intactness of the circumferential mesorectal fascia for the entire length of the specimen.

The grading scale of the quality of the TME specimen is good (complete mesorectal excision with intact mesorectal fascia), fair (complete mesorectal excision with small defects in mesorectal fascia), or poor (incomplete mesorectal excision leaving mesorectal tissue in situ as indicated by large tears in the mesorectal fascia that expose the muscularis of the rectal wall). Surgeons and pathologists should provide a grading of the TME specimen. To facilitate improved TME reporting for surgeons and pathologists, we are working towards a centralized web-based tic-box data entry system for colorectal cancer similar to a system starting up in Alberta

Technical aspects of the quality of TME surgery that directly relate to local recurrence include the quality of the excised mesorectum and whether the radial margin is clear. In the 31% of cases where TME was reported, the TME specimen quality was graded as complete in 88% of cases. In comparison, the Dutch trial reported an incomplete TME rate of 24%. Assessment of the radial margin was reported in 98% of the 411 cases, which is much improved over the 50% reporting rate in 1996. The overall radial margin positive rate for all cases was 14%. In comparison, the Dutch trial reported an overall 17% positive radial margin rate. So, in this restricted sample of our cases we are reporting a good quality of TME surgery. If our use of preoperative radiation is equivalent to the Dutch trial, then these data hold the promise of a low and much improved local recurrence rate for rectal cancer management in BC similar to the Dutch trial.

However, further assessment on the radial margins shows a worrying 27% positive rate in distal third rectal cancer excisions. This distal dissection is more difficult because there is need to dissect the distal mesorectum free from surrounding urogenital organs, pelvic nerves, and internal iliac blood vessels within the more confined distal pelvic space. **With this worrying high positive radial margin rate for distal third rectal cancer, our improvement strategies include a change in preoperative radiation protocol from short 5-day course to long-course 5-week chemoradiation for this group of patients.**

This change is based on the German trial that compared preoperative and postoperative long-course chemoradiation [N Engl J Med 2004; 351: 1731-1740]. In that trial, there was improved local recurrence and increased sphincter-preserving surgery using preoperative long-course chemoradiation. The prolonged delay to surgical excision in the preoperative long-course chemoradiation protocol (5 weeks of treatment then a further 6 weeks) does not result in progression of disease; instead, this prolonged delay to surgery is required for maximum tumour shrinkage that will facilitate clear radial margins for distal third rectal cancer and increased sphincter-preserving surgery.

A second strategy to improve distal third rectal cancer resection is further review of surgical techniques.

Con't on Pg. 4

# IS METASTATIC COLORECTAL CANCER CURABLE IN 2006?

*Sharlene Gill, MD, MPH, FACP, FRCPC, Assistant Professor of Medicine - UBC Medical Oncologist, BC Cancer Agency, Vancouver, BC, Email: sgill@bccancer.bc.ca*

### Systemic Chemotherapy for Metastatic Colorectal Cancer

The goals of chemotherapy in advanced disease are primarily palliative: to prolong survival and improve quality of life. 5-fluorouracil (5FU) remains the most widely employed agent and the integration of newer agents, particularly irinotecan and oxaliplatin, has been associated with significant advances in both response rates and survival.

5FU is a fluorinated pyrimidine which primarily exerts its activity by inhibition of thymidylate synthase, an enzyme involved in DNA synthesis. When co-administered with leucovorin (LV), 5FU is associated with response rates of 20-25% and a median survival of ~12 months. In two analyses, an infusional schedule was associated with enhanced response rates and decreased toxicity when compared to bolus 5FU.Oral fluoropyrimidines may represent a less cumbersome alternative to continuous infusion 5-FU. Capecitabine is an oral pro-drug currently approved for first-line monotherapy in advanced colorectal cancer.

Irinotecan (Camptosar TM) is an inhibitor of DNA topoisomerase I. As a single agent, it has objective response rates of 25-30% in chemotherapy-naïve patients using a weekly regimen.In the year 2000, irinotecan was approved in combination with 5FU/LV as first-line therapy for advanced colorectal cancer based upon Intergroup #0038. In this trial, 683 patients were randomly assigned to IFL (irinotecan plus bolus 5FU and leucovorin), 5-FU/LV or irinotecan monotherapy. A superior response rate of 39% and median survival of 14.8 mos was observed with IFL.

Oxaliplatin (Eloxatin TM) is a diaminocyclohexane platinum derivative which has limited single-agent activity but showed promise when combined with infusional 5FU (FOLFOX). N9741 was an intergroup trial which included a random-assignment comparison of FOLFOX to IFL FOLFOX was associated with statistically improved time to progression (TTP) (8.7m vs. 6.9m), response rate (RR) (45% vs. 31%) and median survival (19.5m vs. 14.8m). IFL resulted in more diarrhea, vomiting, nausea and febrile neutropenia while patients on FOLFOX4 experienced higher rates of paresthesias.

While IFL is no longer recommended for first-line therapy, the combination of irinotecan with infusional 5FU/LV (FOLFIRI) is a reasonable doublet choice for first-line chemotherapy. In the GERCOR study, 220 patients with metastatic CRC were randomly assigned to a sequence of FOLFIRI followed by FOLFOX at failure, or the reverse. Both strategies (FOLFOX-FOLFIRI or FOLFIRI-FOLFOX) achieved impressive equivalent first-line RRs (54% and 56% respectively) and median survivals (20.6 months and 21.5 months).

Recognizing that exposure to all three active chemotherapies extends survival, the strategy of combining them in a single first-line regimen was tested. In a randomized trial of FOLFOXIRI versus FOLFIRI, the triplet yielded statistically superior RR (60% vs 34%), TTP (9.8 vs 6.9m) and overall survival (22.6m vs 16.7m). Diarrhea, vomiting and neutropenia were more common in the triplet arm.

Targeted therapeutics is an area of active interest. Bevacizumab (Avastin TM) is a humanized monoclonal antibody (mAb) to VEGF-A, thus halting the VEGF signaling pathway. The pivotal trial was a comparison of first-line IFL versus IFL plus bevacizumab. Median survival was increased from 15.6 mos to 20.3 mos ($p<0.001$) with the addition of bevacizumab. Notable toxicity was limited to grade 3 hypertension (10.3% vs. 2.3%), increased risk of arterial thrombo-embolic events, and rare reports of gastrointestinal perforation and wound dehiscence. Bevacizumab in combination with first-line 5FU/LV monotherapy has been evaluated in a combined efficacy analysis of three trials and was also associated with improved survival compared to 5FU/LV alone.

At present, therapy with infusional 5FU and oxaliplatin or irinotecan are appropriate choices in reasonable performance status patients with unresectable metastatic CRC. For less fit patients, first-line monotherapy with capecitabine remains a viable choice. It is further reasonable to combine 5FU-based chemotherapy with bevacizumab in the first-line setting.

### Regional Management of Liver-Limited Metastases

The liver is the dominant site of recurrence. The benefit of hepatic metastatectomy is clear, with a 5-year survival attainable in over 1/3 of resected patients. Typically contraindicated in patients with bilobar involvement or multiple lesions, new operative strategies such as sequential hepatic resections, ex vivo tumor resections and preoperative portal vein embolization procedures to induce hypertrophy of the remnant lobe have further pushed the definition of resectability. In addition, nonsurgical methods of ablation including cryotherapy, ethanol injection or radiofrequency ablation offer an alternative regional therapy for lesions not amenable to surgical resection.

Despite surgical advances, most patients will still not be candidates for resection. A neoadjuvant approach in patients with unresectable disease has the potential to downstage to respectability, and improve disease control and potentially, curability. In N9741, 3.3% of randomized patients subsequently underwent metastatectomy.

Con't on Pg. 4

# NETWORK NEWS

**CME**

Unfortunately, the planned Hepatobiliary Travelling Road Show has temporarily been cancelled. We are attempting to reschedule the Kelowna seminar for this fall and if this is successful, we hope to follow with seminars in Vancouver, Victoria and Surrey.

A breast cancer update will be offered in the fall. Seminars in smaller centres are being planned (in conjunction with the Family Practice Oncology Network) as well as a Vancouver based seminar that will be videoconferenced around the province.

**Staff Changes**

Tina Strack has left her position as the SON Network Manager as of May 26th. She is pursuing her dream of living and working in Europe and will be moving to London, England in June. "I have thoroughly enjoyed my time with the SON and working with the BC surgical community. I'd like to thank the surgeons involved in the network for their support, particularly Rona Cheifetz, Noelle Davis and Con Rusnak. I wish the network great success in continuing to improve surgical practice in BC". Yasmin Miller will be taking over Tina's position as of June 26th, 2006.

**Rectal Cancer Project - TME Proctoring Available**

The SON is pleased to announce that funding is available for any surgeon wishing to invite Dr. John MacFarlane to their community for proctoring in TME. Dr. MacFarlane worked with Dr. Bill Heald in Basingstoke, England, the pioneer of TME, and he would be pleased to provide his expertise in this field.

If you are interested in having Dr. MacFarlane visit your community as a proctor, please contact the BC Surgical Oncology Network and we will make arrangements for the visit.

## ARE WE PERFORMING TME IN BC? *Con't from Pg 2*

Given that rectal cancer excision is done by 122 general surgeons in BC (performing from 1 to 34 cases per surgeon per year), surgical technique likely remains variable and can be improved further. We will try to arrange for Bill Heald to visit us to help us review surgical techniques of rectal cancer excision.

In summary, our strategies to improve outcomes from our management of rectal cancer in BC hold the promise of achieving low recurrence rates comparable to the excellent outcomes reported by the Dutch trial.

## IS METASTATIC COLORECTAL CANCER CURABLE IN 2006?

*Con't from Pg 3*

In the Tournigand trial, the resection rates with first-line FOLFOX and FOLFIRI were 13% and 7% respectively. Beyond downstaging, neoadjuvant chemotherapy can also be used as an in vivo test of chemosensitivity to guide post-resection therapy, and may identify those patients for whom surgery would not be appropriate. The potential risks of neoadjuvant chemotherapy may include chemotherapy-induced steatosis, hepatitis, vascular disease, impaired wound healing, myelosuppression and impaired hepatic regeneration.

**Conclusion**

Significant improvements in survival have been achieved in the management of metastatic CRC. The ideal strategy for using available therapies and achieving maximal clinical benefit continues to be defined. Further improvements will continue to be pursued through the trials of multi-modality approaches, pharmacogenomics and the incorporation of novel targeted biologics.

*References available upon request*

# MARK YOUR CALENDARS

## SON Fall Update
## Sentinel Lymph Node Biopsy

Vancouver, BC
November 24th, 2006

Plans are underway for a combined didactic and technical course in issues in SLN Biopsy

**FOR MORE INFORMATION**

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**THE COUNCIL & NETWORK**

The BC Provincial Surgical Oncology Council exists to promote and advance quality cancer surgery throughout the province by establishing an effective Network of all surgical oncology care providers and implementing specific recommendations. The Network will enable quality surgical oncology services to be integrated with the formal cancer care system. Communications to enhance decisionmaking, evidence-based guidelines, a high quality continuing education program, and regionally based research and outcome analyses are the initial priorities.

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