A COMPARATIVE STUDY OF THE ADJUVANT MANAGEMENT OF AND SURVIVAL FROM COLON CANCER IN THE TWO CANADIAN PROVINCES OF NEWFOUNDLAND & LABRADOR AND ONTARIO

DEBRAH WIRTZFELD

A Comparative Study of the Adjuvant Management of and Survival from Colon Cancer in the Two Canadian Provinces of Newfoundland & Labrador and Ontario

Debrah Wirtzfeld MD, FRCSC, FACS

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ABBREVIATIONS

5-FU – 5-fluorouracil
ACS – Acute Coronary Syndrome
ASCO – American Society for Clinical Oncology
AGREE - Appraisal of Guidelines Research and Evaluation
crCIHRt – colorectal Canadian Institutes for Health Research team
CCS – Canadian Cancer Statistics
CIHR – Canadian Institutes for Health Research
CCO – Cancer Care Ontario
CPGs – Clinical Practice Guidelines
CRC – Colorectal Cancer
CPRS - Commune Population Registration System
DSS – Disease Specific Survival
EBI - Evidence-based Implementation
EBM – Evidence-based Medicine
GLIA - Guideline Implementability Appraisal
GIN – Guidelines International Network
HNPCC – Hereditary Nonpolyposis Colorectal Cancer
ICD – International Classification for Disease
IMPACT B2 - International Multicentre Pooled Analysis of B2 Colon Cancer Trial
IRB – Institutional Research Board
LV - Leucovorin
MSI-H – Microsatellite Instability - High
NCI – National Cancer Institute
NCIC – National Cancer Institute of Canada
NIH – National Institutes of Health
NSABP - National Surgical Adjuvant Breast and Bowel Project
NCTRC - Newfoundland Cancer Treatment and Research Center
NFCCR - Newfoundland & Labrador Familial Colorectal Cancer Registry
OCR – Ontario Cancer Registry
OFCCR – Ontario Familial Colorectal Cancer Registry
PCP – Primary Care Physician
QALY – Quality-Adjusted Life-Year
RCT – Randomized Controlled Trial

ABSTRACT

INTRODUCTION: The crCIHRt collaboration between Newfoundland and Ontario (2000-present) is an interdisciplinary study of the determinants of and impact from colorectal cancer (CRC) between these two Canadian provinces. It includes an evaluation of the adjuvant treatment of CRC and overall survival from this common disease. Clinical Practice Guidelines (CPGs) for the adjuvant treatment of surgically curable (Stage I-III) colon cancer have not previously been evaluated in Canada. Canadian Cancer Statistics (CCS) have shown that overall survival from CRC is better in Ontario. The aims of this study were to evaluate whether adjuvant chemotherapy for Stage I-III colon cancer in the two provinces is concordant with accepted CPGs and to contrast overall survival from colon cancer in comparison with data from CCS.

METHODS: In Newfoundland, all incident cases of colon cancer diagnosed between January 1, 1999 and December 31, 2000, ages 20-74 were included. In Ontario, all patients with a high- or intermediate-risk pedigree and a random sample of those with a low-risk pedigree for colon cancer, ages 18-74, diagnosed between January 1, 1999 and June 30, 2000 were offered participation in the study. Data was retrospectively retrieved using a standardized extraction form and quality assurance was undertaken through a random re-extraction by two physician researchers. The charts of all patients with stage II disease were qualitatively assessed to determine what factors were used to recommend chemotherapy to these patients. This was contrasted with CPGs recommending chemotherapy only in stage II patients with 'high-risk' features. An overall survival comparison between the two provinces was contrasted with age-standardized projections

from CCS suggesting that Newfoundland experiences a worse overall survival than Ontario from CRC.

RESULTS: 173/274 (63%) and 364/514 (71%) eligible patients consented in Newfoundland and Ontario, respectively.

No one with stage I colon cancer in either province received adjuvant chemotherapy. 20/55 patients (36%) in Newfoundland and 44/116 evaluable patients (38%) in Ontario received adjuvant therapy for stage II disease. 18/41 patients (44%) in Newfoundland and 30/53 patients (57%) in Ontario with high-risk features received adjuvant treatment, significantly higher than patients without high-risk features. On multivariate analysis, age $\leq$ 50 years was shown to be an independent predictor for the use of chemotherapy in stage II patients. 45/52 patients (87%) in Newfoundland and 108/115 patients (94%) in Ontario with stage III disease received adjuvant chemotherapy.

Kaplan-Meier survival analysis revealed that overall 5-year survival from colon cancer was significantly better in Ontario. Exclusion of patients consented by proxy in Newfoundland negated this survival advantage.

DISCUSSION: Concordance with CPGs for adjuvant chemotherapy in stage II colon cancer was not optimal. This may reflect selection bias of referring surgeons, a paucity of level I evidence and the belief that other factors such as age may play a role in predicting outcome. Ontario showed a significantly better overall survival, however, this advantage was lost when bias introduced through recruitment methods was controlled for. Methods to ensure consistency and appropriate resource allocation in the development, adaptation and implementation of CPGs and the importance of minimizing bias in survival analysis are discussed.

INTRODUCTION

Each year, there are approximately 17,000 patients diagnosed with colorectal cancer (CRC) in Canada.[1] In 2001, there were 6400 deaths from this disease. CRC has the second highest cancer related mortality rate, and is the leading cause of death in the Western world.[2] Although screening has been shown to improve survival,[3,4,5] 50% of patients in North America still present with either stage III or IV disease.[6] Further, the total lifetime cost of treatment for colon cancer alone in Canada for the year 2000 was estimated at $333 million.[7] Most of this cost was comprised of hospital based investigations and treatment that resulted from the late discovery of the disease. These facts point to CRC as a major public health concern in Canada.

In 2000, an interdisciplinary team of investigators from Newfoundland and Ontario were awarded a Canadian Institutes of Health Research (CIHR) grant for the collaborative study of the determinants of and impact from CRC. The overall objectives of the colorectal CIHR team (crCIHRt) were to evaluate and contrast molecular-genetic risk factors, risk modifiers and population health as they pertain to incident cases of CRC diagnosed in the two provinces. Broadly, the aims of the project were to discover novel genetic determinants of CRC by identifying new CRC-causing genes, identify genomic profiles based on common genetic variants that are predictive of CRC risk, explore whether there are inter-provincial differences in risk factors for CRC and in the presentation, treatment and outcome of CRC, develop and evaluate psychometric instruments for monitoring psychosocial and behavioral impacts of genetic testing, assess the efficacy of a risk and health counseling intervention among individuals who have a family history of CRC, evaluate whether patients pursue their risk-appropriate CRC screening, assess the impact

and explore the cost-effectiveness of CRC screening and polyp detection with regard to changes in HNPCC-related cancer risk, identify molecular-genetic markers that are associated with response to therapy and survival, determine the contribution of genetic factors to CRC in older patients (age >75), and develop, evaluate and apply advanced statistical methods for the analysis of complex data relevant to CRC. The breadth of this project necessitated a multidisciplinary focus and included researchers from the fields of clinical epidemiology, statistics, internal medicine, genetics, pathology, nursing, surgical oncology and colorectal surgery amongst others.

In most cases, CRC develops from adenomatous polyps.[8] There is a continuum of change in the mucosa of the colon with progression from dysplasia to in-situ carcinoma and eventually invasive cancer. The progression is thought to take approximately 5 years, although the time course may be contracted in select cases such as those who are felt to clinically or genetically represent individuals from hereditary non-polyposis colorectal carcinoma (HNPCC) kindreds.[9] In order to improve overall survival rates, the disease needs to be detected at an early stage where intervention can impact favorably on long term outcome. Discovery of an abnormality early in the disease continuum, preferably at the stage of an adenomatous polyp or earlier, would be optimal. Population based screening tests aimed at the discovery of polyps have been evaluated and have been shown to decrease cancer rates and improve survival from CRC.[3,4,5] However, once invasive malignancy has been diagnosed, survival rates can be improved only through the use of surgery and other effective adjuvant therapies.

Strictly speaking, adjuvant therapy refers to the administration of a treatment following curative resection of all gross loco-regional disease.[10] In colon cancer (rectal cancer

excluded) adjuvant therapy could be considered for patients with loco-regional disease (Stage I-III) following curative resection of the primary tumor. Level I evidence from more than one randomized controlled trial supports the use of chemotherapy in stage III disease (node positive, no metastatic disease), but not in stage I disease (early cancer localized to the wall of the colon, node negative).[11] Adjuvant chemotherapy is controversial for stage II disease (tumor nearly or completely through the wall of the colon, node negative). As medical knowledge is vast and expanding rapidly, this type of information is often made available through the use of clinical practice guidelines (CPGs) formulated according to the tenets of evidence-based medicine.

Evidence-based Medicine (EBM)

The term 'evidence-based medicine' was coined in 1992 by a working group chaired by Gordon Guyatt at McMaster University.[12] It refers to the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. It integrates aspects of the best research evidence, clinical expertise and patient values. New evidence replaces accepted practice with new diagnostic and therapeutic advances that are more powerful, acceptable and safer. It entails the identification of unique aspects of each clinical encounter, including potential individual risks and benefits, within a background of patient concerns and preferences. It emphasizes that intuition and unsystematic clinical experiences are not sufficient for well informed decision making.

EBM encompasses two fundamental principles.[13] First, evidence alone is never sufficient to make a clinical decision. Risks, benefits, inconvenience, cost, alternate strategies and patient/physician values must always be taken into consideration and are extremely difficult to account for within the realm of EBM. Second, EBM provides a hierarchy of

evidence to aid in clinical decision making. Level I evidence, evidence obtained from the results of more than one well-designed, randomized controlled trial (RCT), provides the highest level of support. Less compelling evidence would be offered from the results of a single RCT (level II), followed by cohort studies (level III), case series (level IV) and expert opinion (level V) evidence. Any relationship, then, between two events could suggest potential 'evidence'. Physicians should be made aware of and attempt to apply the highest available evidence, preferably level I. However, evidence needs to be applied within the constraints of local beliefs, political environments and resource limitations. Level I evidence that people should be screened for a certain disease is not feasible if physicians do not believe in the test and resources would be lost from another area deemed to be more important.

The need for the rapid dissemination of evidence-based medicine has arisen from our constant need for valid, reliable information regarding diagnosis, treatment, prevention and prognosis coupled with our inability to afford endless time per patient in the pursuit of tracking down and assimilating the best current evidence. The advent of resources committed to systematic review and valid concise summaries (eg. the Cochrane Collaboration), the creation of evidence-based journals and the ability to access this information quickly from almost anywhere have aided in the ability of the clinical practitioner to effectively apply the tenets of lifelong learning to everyday practice.

Advent of CPGs in Medicine

Sackett has defined clinical practice guidelines as 'user-friendly statements that bring together the best external evidence and other knowledge necessary for decision-making about a specific health problem'.[14] They have three defining properties: they define

practice questions and explicitly identify all their decision options and outcomes, they explicitly identify, appraise and summarize, in ways most relevant to decision-makers, the best evidence about prevention, diagnosis, prognosis, therapy, harm and cost-effectiveness, and they explicitly identify the decision points at which the valid evidence needs to be integrated with individual clinical experience in deciding on a course of action. The clinician is not told what decision to make, but is given a range of potential decisions. Using the best evidence combined with clinical judgment and patients' values and expectations, the clinician will arrive at their own decision in the best interest of the individual patient. As such, the development and implementation of guidelines is a complex and fluid process, less concerned with the results of level I evidence and systematic reviews which are evidence-driven, but more concerned with the patient as they exist within their current social, economic and political context. Guidelines are 'necessity-driven'[14] ***and tempered by current resources and social structure.*** Although they may incorporate aspects of systematic reviews, the best evidence may not be derived from well developed phase III randomized controlled trials with an appropriate control group. Thus, guidelines should provide information concerning highest levels of evidence for each recommendation set forth.

The development, application and evaluation of clinical practice guidelines necessitate the practice of evidence-based medicine. A physician must ask three questions before adopting a specific clinical practice guideline into their practice. The physician must ask whether the guidelines are valid for the patient population served, whether the guideline is useful and whether the guideline can be applied in their own practice.

Is a guideline valid?

The establishment of a valid guideline entails an exhaustive, non-biased review of the current literature. Each recommendation should be provided with a level of evidence and citation such that the original evidence upon which the recommendation is made can be readily accessed. Thus, the development is best carried out by a large collaboration of investigators encompassing a broad range of expertise in the area of interest. The investigators must be committed to the development of successive updates as new evidence becomes available.

Is this guideline applicable to my patients within my practice or community?

The applicability of a guideline will be determined mostly be local factors. The ability to determine whether a guideline is applicable within a certain community will rest on the strength of the recommendations. Good guidelines will clearly separate the evidence and what might be expected in the typical patient from recommendations as to how the guidelines should best be carried out. If a strong set of recommendations exist, then a number of questions must be answered before applying a particular guideline to a community or group of patients.

1) Is there a significant burden of illness within the community?

If the target illness (i.e. gastric adenocarcinoma) is infrequent, then the pre-test probability or expected event rate may be too low to warrant consideration of the guideline.

2) Are the beliefs of patients or others in the community regarding the value of the intervention or consequences consistent with appropriate implementation of the guideline?

If there is a belief that screening for colorectal cancer does not make a difference or that an intervention to prevent cancer is not a good use of resources (even in a high-risk community), then a guideline recommending intense population screening may not be

useful.

3) Is the cost of implementing the guideline too high in terms of other community resources?

A guideline that would decrease the waiting list time for surgery, but significantly increase the wait time for mental health assessment may not be acceptable.

4) Are the barriers to implementation (i.e. geographic, organizational, legal, and behavioral) too large to overcome?

If colonoscopy as a screening test for colorectal cancer would require the addition of 20 experienced endoscopists doing nothing but colonoscopies, and there is no more endoscopy time currently available, the guideline would be difficult to implement without consideration of organizational issues. This is one of the most important considerations in the use of any guideline.

Decision Analysis

Decision analysis involves an integration of the hierarchy of best available evidence with values or preferences. It allows for elements of uncertainty, and it allows clinicians to compare and contrast the expected consequences of pursuing different strategies. As such, elements are open for debate and modification.

These aids are often outlined graphically with the decision to be addressed on the far left, strategies in the centre and potential outcomes to the right. Extension of this type of analysis to issues of cost leads to an economic analysis that can aid in the interpretation of health care and resource utilization.

Development of Quality CPGs

Guideline Quality Appraisal

With the myriad of guidelines available for patient care, it is imperative that a means of applying scientific rigour to the guidelines themselves be available. In fact, once it has been determined that the need exists for a new, updated or modified set of CPGs, guideline developers should be aware of the end points that define quality before they set out to establish valid and useful guidelines. Health care providers and policy makers should know the quality of any set of guidelines before considering them for implementation in their practice environment.

There have been many tools developed that seek to establish the quality of clinical practice guidelines.[15,16,17] The Guidelines International Network and the World Health Organization[18] have endorsed the AGREE (Appraisal of Guidelines Research and Evaluation) instrument (www.agreecollaboration.org).[19,20,21] The instrument can be used by guideline developers, health care providers, policy makers and educators to ensure that the content of guidelines is valid and reliable. There are 23 elements in 6 domains (scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability and editorial independence) that can be assessed by at least 2 independent appraisers (4 recommended). An overall recommendation is then made as to whether the appraiser would recommend or not recommend the guidelines for use in everyday clinical practice.

The AGREE instrument has been tested in 11 different countries in the first phase of its international project.[20,21] Following modification; it was evaluated/validated in 18 countries with reliable results.

Adaptation and Implementation of CPGs: Knowledge Translation

Adaptation

Adaptation of guidelines involves a systematic approach to the endorsement and/or modification of a guideline produced in a particular organization or cultural context for use in another.[22] It is a process that can be used for customizing current guidelines rather than relying on the sequential development/publication of de novo guidelines for each region and/or locality (www.adapte.org).[23] The rationale, well stated at the website, basically states that with limited time and resources and with the large input required for the development and maintenance of high quality guidelines, a means to adapt valid and well written guidelines to local circumstances is required. The aims of the ADAPTE consortium are to reduce the resources that go into the development of duplicate guidelines and perpetuate the use of well designed and validated guidelines that currently exist in many areas of medicine. The process involves a period of initiation to the aims of the process, a multidisciplinary review of current guidelines that exist for an important medical concern within the local community (given a prevalent condition, concern about current treatment and the overall perception that change is possible through guideline recommendations), acceptance in part or in whole of current guideline recommendations and development of an adapted guideline. Stakeholders are sought for input prior to implementation. It recognizes that guideline adaptation is part of a larger process that entails knowledge of the development of valid, high quality guidelines (ie. use of the AGREE instrument) and appropriate implementation strategies (see below). As such, it is part of the Guidelines International Network (GIN) that aims to ensure validity and reproducibility in all aspects of guideline use. The site includes a comprehensive manual and resource toolkit that can be obtained with minimal feedback to the ADAPTE investigators.

Dissemination and Implementation

Dissemination has been defined as 'an educational intervention that aims at influencing targeted clinicians attitudes to, and awareness, knowledge and understanding of, a set of guidelines'.[24,25,26] Dissemination can be achieved through publications, postal distribution to the target audience, CME, professional development programs, symposia and lay/medial media.[27] Publication alone fails. Implementation refers to 'turning changes in attitude and knowledge into changes in medical practice' or 'the concrete activities an interventions undertaken to turn policies into desired results'.[28]

Most strategies have been directed at health care professionals rather than the patient, the medical department or health care organizations. Passive implementation strategies are of limited value. More recently, the concept of evidence-based implementation (EBI) strategies has arisen.[29] These strategies involve the development of evidence-based guidelines based on a thorough description of evidence-practice gaps and barriers to change at the level of the patient, health care provider(s) and organization of the teams/departments. Guidelines should be simple and easy to use, based on reputable sources and simplify decision making. They should be based on good quality evidence, compatible with existing values and contain concrete descriptions of desired actions. As part of a whole process of implementation, reminders at both the group and individual level must be readily visible and audit/feedback of involved parties should be easily accessed.

Impediments to the Implementation and Use of Guidelines

It is well known that clinical practice guidelines have little effect on changing physician behavior.[30,31,32,33] An exhaustive search of the literature has classified potential barriers into those involving physician factors (guideline awareness and familiarity, agreement with

guidelines, access to treatment/ability to overcome current practice inertia), patient factors (type of test, patient education) and issues surrounding resource allocation.[33,34] It should be noted that this does not account for patient variables such as comfort with guidelines and belief in recommendations.

Physician Barriers to the Implementation of Guidelines

Physician awareness and familiarity

The European Panel on the Appropriate Gastrointestinal Endoscopy (EPAGE) has evaluated the use of colonoscopy and conformity with guideline recommendations in Spain.[35] 350 sequential patients referred to an open endoscopy unit between May 1 and June 30, 2004 were assessed for an appropriate indication.

Of 350, 38 (11%) were excluded as the indication given was not included in the guidelines. 239/312 (77%) were deemed to have an appropriate indication and 73/312 (23%) an inappropriate indication. Diagnostic yield for those patients with an indication was 42% and without an indication was 21% (p=.001). There was a significant difference between specialties (gastroenterologists were more likely to suggest an appropriate indication) and as a result of patient age (older patients were more likely to have an appropriate indication). Although not directly evaluated in this study, the authors suggest that awareness and familiarity with guidelines was responsible for higher rates of appropriate indications in gastroenterologists. They suggest that the implementation of guidelines for the appropriate use of colonoscopy could improve suitable use of limited resources, decrease waiting times and facilitate access for appropriate indications.

One study that specifically evaluated physician familiarity and implementation of guidelines for CRC screening involved interviewing 50 primary care physicians (1998-

1999) in the Rehovot region of Central Israel and review of 1000 charts of their asymptomatic patients between the ages of 50 and 70.[36] Rehovot is a densely populated area with easy access to medical care through a single centre. Screening guidelines had been widely disseminated and reviewed at several meeting targeting PCPs.

Almost all participants endorsed screening. The appropriate use of FOBT and sigmoidoscopy was 40% and 12%, respectively. Only 4 (8%) were correct in the use of both techniques. Most estimated that >25% of the targeted population had been screened, when only 92/1000 (9.2%) had FOBT and 14/1000 (1.4%) had sigmoidoscopy. There was no instance where a recommendation was made and subsequently declined by the patient. Only 2.6% of all CRC diagnoses were the result of screening programs.

A second study explored the awareness of clinical practice guidelines for CRC screening in Canada.[37] The authors wished to evaluate the effect of a revision in the Canadian Task Force on Preventive Health Care (CTF-PHC) guidelines on screening beliefs and clinical practice patterns of primary care physicians. A quasi-random sample of 160 physicians was undertaken in June-July 2001 and April-July 2002, the latter 9 months after publication of the guidelines. There was a 47% response rate. Recommendation of screening for average risk increased from 43% to 60% ($p=0.02$). 30% stated that the CTF-PHC guidelines were viewed as a source of information regarding CRC screening, and 24% were aware of revisions. Those who did not recommend average risk screening felt that the data were inconclusive and that the guidelines actually do not support screening.

The authors acknowledge that there may be a multitude of factors responsible for the increased recommendation for screening and that the short time period from the publication to survey may not reflect the true impact of the guideline revisions. Similar to the

recommendation for chemotherapy for patients with high-risk stage II colon cancer, perceived inadequate strength of the data upon which guidelines were established may be responsible for low rates of adherence.

These studies elegantly point to the downfall of viewing guideline development as devoid of the responsibility of ensuring a process by which implementation can be assessed. It is certainly not entirely the responsibility of the PCP to make themselves aware of all potential guidelines and to determine for which the practices of evidence-based medicine have been applied. The development, applicability, resource utilization and outcome assessment should be undertaken as an interconnected process that ensures improvements in overall patient health and care.

Agreement with guideline recommendations

Guidelines will need to be considered in the context of the local environment and may require modification and regular updates to reflect local circumstances.[38] In an Italian study exploring the use of upper intestinal endoscopy for dyspeptic symptoms, endoscopy was recommended for patients under the age of 45.[39] It was felt to be an appropriate recommendation for this locale as gastric cancer rates are high and found in a substantial number of people under the age of 45. The same degree of agreement may not hold in another environment where gastric cancer is less common in this age group and the return from endoscopic screening not deemed to be worthwhile.

Access to treatment/ability to overcome practice inertia

Concordance with guidelines has been shown to correlate with specialty interest and access to resources.[40,41] A survey questionnaire of primary care physicians, internists, gastroenterologists and surgeons in Canada showed that specialists with ready access to

colonoscopy (gastroenterologists, surgeons) were more likely to recommend this test as a screening test to their patients. However, all respondents were equally as likely to agree that colonoscopy was the most sensitive and effective screen and the one that they would choose for themselves.

Patient Barriers to the Implementation of Guidelines

Type of test

There is some evidence in colorectal cancer screening that the type of test recommended can impact compliance rates.[42] Using a cluster-randomized two-arm trial, these authors randomly assigned 20 general practitioners with an average of 150 patients between the ages of 50 and 74 to recommending either fecal occult blood testing (1449 patients) or sigmoidoscopy (1538 patients) as an initial screen.

The probability of participation was statistically greater in patients randomized to invitation for FOBT (2.7, 95% CI = 2.0-3.8). 19.1% of the initial participants in the FOBT arm and 10% in the sigmoidoscopy arm failed to complete testing. A statistically higher compliance rate was obtained with FOBT (17.2%, 95% CI = 2.5-25.7) than sigmoidoscopy (7.0%, 95% CI = 5.7-9.0). Multivariate analysis showed that the probability of testing decreased as the distance from the center increased (RR = 0.95 for 1 km increase, 95% CI = 0.91-0.99) and that the type of provider impacted probability of testing (RR = 0.60, 95% CI = 0.40-0.80). This again points to the influence of access and potential provider approach and/or bias on completion rates.

Patient education

In order to be appropriately counseled on guidelines and recommendations, members of the population must possess a certain level of education about a particular topic and have

access to appropriate resources. For example, the population must be made aware that even if they have no family history of CRC and no gastrointestinal symptoms (assuming they know the specific symptoms to look for), diagnostic evaluations that may aid in the early detection of disease are available.

The Precaution Adoption Process Model (PAPM) suggests the steps that a person must proceed though prior to the adoption of a health-related behaviour.[43,44] These include 1) unaware (no knowledge of a specific problem); 2) unengaged (knowledge, but not as to how it might apply to their specific circumstance); 3) deciding (aware that the problem may personally affect them, but undecided on what their reaction to this might be; 4) decision (yes or no); and, action.

Thus, the first step in the education of the public is to make them aware that a specific problem exists. For example, may people believe that they need not worry about screening for colorectal cancer as they do not have any gastrointestinal symptoms. The public is not aware of a basic tenet of a screening test – that individuals be identified in a pre-symptomatic phase at a point where a known and acceptable intervention will prolong life or prevent morbidity. This model further surmises that once the public is made aware of this fact, the individual still needs to recognize that this particular recommendation applies to them personally. A person might accept that screening is warranted in the asymptomatic phase, but feel that they lead a 'healthy' lifestyle and are therefore not at risk. It must be understood by the public that the current state of medical knowledge can only explain about 10-15% of colorectal cancer under the heading of 'genetic/familial'.[8] The remaining 85-90% can not be explained definitively by any combination of exposure/environment factors. Thus, as a society we have chosen the age of 50 as the point at which average risk

individuals should begin screening for this disease.

Presuming that we can target those over the age of 50, it is up to the individual to decide what their course of action might be. At this point in the process, it is imperative that the system have reasonable options available to the individual who presents for population based screening. There must be an easy and affordable avenue available for those who wish to take action. Unfortunately, neither Canada nor the United States is at a point where screening had progressed much beyond individual request/demand. Education and resource allocation have lagged behind recommendations/guidelines that have been put forth by subspecialty societies.

Resource Barriers to the Implementation of Guidelines

Resource allocation is not often overtly considered in the formulation and dissemination of clinical practice guidelines.[45] The American College of Chest Physicians (ACCP) established a task force that met in March 2005 to consider how resource allocation should be incorporated into the development and structure of guidelines, including consideration of downstream differences in allocation. Omission of resource related issues is not feasible in today's market. Policy makers and governments will unlikely be swayed unless strong consideration is given to cost, including alternative options where the resources might be more adequately distributed.

The task force made several recommendations regarding incorporation of resource issues. Guideline developers should consider the inclusion of a health economist. This does not mean that each guideline needs an exhaustive delineation of time and expense, rather that a structured approach be followed. A formal economic analysis might include consideration of health care alternatives and future cost savings in terms of the magnitude of cost

differential.

Developers should also define the target audience. If the guidelines are felt to be widely applicable, then consideration should be given to a description of patient demographics and how these might be expected to impact on compliance. One component of this would be determination of the cost of an intervention per quality-adjusted life-year (QALY) gained. One model suggests that interventions in excess of 100 000 per QALY are unaffordable, while interventions costing < 20 000 per QALY are cost effective.[46] In a less affluent section of North America or in poor countries, 20 000 per QALY may not be feasible. Finally, developers need to consider how the target audience would be expected to respond to a particular recommendation. For example, two communities matched for socio-economic status might be willing to 'pay' more or less for a particular health care benefit when competing forces are considered.

Identification of Obstacles to Guideline Implementation

Although tremendous efforts and resources have been expended in the development and implementation of clinical practice guidelines, there has not been great success noted in terms of documented improvements in health care. In fact, substantial waste of time, resources and manpower have been noted.[47,48,49] It is important to note the factors *intrinsic* to the guideline that may result in failure, and to remedy these during development and early implementation.

The implementability of a set of guidelines refers to the 'set of characteristics that predict the relative ease of implementation of guideline recommendations'.[50,51] Toward this end, the Guideline Implementability Appraisal (GLIA) tool has been developed and validated to assist in the dissemination of clear, concise, valid guidelines.[51]

The authors began by defining the attributes of a guideline that might be expected to impact on implementability. From this, 10 dimensions were developed consisting of 31 questions. The GLIA tool is available for download at http://ycmi.med.yale.edu/GLIA.[52] The initial dimension (Global) contains 7 questions and refers to the instrument as a whole. Each of the remaining 9 dimensions (Decidability, Executability, Effect On Process Of Care, Presentation & Formatting, Measurable Outcomes, Apparent Validity, Novelty/Innovation, Flexibility and Computability) can be applied to each individual guideline recommendation. Each is given a rating of 'Yes – the recommendation meets this criterion fully', ' No – the recommendation does not meet this criterion', '? – rater is unable to address this question because of insufficient knowledge or expertise in this area', or 'NA – criterion is not applicable to this recommendation'. Outside help should be obtained to resolve items marked by '?'. When 'No' is recorded, the barrier to implementation is recorded with a brief description. Suggested remedies are also noted.

This tool was validated at the 2002 conference on Guideline Standardization. Good inter-rater concordance was noted, with the observation that the criteria of executability (communicating exactly what to do) and decidability (communicating exactly when to carry out a response) seemed to be ultimately important.

CPGs in Colorectal Cancer

Although there have been numerous CPGs established for the screening,[53,54,55] treatment[11,56] and surveillance[53,57,58] of CRC, there have been limited resources dedicated to evaluation of the successful implementation of such. The translation of guidelines and other scientific evidence into clinical practice is extremely difficult.[59] It is estimated that up to 40% of patients do not receive care that might be compatible with highest level

scientific evidence; whereas 20% of patients may receive care that is otherwise harmful or not necessary. Even with well designed strategies, average changes of only about 10% in terms of guideline adherence have been reported.[30,31,32]

CPGs: Adjuvant Treatment of Stage I-III Colon Cancer

The 1991 National Institutes of Health (NIH) Consensus Conference on the adjuvant treatment for colon and rectal cancer was the first recognized effort to establish guidelines for the standard postoperative treatment of this disease.[11] These guidelines have not been updated by the original authors, although subsequent reports have reinforced the conclusions and suggested a benefit to patients given adjuvant chemotherapy for 'high-risk' Stage II colon cancer.[60,61]

NIH Consensus Conference Recommendations[11]

The treatment of colon cancer was considered separately from that of rectal cancer (defined as distal extent of the tumour within 12 cm of the anal verge). Following review of level I evidence garnered from randomized controlled trials of adjuvant therapy for CRC, the authors of this paper concluded that there was adequate data to support a survival benefit from adjuvant 5-FU based chemotherapy administered following curative resection for Stage III (node positive) colon cancer.

Adjuvant therapy for stage II colon cancer – Systematic Review[60,61]

The National Surgical Adjuvant Breast and Bowel Project (NSABP) performed an analysis of the results of its four published trials on adjuvant chemotherapy: two comparing surgery alone with surgery plus adjuvant 5-FU based chemotherapy and two comparing different chemotherapy regimes.[60] 1565/3820 patients (41%) had stage II disease. Two pooled treatment groups were compared: one comprising the less effective treatment group from

each study and the second comprising the more effective group. There was a 30% relative reduction in risk in the more effective treatment group for the patients with stage II disease. Improvement in mortality was found for all subgroups studied, regardless of presence of adverse prognostic factors. However, the studies evaluated in this systematic review did not have the same treatment and control arms and there was no direct comparison of standard 5-FU/LV to surgery alone in any study.

The International Multicentre Pooled Analysis of B2 Colon Cancer Trial (IMPACT B2) analyzed the results from 5 RCT comparing 1016 patients with stage II disease randomized to 5-FU/LV (507) or observation (509).[61] It did not find a survival benefit in the group that received chemotherapy. With a median follow-up of 5.75 years, there was no difference in overall survival (82% vs 80%; HR = 0.86; 90% CI = 0.68-1.07) or event-free survival (76% vs 73%; HR = 0.83; 90% CI = 0.72-1.07). In the multivariate Cox analysis, age and tumour grade were the only independent predictors of overall and disease-free survival. Prognostic factors such as perforation, bowel obstruction, venous invasion and number of examined nodes were not included in this analysis. A subsequent pooled analysis of 7 RCTs including those from IMPACT B2 showed an improvement in 5-year DFS in 1440 stage II patients (76% vs 72%, p=0.05).[62] However the difference in OS at 5 years was not significant (81% vs 80%, respectively). Significant histological predictors included tumour grade and bowel wall invasion. Other potential high-risk factors were not evaluated in this study.

The consensus statement of the Fourth International Conference on Colorectal Cancer stated that 'the relative effect of chemotherapy is the same in Dukes' C (stage III) and in

Dukes' B (stage II) colon cancer; whereas the absolute survival benefit is smaller in patients with Dukes' B cancer because their risk of death is smaller.[63]

Subsequent to this declaration, the results from the QUASAR study have been published in abstract form.[64] Between June 1994 and December 2003, 3238 patients (91% with stage II disease) were randomized to either 5-FU based adjuvant chemotherapy or observation. At a median follow-up of 4.2 years, the 5-year survival rate was significantly better in those treated with adjuvant chemotherapy (80.3% vs 77.4%, HR = 0.83, 95% CI = 0.71-0.97) as was the 5-year disease-free recurrence rate (22.3% vs 26.2%, HR = 0.78, 95% CI = 0.67-0.91). In evaluation of stage II patients only, there was a significant absolute reduction in the number of deaths with adjuvant chemotherapy, 224 vs. 262, p = 0.04. Final publication, including analysis of prognostic factors, is pending.

It has been estimated that a randomized clinical trial of at least 4700 patients with stage II disease would be required in order to detect a 4% survival benefit at 5-years with an estimated baseline 5-year survival of 75%.[65] There is no study that approaches these numbers, and it is unlikely that there even will be.

CCO and ASCO recommendations for high-risk stage II colon cancer[66,67]

Given the conflicting results of the systematic reviews, Cancer Care Ontario (CCO) and the American Society of Clinical Oncology (ASCO) have established expert panels that have performed their own meta-analyses.[66,67] The results from both reviews have not shown a statistically significant benefit in terms of overall survival. However, certain patient and/or tumour characteristics in patients with stage II disease have been shown to be associated with a decrease in overall survival approximating survival of patients with stage III disease. For this reason, both CCO and ASCO have recommended that patients who possess these

'high-risk' characteristics be considered for administration of adjuvant 5-FU based chemotherapy.

CCO guidelines[66]

This collaborative review assessed 37 RCTs and 11 meta-analyses (n = 20,317). In these studies the proportion of patients with stage II disease (either colon or rectal cancer) ranged from 23 to 100%. The evidence for stage II disease was derived mostly from the results of a meta-analysis including 1016 patients contrasting 5-FU/folinic acid vs observation alone. There was no improvement in disease-free or overall survival in patients who received adjuvant chemotherapy.

Further meta-analysis was performed by the authors in 4187 patients (18 trials) that included a surgery alone arm. The reduction in relative risk of mortality was 0.87 (CI = 0.75-1.01, p=0.07). However, adjuvant therapies were not consistent across included trials. The authors concluded that there is evidence to suggest improvements in disease-free survival with the use of adjuvant chemotherapy in patients with stage II disease, though not necessarily overall survival. They suggest that patients should be made aware of the evidence, and where appropriate offered participation in clinical trials.

ASCO guidelines[67]

An expert panel was convened to address the issue of adjuvant chemotherapy for stage II colon cancer following curative resection as SEER-Medicare data suggested that a significant number of these patients were receiving chemotherapy without the benefit of conclusive data suggesting a benefit. The guidelines set forth sought to address whether all patients with stage II disease should be offered adjuvant therapy, whether identifiable high-risk factors should guide chemotherapy and what factors clinicians felt were important in

offering adjuvant chemotherapy to patients with stage II disease following curative resection. The authors used data largely derived from the CCO consensus panel.

Although systematic review did not support the routine use of adjuvant chemotherapy in stage II colon cancer following curative resection, the authors of the consensus panel stated that it should be considered in patients with 'poor prognostic factors' (clinical presentation with malignant bowel obstruction or perforation at the tumor site, poor differentiation, presence of lymphatic/vascular and/or perineural invasion and tumor aneuploidy). Subgroup analysis has shown that patients with these factors tend to have a survival in the range of patients with stage III disease. Therefore, it was recommended that adjuvant chemotherapy be considered.

While molecular features such as tumor microsatellite instability (MSI) status may be important,[68,69,70,71] these have not been emphasized in currently accepted guidelines. Although the approach to the treatment of stage II colon cancer is evolving, adjuvant treatment is currently recommended for high-risk stage II patients (clinical obstruction or tumor perforation at presentation, T4 lesion, poor differentiation, lymphatic invasion, perineural invasion, vascular invasion or mucin production)[66,67] and all stage III patients following curative resection in an attempt to improve overall survival from this disease.

Overall Survival: Stage I-III Colon Cancer

Canadian Cancer Statistics (CCS) are developed by a Steering Committee of the National Cancer Institute of Canada (NCIC) and the Canadian Cancer Society (CCS).[72-77] The Committee includes representatives of the NCIC, the CCS, Health Canada, Statistics Canada, the Canadian Council of Cancer Registries and university-based/(provincial/territorial) cancer agency-based cancer researchers. The provincial and

territorial cancer registries are responsible for the review and supply of incidence data which form the basis of statistics published by the annual report. Statistics have been published every year since 1987. Information on the respective cancer registries can be accessed for Newfoundland & Labrador at www.nctrf.nf.ca[78] and Ontario at www.cancercare.on.ca.[79]

Data reported by CCS from 2002-2007,[72-77] using actual reported deaths from CRC and estimated five-year age adjusted relative survival from CRC, showed that overall survival was better in Ontario as contrasted with Newfoundland (data for colon cancer alone not available). For example, estimated age-standardized mortality rates for CRC in 2002 were reported as 25/100,000 and 21/100,000 for males in Newfoundland and Ontario, respectively.[72] The National estimate was 22/100,000 for this time period. The estimated age-standardized mortality rates for CRC for 2002 in women were reported as 14/100,000 and 12/100,000 in Newfoundland and Ontario, respectively. The National estimate was 14/100,000 for this same time period. This same trend was noted for each year between 2002 and 2007.[72-77]

The collaborative nature of the crCIHRt allows for a comparative evaluation of potential differences in overall survival between Newfoundland and Ontario for 1999 and 2000 using a population-based approach. Further, this comparison can be contrasted with survival data reported by CCS that would suggest that survival from CRC in Newfoundland is worse than that reported in Ontario.

THESIS OBJECTIVES AND AIMS

The objectives of this thesis were to:

1) Outline the NIH recommendations for adjuvant chemotherapy in colon cancer and the strength of evidence in support of adjuvant therapy for stage II disease.
2) Determine concordance rates with clinical practice guidelines (CPGs) recommending adjuvant chemotherapy for high-risk stage II colon cancer patients in Newfoundland and Ontario. **Paper accepted for publication in the Canadian Journal of Surgery.**
3) Explore factors involved in the development, adaptation and implementation of CPGs.
4) Outline sources of bias in the survival analysis for colon cancer in the crCIHRt study: Newfoundland vs. Ontario.
5) Compare and contrast the objectives of and statistical approaches to survival analysis: crCIHRt vs. Canadian Cancer Statistics (CCS).

The specific aims of this thesis were to:

1) Evaluate whether the administration of adjuvant chemotherapy for Stage I-III colon (excluding rectal) cancer in the provinces of Newfoundland and Ontario for the time period 1999-2000 was concordant with accepted CPGs
2) Compare and contrast overall survival from colon (not rectal) cancer in the crCIHRt study to data from CCS for the time period 1999-2000.

METHODS

Study approvals

All study procedures were approved by local IRBs and the advisory committee of the NIH Cooperative Family Registries for Colorectal Cancer Studies.

Recruitment

In Newfoundland, all incident cases of colon cancer in patients aged 20-74 diagnosed between January 1, 1999 and December 31, 2000 were offered participation in the study. The Newfoundland & Labrador Familial Colorectal Cancer Registry (NFCCR) is a true population based registry that collected information on everyone diagnosed with CRC between the ages of 20 and 74 years from 1999 to 2003. Each person with an ICD10 code to indicate colon (153) or rectal (154) cancer was identified by the Newfoundland Cancer Treatment and Research Center (NCTRC). Pathology reports were retrieved and reviewed by the team pathologist to ensure a diagnosis of adenocarcinoma, signet ring carcinoma or pseudomyxoma accompanied by adenocarcinoma. In this study, everyone diagnosed with colon cancer (153) had a letter forwarded to their attending physician as first contact describing the study as well as details of whom to contact should they be interested in participating. If an individual was deceased or at their preference, the next of kin was identified by several methods including family physicians, nursing clinics, etc. Each next of kin was then contacted in the same manner and asked to consent to a review of their affected family member's medical records (proxy consent). This was undertaken as a means of improving recruitment into the study as data collection was initiated somewhat later in Newfoundland.

In Ontario, patients enrolled in the Ontario Familial Colorectal Cancer Registry (OFCCR), an NCI-funded consortium for the study of the genetic epidemiology of colorectal cancer, were asked to participate. The OFCCR is 1 of 6 international sites participating in the Cooperative Familial Registry for Colorectal Studies established by the NCI. The population-based Ontario Cancer Registry (OCR) was used to identify all cases of invasive colon cancer diagnosed among residents of Ontario in patients aged 18-74 between January 1, 1999 and June 30, 2000. Following completion of a family history questionnaire, all patients with a high- or intermediate-risk pedigree and a 25% random sample of patients with a low-risk pedigree were recruited into the study. Patients consented to the extraction of their medical records for information pertaining to the diagnosis and treatment of their disease. Proxy consents were not sought in Ontario.

Chart extraction and data collection

Following informed consent, medical records were retrospectively reviewed and abstracted by trained Health Record Technicians or Research Nurses. The standardized abstraction form (Appendix B) included information on patient demographics, diagnosis (symptoms, location of diagnosis, site of cancer and date of diagnosis), surgical intervention (date, type of surgery, operative findings, hospital/surgeon), pathology (stage, #lymph nodes, tumor differentiation/cell type, margins, perineural/lymphovascular invasion), adjuvant treatment (start date, type of chemotherapy), follow-up (metachronous primary, first documented locoregional and/or distant recurrence and treatment), time to last follow-up and/or death and cause of death.

In order to verify the accuracy of data, approximately one half of the charts were randomly reviewed by two physician researchers. All records for patients with stage III disease who

did not receive adjuvant chemotherapy (n=14) were reviewed. The charts of patients with stage II disease were assessed to determine the presence/absence of high-risk features (clinical obstruction or tumor perforation at presentation, T4 lesion, poor differentiation, lymphatic invasion, perineural invasion, vascular invasion or mucin production) and whether these were used to guide chemotherapy recommendations.

Statistical analysis

Descriptive statistics were used where appropriate. χ^2 analysis was used to test for significant differences in categorical variables, including stage. Multivariate logistic regression was performed to identify independent predictors for receipt of chemotherapy in stage II patients. Kaplan-Meier survival analysis was used to contrast overall survival, in months, as a function of province of diagnosis. Cox Regression analysis was used to evaluate the proportionate variance attributable to defined factors in the assessment of overall survival. Results from the crCIHRt survival analysis were contrasted with information available for the same time period from CCS.

RESULTS

Recruitment and Demographics

In Newfoundland, there were 274 incident cases of colon cancer diagnosed between January 1, 1999 and December 31, 2000. 173/274 patients (63%) consented to participate in the study (Table 1). Of these, 117/173 patients (68%) were consented directly and 56/173 (32%) were consented by proxy, either at the patient's request or because the patient was deceased.

The Ontario Cancer Registry (OCR) recorded 2464 incident cases of colon cancer diagnosed in the province between January 1, 1999 and June 30, 2000. Of these, 1031 (42%) completed a family history questionnaire and were recruited into the Ontario Familial Colorectal Cancer Registry (OFCCR). 979/1031 (95%) completed the questionnaire. All patients who were found to have a high-risk pedigree (28/979 patients, 3%), an intermediate-risk pedigree (331/979 patients, 34%) and a 25% random sample (155/620 patients) of patients who reported a low-risk pedigree (155/979 patients, 16%) were deemed eligible for inclusion in this study (514/2464 incident cases = 21%). 364/514 (71%) consented to participate. All 364 patients were consented directly as proxy consents were not sought in Ontario (Table 1).

Demographic data for Newfoundland and Ontario can be seen by reference to Table 2. The proportion of subjects $\leq$ the age of 50 was approximately equal between the two provinces, whereas there were significantly more women in Newfoundland ($\chi^2 = 7.34$, $p = 0.01$, $df = 1$). The overall stage at presentation was significantly more advanced in Newfoundland ($\chi^2 = 33.200$, $p = 0.000$, $df = 3$), with 25% of patients in Newfoundland and 9% of patients in Ontario being assigned stage IV status. When those consented by proxy in Newfoundland

were excluded from the data analysis, the significant effect of stage was lost ($\chi^2 = 6.154$, p = 0.188, df = 4), with 7% of patients in Newfoundland now assigned stage IV status. This exclusion was performed as almost all patients consented by proxy were stage IV and the outcome of patients with stage IV disease consented by proxy was significantly different .from stage IV patients who were directly consented in Newfoundland (Figure 1). The median survival was approximately 9 months in 34 stage IV patients who were consented by proxy as contrasted with 25 months in 32 stage IV patients who were directly consented. Proxy consents were not sought in Ontario.

There was no demographic data available for those patients who did not consent to participate in either province

Adjuvant Chemotherapy as a function of stage

Stage I – No adjuvant chemotherapy recommended by CPGs

Of the 21 stage I patients in Newfoundland and the 60 stage I patients in Ontario, none were administered adjuvant chemotherapy (Table 3).

Stage II – Chemotherapy recommended with high-risk features

In Newfoundland, 20/55 stage II patients (36%) were initiated on adjuvant chemotherapy following curative resection (Table 3).

Of the 55 patients diagnosed with stage II colon cancer in Newfoundland, 41 (75%) had at least one high-risk feature (Figure 2a). Of these high-risk patients, 29/41 (71%) were referred to medical oncology and 18/29 patients (62%) were initiated on adjuvant chemotherapy (44% of the entire high-risk cohort). Therefore, 23/41 patients (56%) with high-risk features in Newfoundland were not offered adjuvant chemotherapy (Figure 3). 12/23 patients (52%) were never referred to medical oncology by the operating surgeon or

family doctor. Of the 11 patients (48%) who were referred to medical oncology, one was felt to be medically unfit, one did not have the issue revisited after work-up for a benign liver lesion, 4 were noted to have 'high-risk features for which adjuvant chemotherapy has shown no definitive benefit', and 5 were felt to have 'no high-risk features' although at least one was noted in the standardized tumor pathology summary.

14/55 stage II patients (25%) in Newfoundland were classified as low-risk (Figure 2a). Of these, 11/14 patients (73%) were assessed by medical oncology and 3/11 (27%) received adjuvant therapy (21% of the low-risk cohort). This was based solely on the presence of tumor ulceration. The latter was not strictly considered a high-risk feature for the purposes of this study as it is not identified in the CCO and ASCO guidelines. The receipt of adjuvant chemotherapy did not differ as a function of risk status in Newfoundland.

In Ontario, 44/116 evaluable patients (38%) were initiated on adjuvant chemotherapy following curative resection (Table 3). The absence of standardized pathology reporting in the remaining 16/132 (12%) made this determination impossible. Most often, the presence of lymphovascular invasion was not noted.

Of the 116 evaluable patients diagnosed with stage II colon cancer in Ontario, 53/116 patients (46%) were high-risk and 63/116 patients (54%) were considered low-risk (Figure 2b). Of 53/116 patients (46%) considered high-risk, 36 (68%) were referred to medical oncology and 17 (32%) were not. 30/36 patients (83%) referred received adjuvant chemotherapy. We were unable to determine from an assessment of the initial medical oncology consultations why the other 6 patients were not offered or initiated on adjuvant chemotherapy.

63/116 stage II patients (54%) in Ontario were classified as low-risk. Of these, 22/63 patients (35%) were assessed by medical oncology and 14/22 (64%) received adjuvant chemotherapy (22% of the low-risk cohort). The reasons for this were not stated. The receipt of adjuvant chemotherapy differed significantly as a function of risk status in Ontario ($\chi^2 = 14.0$, $p = 0.000$, $df = 1$).

Adjuvant chemotherapy as a function of Age – Stage II

As the proportion of low- and high-risk patients who received adjuvant chemotherapy (low-risk = 21% in Newfoundland and 22% in Ontario; high-risk = 44% in Newfoundland and 57% in Ontario) did not differ significantly as a function of province, data from the two provinces was combined for further analysis.

Multivariate logistic regression was performed to identify independent predictors of those who received chemotherapy. Variables included in the model were High-risk status (relative odds = 3.82, 95% CI 1.87, 7.81), Province (NS) and Age > 50 at diagnosis (relative odds = 0.38, 95% CI 0.14-1.03). The proportion of those who received chemotherapy was 68% in those aged </= 50 years and 36% in those > 50 years. There was a strong trend towards using chemotherapy in the younger group independent of high-risk status.

Stage III – Adjuvant chemotherapy recommended by CPGs

The majority of patients with stage III colon cancer were administered adjuvant chemotherapy (Table 3).

In Newfoundland, 45/52 (87%) patients with Stage III colon cancer received adjuvant chemotherapy. Of the 7 who did not, 3 patients died postoperatively, one had a delayed

postoperative course following an anastomotic leak, one was treated for a synchronous retroperitoneal lymphoma and three were not referred (no reason given).

In Ontario, 108/115 (94%) were administered adjuvant chemotherapy. There was no information available for 4 patients, one patient refused therapy, one had metastatic breast cancer and there was no reason given for the final patient.

Survival Analysis: crCIHRt – Ontario vs Newfoundland & Labrador

Kaplan-Meier survival analysis comparing overall survival between Newfoundland and Ontario (Figure 4a) revealed that Ontario had a significantly better overall survival than Newfoundland (Mantel-Cox = 18.211, p = 0.000, df = 1). However, once the survival curves extend beyond approximately 12 months, they remain parallel for most of the duration of the comparison. Multivariate Cox Regression analysis, confirmed that most of the variation was noted in the first year after diagnosis (Figure 5). For this reason, patients consented by proxy were once again excluded from the analysis (Figure 4b). This resulted in a loss of significance in the statistical representation of the survival function (Mantel-Cox = 3.073, p = 0.08, df = 1). The resultant Cox Regression analysis was now shown to cross unity for the first year following diagnosis (Figure 6).

DISCUSSION

In 1991, the NIH published the first evidence-based guidelines for the use of adjuvant chemotherapy in colon cancer.[11] Level I evidence recommended adjuvant chemotherapy for stage III patients only. Although the findings from subsequent systematic reviews did not support the routine use of adjuvant chemotherapy in stage II patients, it should be considered in those with high-risk features.[66,67]

The results of our study revealed that patients with stage I and III colon cancer were managed according to current recommendations in both provinces. Clearly, guidelines supported by adequate level I evidence have been acknowledged by the appropriate target audience, including surgeons and medical oncologists, resulting in successful implementation.

Although patients with high-risk stage II disease were significantly more likely to receive chemotherapy than patients with low-risk stage II disease, our data would suggest that other information was used in the decision to offer adjuvant chemotherapy to these patients. The Newfoundland data revealed that this was in part due to the failure of surgeons or family doctors to refer patients to medical oncology and in part due to the medical oncologists 'not believing in' or being unaware of the data with regard to high-risk stage II patients. We are unable to comment as to whether this reflects a lack of knowledge on the part of surgeons and/or family physicians as to the potential benefit for high-risk patients, whether surgeons and/or family physicians do not feel that the evidence is strong enough to warrant referral for stage II patients, or whether other factors such as resource allocation are at play. The failure of medical oncologists to recommend chemotherapy likely reflects a paucity of level I evidence or the belief that other factors are more

important in the decision to recommend adjuvant chemotherapy to this cohort of patients. Our data suggest that patient age influenced the decision to offer adjuvant chemotherapy in that age $\leq$ 50 was an independent predictor of chemotherapy use on multivariate analysis. This requires further investigation as younger age tends to be correlated with high frequency microsatellite instability (MSI-H) tumors.[80,81] There is evidence that patients with MSI-H tumors may not derive the same benefit from 5-FU based chemotherapy.[82] Thus, the use of age alone as an adverse prognostic factor in the decision to administer 5-FU based adjuvant chemotherapy may not be sound. The complex process of delineating which stage II patients should be considered for adjuvant chemotherapy following curative resection lacks the strong evidence base that has been well established in sound CPGs regarding adjuvant chemotherapy for stage III colon cancer patients.

Mechanisms to Improve Concordance with CPGs for Stage II Colon Cancer

Physicians are reluctant to change their behavior even in the face of evidence-based guidelines that seek to improve aspects of health care access, treatment and outcome.[83-87] As previously discussed, the introduction of new guidelines does not automatically translate into doctor and/or patient acceptance.[38] Further, improvements in compliance rates have been modest, in the range of 10%, for most implementation programs. Based on the known limitations to the effective implementation of guidelines as outlined in the preceding aspects of this paper, several authors have outlined a multidisciplinary approach to the development, dissemination and use of evidence-based guidelines.

Scott *et al* (2004)[88] have outlined a model that attempts to incorporate the interests and beliefs of all parties involved in order to establish a vested interest in guideline development and eventual incorporation into the clinical practice setting. In the case of

stage II colon cancer patients, this would refer to all physicians, other health care providers, administrators and others that have an interest in delivering the best available treatment within the constraints of resource allocation. Those invested in the process would start out by establishing a strict definition of the population to which the guidelines will refer, stage II colon cancer patients, acknowledging that the associated disease burden is a significant concern. Delineation of 'evidence-practice' gaps must be sought in order to strengthen the perceived need for guidelines to improve and standardize health care. A small number of interested individuals would then review the published literature with an aim toward acknowledgement of pre-existing valid guidelines and how these might be adapted with acknowledgment of the original source. Importantly, a panel of experts and ***potential end-users***, including local experts, would then convene to discuss the guidelines within the context of local conditions and beliefs. The two questions asked would be: 1) Who are the experts or senior clinicians who could criticize, disagree with, or disendorse the finished guidelines if not consulted during the development process? and 2) Who are the end-user clinicians who will ignore the guidelines if the latter fail to meet their clinical needs?. The aim of this panel would be to reach consensus based on strength of evidence and level of agreement, establish style of presentation, method(s) of dissemination and review/update schedules.

Guideline structure should be as simple and unambiguous as possible. The use of the CCO and/or ASCO guidelines for the treatment of stage II colon cancer patients, in a format such as an easy to follow algorithm and/or flow charts should be used that incorporate clear and concise decision points. Access to further information should be easily referenced. Measures of risk and benefit should be reported where known and absolute risk reductions

should be made available when possible. Several small pilots of interested individuals should be employed prior to proposed widespread dissemination.

While there are many systems available to implement guidelines, a multifaceted step-wise approach will lead to the greatest gains in compliance. Use of a system such as the PRECEDE model would be acceptable.[89] This model includes a predisposing phase, an enabling phase and a maintenance phase.

The predisposing phase raises awareness of guidelines through discussions/presentations to targeted parties outlining evidence-practice gaps in the current care, such as when patients with stage II disease should be consulted to medical oncology. The easiest scenario might be to incorporate an algorithm that would have all patients with stage II disease referred to medical oncology following surgical resection of the primary colon tumour. Discussion would focus on the existing clinical culture and means by which patient care could better be achieved. The enabling phase allows users to better understand the full intent of the guidelines and how to access/apply them. Guidelines would be readily accessible and educational strategies employed at regularly scheduled interactive, case-based small group seminars and workshops that allow for discussion of individualized application of the guidelines. This might include a discussion of when, how and if age should be considered in patients presenting for consideration of adjuvant therapy. Opinion leaders, involved in the prior development of the guidelines, should be readily used to promote uptake and detail likely improvements to be gained by the successful implementation of the guidelines. One-on-one support and electronic prompts, reminders and checklists should be available and incorporated into the patient care pathway. Support should be readily available. The maintenance phase consists of feedback of results and clinical audits. Anonymized peer-

reference feedback on the group, specialty or hospital level should be provided.

Use of this strategy has been shown, in at least one study, to significantly improve patient care over time.[89] Significantly more patients received appropriate tests and medications during prescribed time limits when presenting with acute coronary syndrome (ACS). Baseline rates of several procedures (early coronary angiography) were already in the 90% range, and thus improvements were less noticeable.

Although there are many more systems such as this described in the implementation literature,[90,91] the basic principles of a multi-faceted approach with involvement of stakeholders from an early stage (guideline development), use of an 'awareness phase', interactive educational strategies, access to support and ongoing audit, assessment and feedback are features of all. Guidelines need to be flexible and amenable to changes reflective of the local flavor. Only in this way can the main goals of guideline implementation – best application of evidence-based medicine, improved patient care (decreased morbidity, increased patient satisfaction and improved survival) and more effective resource allocation – be realized.

crCIHRt Kaplan-Meier survival analysis: Newfoundland vs. Ontario

Kaplan-Meier survival analysis showed that Ontario enjoyed a significant overall survival advantage. At first glance, this seems reasonable given that it parallels data reported by CCS from 2002-2007,[72-77] where actual reported deaths from CRC and estimated five-year age adjusted relative survival from CRC were better in Ontario (data for colon cancer alone not available). For example, estimated age-standardized mortality rates for CRC in 2002 were reported as 25/100,000 and 21/100,000 for males in Newfoundland and Ontario, respectively.[72] The National estimate was 22/100,000 for this time period. The estimated

age-standardized mortality rates for CRC for 2002 in women were reported as 14/100,000 and 12/100,000 in Newfoundland and Ontario, respectively. The National estimate was 14/100,000 for this same time period. This same trend was noted for each year between 2002 and 2007. However, it should be stated that while CCS estimates deaths from CRC for a particular year, the crCIHRt study retrospectively evaluated overall survival in a single cohort of subjects followed over time.

The survival comparisons between Newfoundland and Ontario were not based on calculated age-standardized estimates of trends over time, but rather on evaluation of a defined cohort for the period 1999-2000. Survival analysis requires techniques that can deal with the censoring of data as not all subjects who will eventually 'experience the variable of interest' will have done so by the time that calculations are undertaken. Kaplan-Meier survival analysis is used to estimate the length of time to reach a certain endpoint, namely death. It is the conditional probability of survival, as defined by the hazard ratio, for each time interval given that a subject who has survived to the beginning of the interval will still be alive at the end.[92] The conditional probability of survival (the probability of surviving to the end of the interval given that the subject was alive at the beginning of the interval) is determined, with the product of the conditional probabilities defining survival to a particular point in time. These estimates of survival probabilities are represented, or modeled, as a survival curve. The curve represents a step function with sudden changes in estimated probability corresponding to the time that events occurred and indicated by vertical lines. The assumptions of Kaplan-Meier survival modeling are that: 1) those patients who are censored will have the same survival as those who continue to be followed, 2) the survival probabilities are the same for subjects recruited early and late in

the study, and 3) that the event happens at the time specified.

The three assumptions upon which the Kaplan-Meier survival analysis is based were not upheld in the crCIHRt survival comparisons. As such, bias introduced through differential methods of 1) recruitment of subjects (violation of assumption 2), 2) patient follow-up/time to data censor (violation of assumption 3), and 3) death recording (violation of assumption 1) could account for most of the variance between the two provinces. ***The following discussion shows that control for these factors, when possible, can negate the significant survival advantage for colon cancer reported in Ontario by Kaplan-Meier survival modeling.***

<u>Bias in recruitment methods</u> – violation of the assumption that the survival probabilities are the same for subjects recruited early and late in the study

The crCIHRt was established as a collaborative effort between the provinces of Ontario and Newfoundland in 2001. Recruitment of individuals to this arm of the study was initiated in Ontario approximately 2 years prior to initiation in Newfoundland. As such, Newfoundland investigators sought to recruit a similar ratio of subjects into the study by seeking 'proxy consent'. At the patient's request, or if the patient was deceased at the time contact was made, next-of-kin were approached to obtain consent for retrospective chart review. 32% of subjects recruited to the study in Newfoundland were obtained through proxy consent. In contrast, all individuals consented in Ontario were alive at the time of recruitment and were 'directly consented'. In order to explore the difference in survival between those consented by proxy and those directly consented, we looked specifically at the survival of stage IV patients in Newfoundland. Almost all patients consented by proxy were stage IV and had been consented for retrospective chart review after their death. The

median survival for stage IV patients consented by proxy in Newfoundland was 9 months in 34 patients as contrasted with stage IV patients consented directly in Newfoundland, where median survival was found to be 25 months in 32 patients.

This inequity could account for the finding that the slopes of the Kaplan-Meier overall survival analysis become parallel after approximately 12 months and the suggestion from the Cox proportional hazards regression analysis that the major source of the variance is found within the first 12 months. For that reason, those consented by proxy in Newfoundland were excluded from the analysis. The subsequent survival statistic was not statistically significant and the Cox Regression model now crossed unity for the first year following diagnosis. This does not exclude other sources of bias in either direction or a true difference in survival between the two provinces.

Bias in loss to follow-up/time of data censor* – *violation of the assumption that the event happens at the time specified

In survival analysis, non-standardized protocols for follow-up can impact on statistical estimates. The Kaplan-Meier survival estimate is based on the premise that 'the probability of surviving k or more periods from entering the study is a product of the k observed survival rates for each defined period (the cumulative proportion surviving).[93] If survival is recorded in months, and follow-up is random or significantly different between two populations, then the measure of median survival will be skewed. The retrospective nature of the data procurement in the present study did not account for potential differential follow-up regimes in the two provinces. In fact, ASCO[94] recommends patients be followed 'every 3 months for the first 2 years' while CCO[95] recommends that patients be followed 'at least every 6 months for the first three years'. This is further confounded by the fact

that not all patient follow-up is performed by oncologists. Although we might expect these issues to have a more profound effect on recognition of recurrence, they might have also resulted in non-random effects on survival analysis given the fact that investigators in Newfoundland & Labrador relied on methods other than procurement of death certificates to ascertain survival data (see below under 'Bias in death recording'). Unfortunately, data related to follow-up patterns was not collected for this study, and thus, the impact or even the direction of such bias cannot be calculated or estimated.

Bias in death recording* – *violation of assumption that those patients who are censored will have the same survival as those who continue to be followed

In Ontario, survival data was obtained through the use of death certificates. OFCCR cases are linked with the Ontario Cancer Registry database. The latter is regularly updated with linkages through the Ontario Mortality database. In some cases, vital status information was received from relatives of deceased cases. Information on disease specific survival (DSS) was not available for analysis. In Newfoundland & Labrador, ethics approval did not allow for the use of death certificates. As such, investigators used clinic charts, obituaries from papers published across Newfoundland and family contact through the dedicated newsletter of the crCIHRt. Information was collected to allow for determination of disease specific survival (DSS). Data is not yet available as to how many subjects were lost to follow-up over the time course of the study.

We cannot assume that both means of collecting survival data were equal in terms of delineating alive vs. dead. There is some data to suggest that there may be inaccuracy of up to 20% in death determination alone, depending on method of procurement, regardless of cause of death.[96] These authors contrasted the accuracy of 4 methods of mortality

recording for 1999-2000 in a rural district of Vietnam. They looked at reported deaths in 11,089 households collected by quarterly household follow-ups, census data, the Commune Population Registration System (CPRS) and a neighborhood survey. Using quarterly household follow-up as the gold standard, it was shown that the census missed 19 deaths, the CPRS missed 89 deaths (19%) and the neighborhood survey over-reported actual deaths. The fact that overall survival was significantly worse in Newfoundland may be partly explained by factors associated with the different means of death ascertainment in the two provinces. As with method of follow-up, the presence and/or direction of this bias cannot be ascertained given the retrospective nature of this study.

As disease specific survival (DSS) was not directly assessed in Ontario, no direct comparison between the provinces was possible in the crCIHRt study. However, it has been shown that death certificates can be extremely inaccurate.[97-100] A meta-analyses showed that at least 1/3 of death certificates are likely to be incorrect, mostly the result of inaccurate recording of cause of death.[98] Many of these errors likely arise as the result of limited previous experience with the patient prior to their death, house staff inexperience, fatigue, time constraints and perceived unimportance of the death certificate.[97,101] The means of ascertaining death and cause of death in Newfoundland may have allowed the investigators access to more complete, or at the least different, information. This would have made comparisons of DSS, if possible, fraught with potential bias.

crCIHRt vs Canadian Cancer Statistics

The following discussion contrasting the survival analyses for colon cancer in the crCIHRt study and mortality information derived from CCS for CRC is hypothetical given that the central purpose and statistical methods invoked differ between the two reports. In fact,

CCS explicitly acknowledges that "It is not appropriate to compare the age-standardized rates presented here with those from publications that employ a different standard population".[72-77] Therefore, the main purpose of this section is to contrast statistical methods used in the derivation of incidence and mortality data as they relate to the central purpose of the data.

Central purpose: crCIHRt vs Canadian Cancer Statistics

crCIHRt

The crCIHRt was initiated in 2001 as a joint effort by a multidisciplinary team of investigators from Newfoundland and Ontario to study incident cases of CRC in the two Canadian provinces. The collaboration was established through the CIHR when funding was sought to fulfill similar aims by investigators in the two provinces. The objective was to compare and contrast epidemiologic, genetic and nutritional influences on the incidence and mortality related to colorectal cancer between the two provinces for a single, defined period of time. Use of a population-based study was an important element that resulted in an accurate assessment of the most important variable currently related to cancer outcome, stage of disease. As such, the study sought to delineate important environmental and genetic influences on the development of CRC cancer and to explore resource allocation and outcome, as a function of stage, between the two provinces. Although it sought to act as the impetus for further research, it was not meant to aid, explicitly, in decision making, priority setting or resource allocation at the individual, community or provincial level.

Canadian Cancer Statistics

The main purpose of CCS is to provide health professionals, investigators and policy-makers with information pertaining to the incidence and mortality of common cancer types

by age, gender, time period and province/territory.[72-77] It acts, through the use of standardized statistical estimates, to stimulate new research and assist in decision-making and priority setting at all levels. As such, the data provided deals not only with time point estimates of incidence and mortality, but with actual and estimated trends over time.

Statistical methods: crCIHRt vs Canadian Cancer Statistics

crCIHRt

Colon cancer incidence or survival rates were not calculated as part of the crCIHRt study as this was not necessary to fulfill the central objectives of the study. However, it was possible to make crude comparisons between Newfoundland and CCS, as the actual number of reported cases of CRC for 1999 and 2000 were recorded in the Newfoundland arm of the study and can be compared to those extracted for the corresponding years from the 2003[73] and 2004[74] Canadian Cancer Statistics, respectively. For the two years combined, there were 420 reported cases in males and 270 reported cases in females for a total of 690 cases reported to CCS by the Newfoundland Cancer Registry. If we assume that 70% were colon cancer based on previous estimates,[102] there should be about 483 patients diagnosed with colon cancer in Newfoundland between January 1, 1999 and December 31, 2000. As our study was limited to patients between 20 and 74, we would have excluded some of these people. It is likely, however, that some patients were missed by our study as over 200 patients are unaccounted for and not all of these would be expected to fall outside the defined age range. The reasons for this are uncertain as the data was extracted from the same source.

In the crCIHRt study, overall mortality was evaluated using Kaplan-Meier survival analysis. The main outcome measure was estimated time to death for a cohort of patients

from Newfoundland or Ontario diagnosed with colon cancer from 1999 to 2000.

Canadian Cancer Statistics

The statistical analysis employed by CCS involves the standardization of incidence and mortality rates based on the 1991 Canadian population in order to provide appropriate age-standardized rates.[72-77] Data provided by the provincial and territorial cancer agencies is used in conjunction with projected changes in population size and distribution (ie. age, gender) supplied by Statistics Canada to estimate the probability of developing and dying from cancer, as well as potential years of life lost to this disease. Incidence and mortality rates are estimated for each age group, cancer site and gender by fitting Poisson regression analyses to the provincial and territorial yearly values. Poisson regression assumes that annual incidence fulfills the criteria of independent Poisson random variables with a mean which is the product of the annual population size and the (true) annual incidence rate.[72-77] It further assumes that the length of the observation period is fixed in advance and that the events occur at a constant average rate. It is used to model random events in time and expresses the probability of a number of events occurring in a fixed period of time if these events occur with a known average rate and independently of the time since the last event. The Poisson distribution is a nonparametric statistic used to estimate rates when the outcome measure is rare in the overall population. It can be used to estimate future rates based on past performance and projected future census data. The purpose is not to define the survival function for a particular cohort of patients, but rather to estimate burden of future disease to aid in planning and resource allocation. Estimates from CCS have performed well in comparison to actual data which becomes available, on average, with a delay of 4-5 years.[34-39] Unlike the crCIHRt, assumptions of the Poisson distribution,

including a fixed observation period and events occurring at a constant average rate over time, are met by annual reporting of provincial/territorial incidence and mortality data and the use of projected estimates based on pasts trends or averages over time. Follow-up is not an issue as data modeling of future mortality rates is not cohort dependent, but based rather on past incidence trends and projected population size.

Outcome measures: crCIHRt vs. Canadian Cancer Statistics

The central question that we wished to address by comparison to CCS was whether crCIHRt data was accurate and whether there truly exists a greater incidence and mortality from CRC in Newfoundland as suggested by data in actual and projected estimates of CCS. It would appear that our data is not complete and that there are sources of statistically immeasurable bias that do not allow us to answer this question.

The finding of different projected survival estimates using the data accrued from the crCIHRt (Kaplan-Meier Survival Estimate, Newfoundland vs. Ontario) and CCS (Age-standardized Poisson regression estimates of incidence and survival by province) reflects differences in stated objectives and statistical analyses based on the type of data collected. In fact, direct comparison of the conclusions from the two sources is not valid given that data was collected to fulfill different purposes. The crCIHRt sought to compare two provinces at a point in time in order to determine if differences existed between the two populations in terms of stage at presentation, treatment and outcome. It was meant to answer questions related to how well things have been done in the past. In contrast, CCS sought to project incidence and mortality data based on past trends and estimated population size. It was meant to answer questions related to how resource and manpower allocation should proceed into the future. Thus, estimates of a higher incidence and

mortality burden in Newfoundland vs. Ontario as reported by CCS are reliable and reproducible given the Poisson method.

CONCLUSIONS

1) The strength of evidence in support of chemotherapy for high-risk stage II colon cancer patients is level 5 (Expert recommendations based on the best available data from multiple systematic reviews).
2) The concordance rates in Newfoundland and Ontario with CPGs recommending adjuvant chemotherapy for high-risk stage II colon cancer patients were low. It appeared that other factors, including age, were considered.
3) The development, adaptation and implementation of CPGs is a complex process that should incorporate validated tools that address each of these aspects.
4) The assumptions of Kaplan-Meier survival analysis were violated in the comparison of overall survival between Newfoundland and Ontario. Only the contribution of time of entry into the study could be statistically controlled for through the exclusion of those consented by proxy in Newfoundland.
5) As the objectives of and statistical approaches to survival analysis differed between the crCIHRt and CSS, direct comparisons of survival are not valid.

The rise of evidence-based medicine has lead to the development of clinical practice guidelines that are aimed at providing and standardizing the best medical care for the population within the confines of resource limitations. The use of guidelines is a complex process that demands expertise in the areas of literature assessment and guideline development, adaptation to a particular population and set of circumstances and implementation strategies. Those interested in guideline development need to consider the appropriate questions to ask, what the best available data would recommend and

mechanisms of dissemination, adaptation and implementation. There are numerous methods that have been developed and standardized by multidisciplinary expert panels that address the issues surrounding each of these areas. It is imperative that those involved with guideline development be aware of these tools and use them in order to develop valid, reproducible guidelines that can be reasonably implemented at the level of the target audience given local circumstances and potential resource limitations. As this is a resource intense process, both in terms of financial resources and manpower, validated instruments that have been developed to assist in all aspects of this process should be considered. International collaborative efforts at all levels will hopefully lead to more standardized patient care, within the limits of local resource limitations and beliefs. Only in this way can improvements in patient care including decreased morbidity, increased patient satisfaction and improvements in overall and disease specific survival be accurately and reproducibly recognized.

Accurate determination of survival is an equally complex process. The methods used by the crCIHRt investigators violated all assumptions of the Kaplan-Meier survival statistic. Bias introduced through differential methods of subject recruitment, ill-defined patient follow-up protocols and dissimilar means of assessment of the outcome of interest needs to be minimized. Comparisons of this nature that extend over more than one locality need to be highly controlled, starting at the point of what research questions are valid and reasonable given available data. Unfortunately, aside from bias introduced secondary to method of recruitment into the study, we are unable to statistically control for other factors. All statistics used in survival analysis, such as the log-rank test and Cox proportional hazards regression analysis, make similar assumptions and thus may not be valid to analyze

this data. Therefore, unless it can be confirmed that similar times to follow-up were used in each province and death certificates are made available for comparison in Newfoundland, the conclusions of our data are not statistically sound.

Database development, such as that described for the study of CRC by the crCIHRt, needs to become more standardized and reproducible across time and place. As has been shown, unless comparable entry times and follow-up protocols are in place, the resultant bias will make it difficult to draw valid conclusions from comparative studies of this nature. Prospective collaborative databases that attempt to capture accurate, reproducible data will be best suited to answer the types of questions addressed in this paper. Only in this way will valid results that can guide future treatment protocols and legitimate guidelines be realized.

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	Newfoundland	Ontario
Total eligible	**274**	**514**
Total Consented	**173 (63%)**	**364 (71%)**
Direct Consent	**117 (68%)**	**364 (100%)**
Proxy Consent	**56 (32%)**	**0**

Table 1. Method of consent: Newfoundland vs. Ontario

	Newfoundland	Ontario
Number Consented	**173**	**364**
Age ≤ 50 **Age > 50**	**20 (12%)** **153 (88%)**	**56 (15%)** **308 (85%)**
Female **Male**	**73 (42%)** **100 (58%)**	**183 (50%)** **180 (50%)**
Stage **(Proxies included)**	**I = 21 (12%)** **II = 57 (33%)** **III = 52 (30%)** **IV = 43 (25%)**	**I = 61 (17%)** **II = 141 (39%)** **III = 115 (31%)** **IV = 31 (9%)** **Unknown 16 (4%)**
Stage **(Proxies *excluded*)**	**I = 20 (17%)** **II = 50 (43%)** **III = 39 (33%)** **IV = 8 (7%)**	**See 'Proxies included'**

Table 2. Demographics of Study Population

Stage at Diagnosis	Newfoundland	Ontario	Total
Stage I	0/21	0/60	0/81
Stage II	20/55 (36%)	44/116 (38%)	64/171 (37%)
Stage III	45/52 (87%)	108/115 (94%)	153/167 (92%)

Table 3. Adjuvant Chemotherapy by Stage

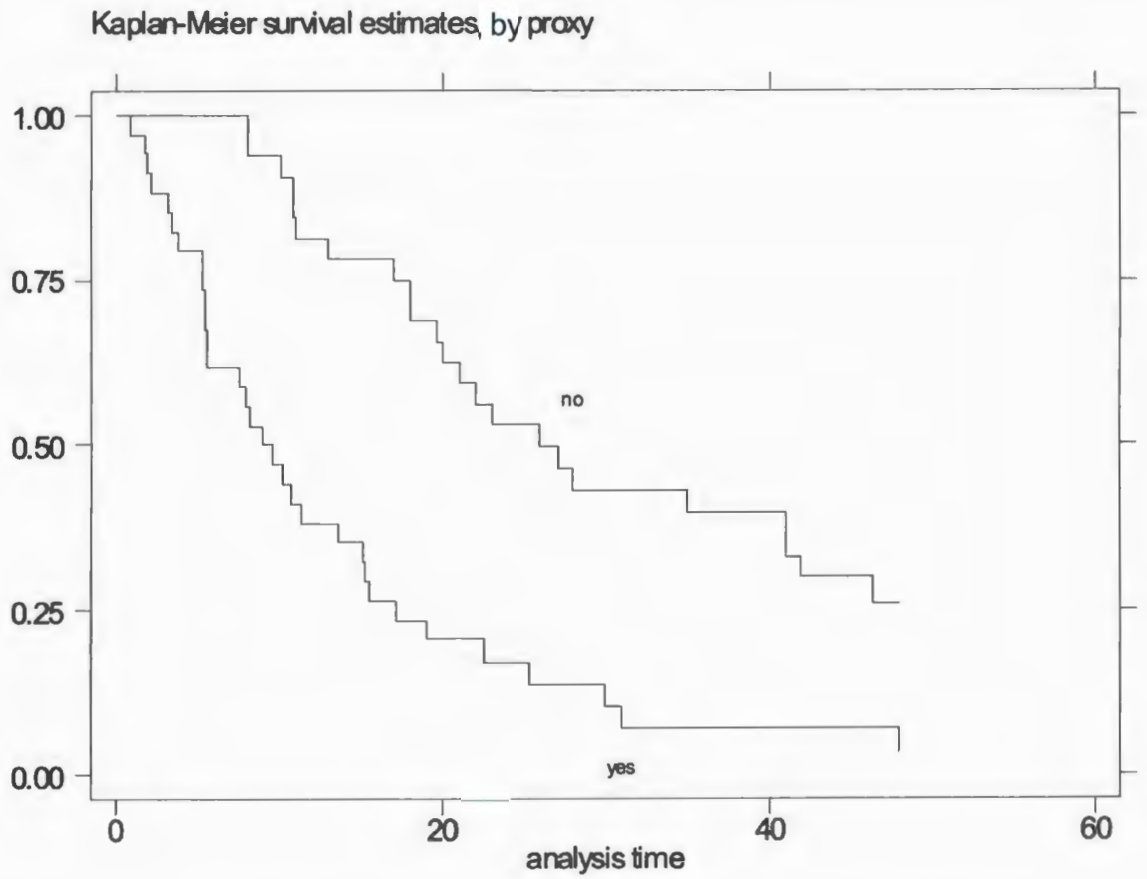


Figure 1. Kaplan-Meier Survival Analysis, Newfoundland: direct (no) vs. proxy (yes) consent

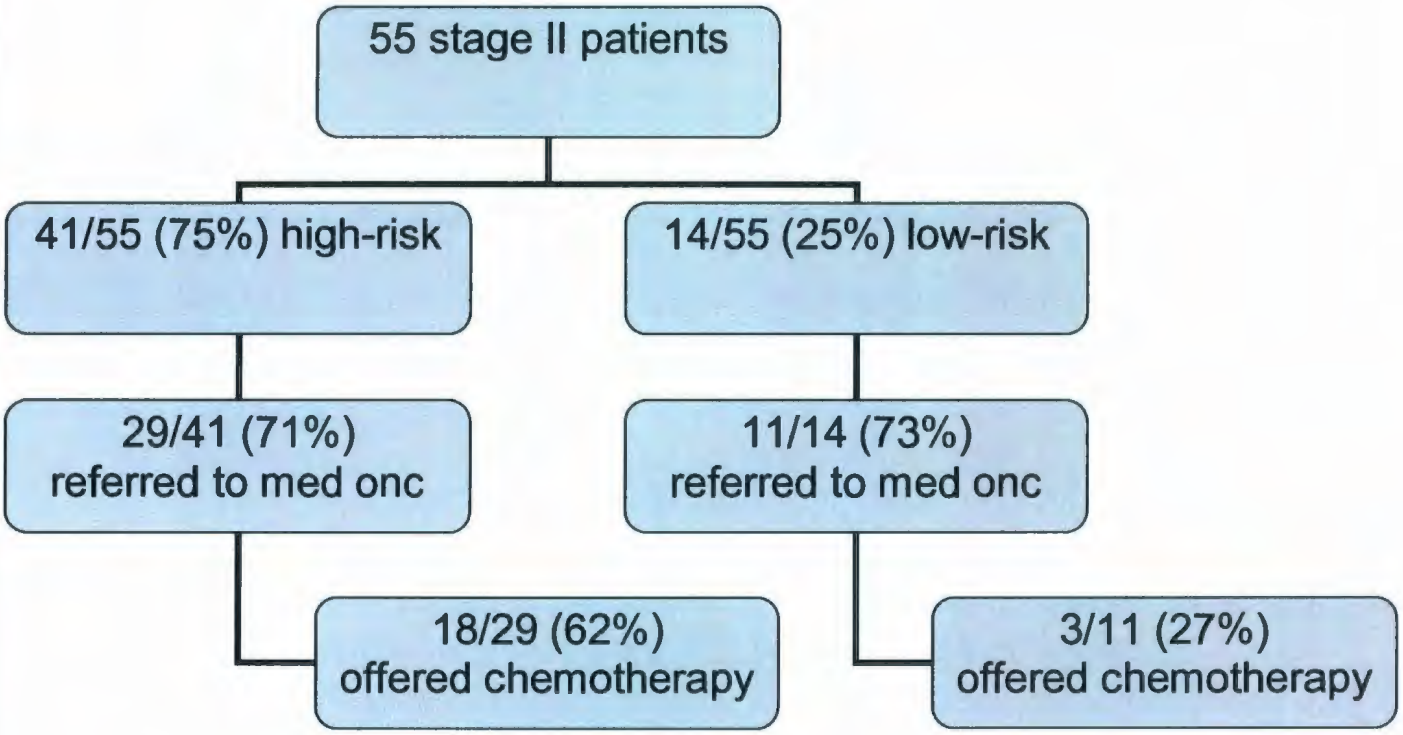


Figure 2a. Receipt of adjuvant chemotherapy as a function of risk status in Newfoundland (Stage II)

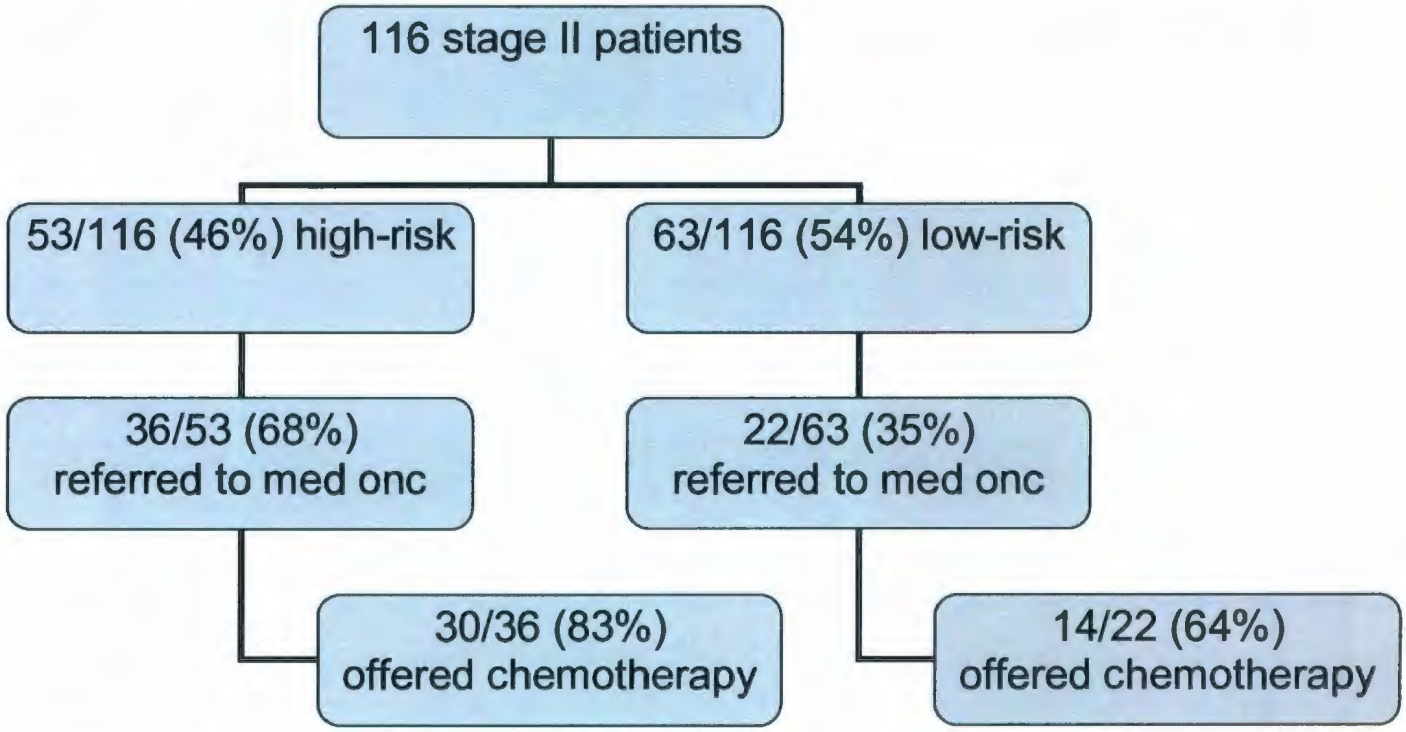


Figure 2b. Receipt of adjuvant chemotherapy as a function of risk status in Ontario (Stage II)

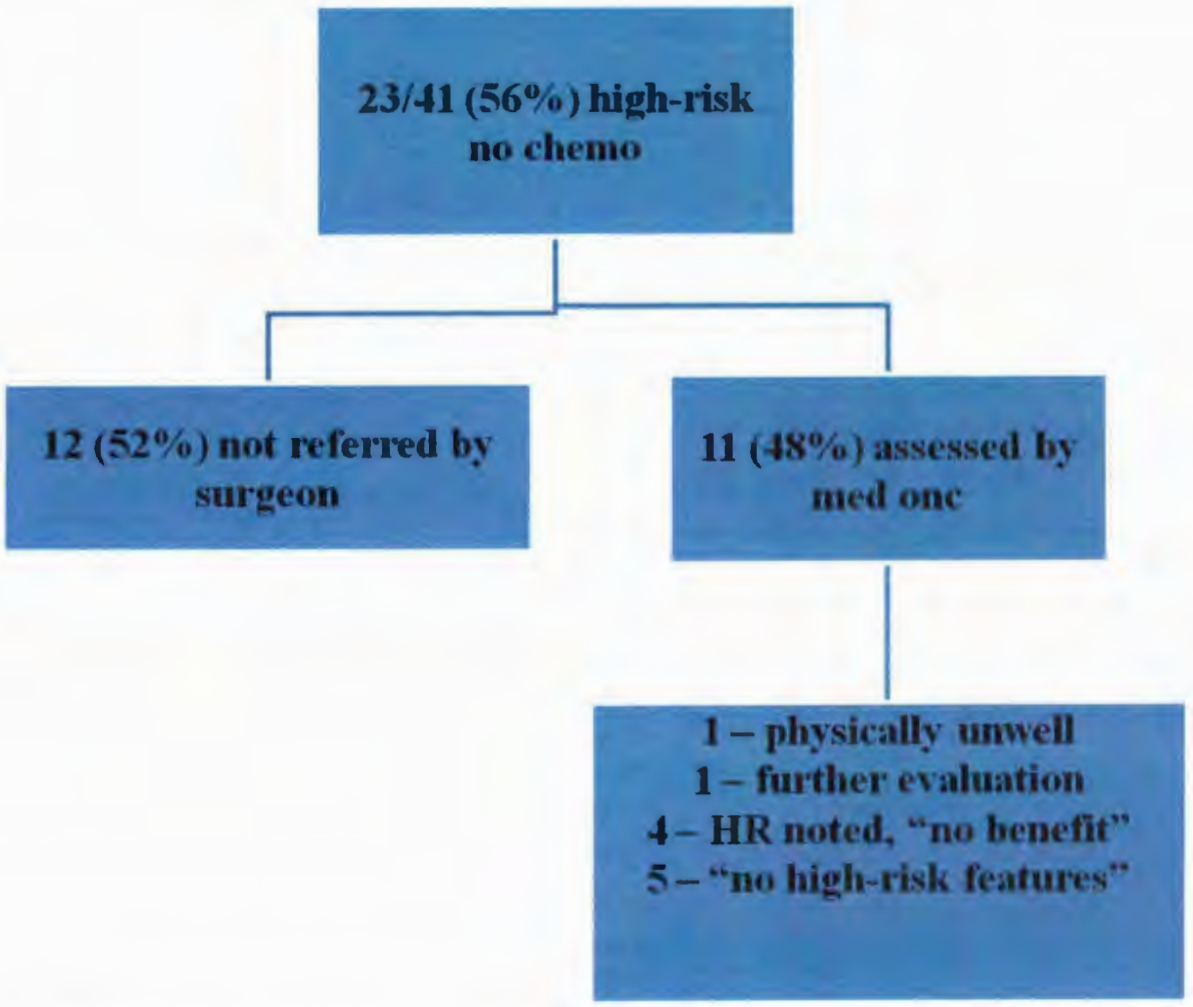


Figure 3. Fate of stage II patients who were high-risk who did not receive adjuvant chemotherapy

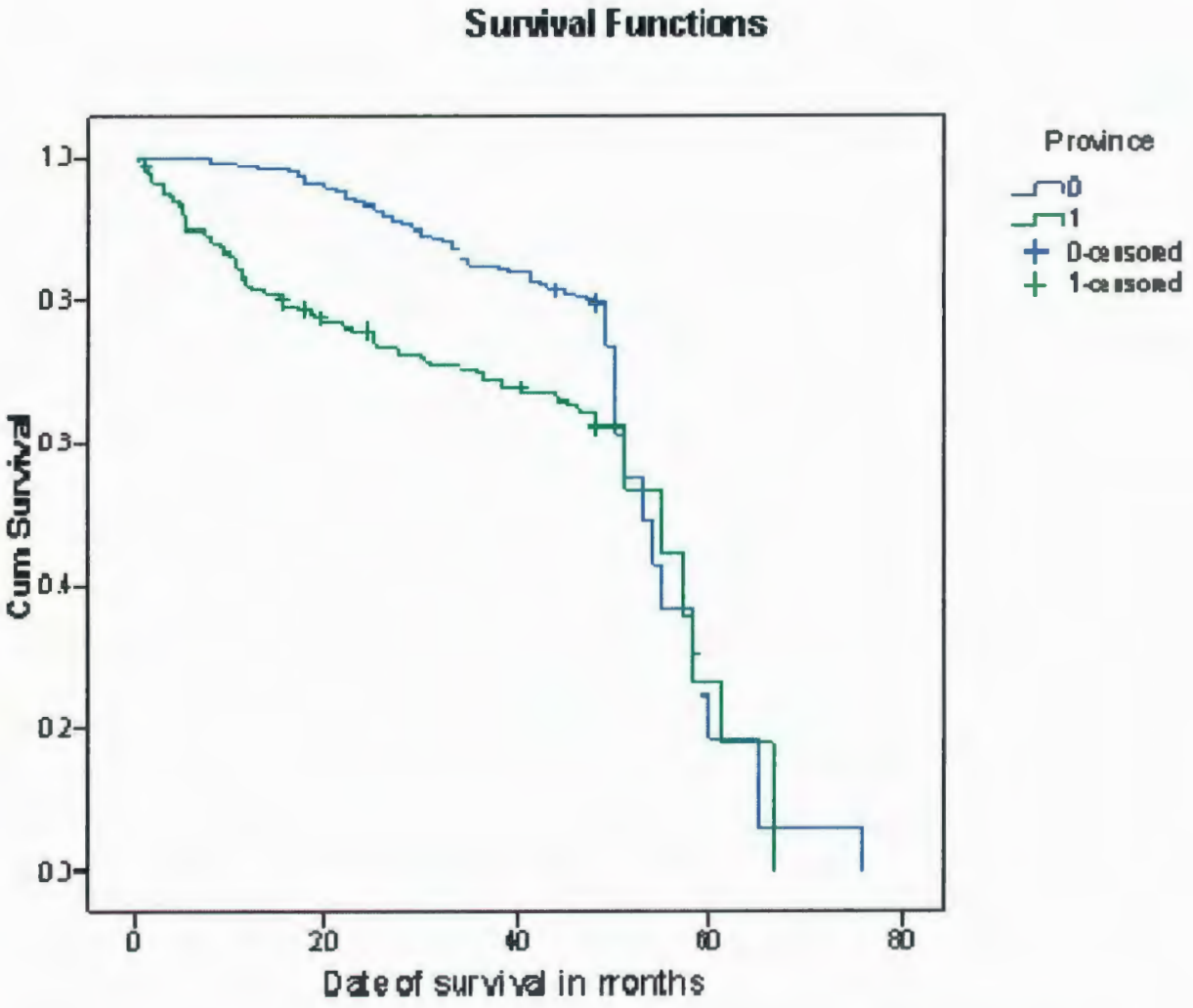


Figure 4a. Kaplan-Meier Survival Analysis, Overall Survival Newfoundland vs. Ontario

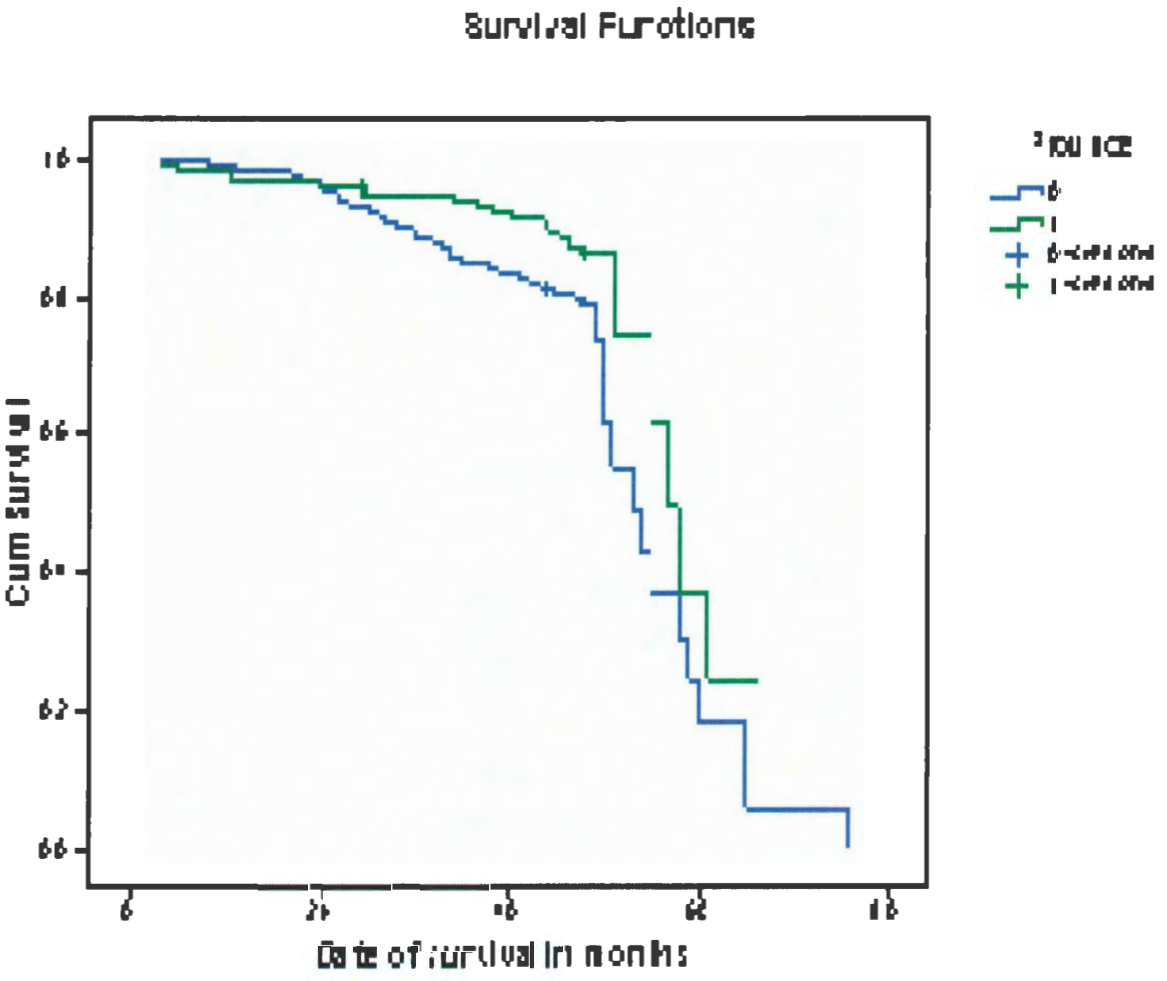


Figure 4b. Kaplan-Meier Survival Analysis, Overall Survival Newfoundland vs. Ontario (proxies excluded)

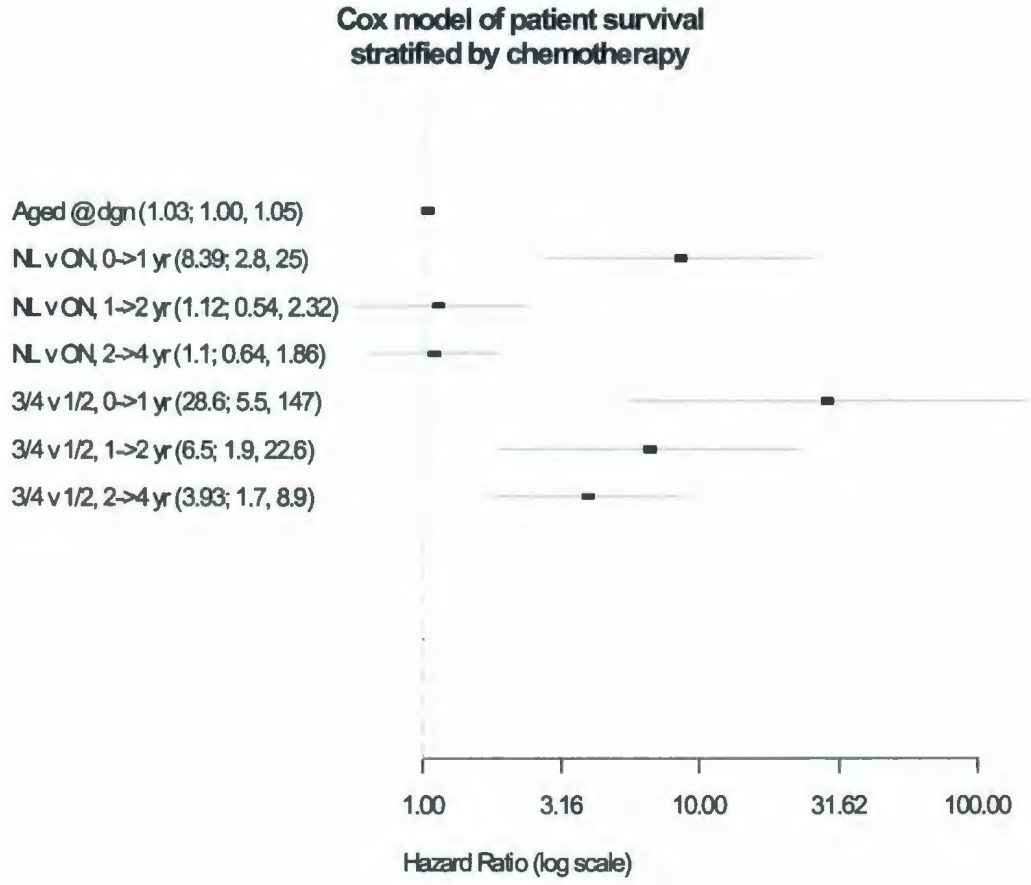


Figure 5. Cox Proportionate Regression Analysis, Survival Newfoundland vs. Ontario

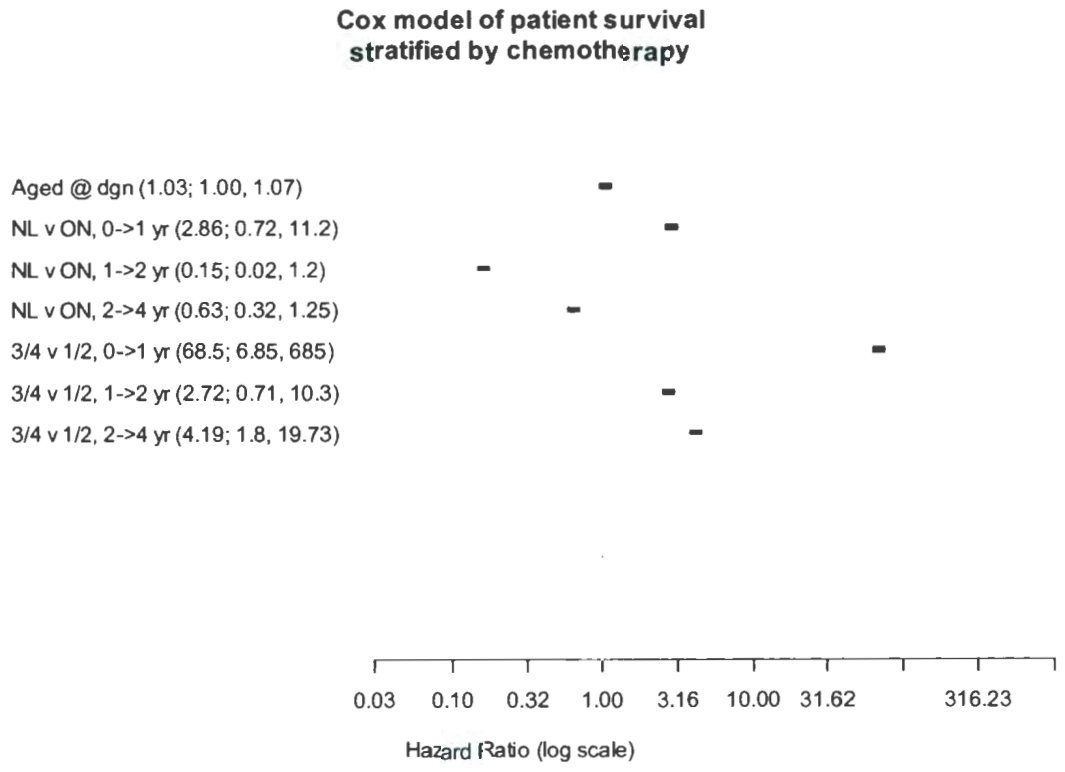


Figure 6. Cox Proportionate Regression Analysis, Survival Newfoundland vs. Ontario (proxy consents excluded)

APPENDIX A – DATA EXTRACTION FORM

Name: _____, _____
LAST **FIRST**

Sex:

☐	Male
☐	Female
☐	Unknown

Date of Birth:

DD	
MM	
YYYY	

CLINICAL DIAGNOSIS AND TREATMENT - BASELINE

1. Place of Diagnosis:

Name	City or Town	MOH Code

2. Site of Cancer(s):

Cancer	Site Name	4-Digit ICD-9 Code
1.		
2.		
3.		
4.		
5.		

3. Date of initial diagnosis of colorectal cancer (please use histological date i.e. Date of pathology report):

DD	
MM	
YYYY	
☐	Unknown

4. Preoperative symptoms (please check all that apply):

☐	None, asymptomatic (detected by screening)
☐	Bleeding
☐	Constipation
☐	Diarrhea
☐	Pain
☐	Weight Loss
☐	Other Please Specify: _____
☐	Unknown

5. Method of colorectal cancer diagnosis:

□	Colonoscopy
□	Rigid sigmoidoscopy
□	Flexible sigmoidoscopy
□	Sigmoidoscopy NOS
□	Barium enema
□	Chest x-ray
□	Chest CT scan
□	Abdominal/Pelvic CT scan
□	Ultrasound
□	Other Please Specify: _____
□	Unknown

6. Type of definitive surgery for colorectal cancer (SEER coding used) (please attach all pathology and operative reports for this colorectal cancer):

□	None
□	Local tumour destruction, i.e. laser, electrocautery
□	Local surgical excision with specimen i.e. polypectomy, snare
□	Segmental resection, not hemi-colectomy i.e. cecectomy, appendectomy, sigmoidectomy, partial resection of transverse colon and flexures, iliocolectomy, enterocolectomy, partial colectomy, NOS □ Low Anterior
□	Hemi-colectomy, but not total. Right or left, must include a portion of transverse colon
□	Abdominoperineal resection
□	Total or subtotal colectomy, not rectum
□	Colectomy NOS
□	Segmental colectomy + other organs (*Please specify below)
□	Hemi-colectomy + other organs (*Please specify below)
□	Total or subtotal colectomy or + other organs (*Please specify below)
□	Abdominoperineal resection + other organs (*Please specify below)
□	Other Please Specify: _____
□	Unknown

*If Other Organs were removed:

□	Spleen
□	Gallbladder
□	Appendix (not a part of colon resection)
□	Stomach
□	Pancreas
□	Small intestine
□	Liver
□	Abdominal Wall, Retroperitoneum
□	Adrenal
□	Kidney
□	Bladder
□	Urethra
□	Ovary
□	Uterus
□	Vagina
□	Prostate

☐	Other Please Specify: _____
☐	Unknown

7. If no surgery was performed, reason:

☐	Patient Refusal
☐	Antecedent Death
☐	Medical Contraindication
☐	Other Please Specify: _____
☐	Unknown

8. Summary of disease from pathology report only:

pT	
pN	
pM	
☐	Unknown

9. If pN1 or greater (*if pN0 pls. go to #14*):

Number of Nodes Reported	
Number of Nodes Positive	

10. Pathological Stage of disease (from all information available):

T	
N	
M	
☐	Unknown

11. Stage of disease at initial diagnosis (from all information available)

☐	Stage 0
☐	Stage 1
☐	Stage 2
☐	Stage 3
☐	Stage 4
☐	Unknown

12. Other Pathology Identified:

Yes	**Type:**	**No**	**Unknown**
☐	☐ Crohn's Disease ☐ Ulcerative colitis ☐ Diverticulosis/it is ☐ Perforation ☐ Other Please Specify: _____	☐	☐

13. Preoperative CEA (carcinoembryonic antigen):

☐	Yes _____ ug/L
☐	No
☐	Unknown

14. Date of Blood Test for Preoperative CEA:

DD	
MM	

YYYY	
☐	Unknown

15. Date of surgery:

DD	
MM	
YYYY	
☐	Unknown

16. Primary surgery hospital:

Name	City or Town	MOH Code

17. Operating Surgeon:

18. Operative findings, local (residual tumour) (please obtain information from the operative report and/or the discharge summary)

☐	Tumour *not entirely* resected
☐	Tumour *entirely* resected
☐	Unknown

19. Operative findings, Distant (pls. obtain info. from the operative report &/or the discharge summary):

No Metastatic Disease	Metastatic Disease Found	Type of Metastatic Disease Found:	Unknown
☐	☐	☐ Ascites ☐ Mesenteric nodes, other than in mesentery of planned resection ☐ Liver ☐ Lung ☐ Omentum ☐ Abdominal wall ☐ Ovaries ☐ Bone ☐ Peritoneum ☐ Mesentery ☐ Other Please Specify: _____	☐

20. Margins:

Negative	Positive	Unknown
☐	☐ Proximal ☐ Distal ☐ Radial ☐ Other Please Specify: _____	☐

(CONCURRENT) PRIMARY DIAGNOSIS #_____ Please see Ques.#2 to identify Site #.
(Please complete a separate form for each primary diagnosis).

21. Grade of Primary:

Well Differentiated	Moderately Differentiated	Poorly Differentiated	Undifferentiated	Unknown
☐	☐	☐	☐	☐

22. Cell Type:

	Adenoca.
☐	NOS
☐	Mucinous
☐	Signet ring cell
☐	Other Please specify: _____
☐	Unknown

23. Vascular Invasion:

☐	Yes
☐	No
☐	Unknown

24. Lymphatic Invasion:

☐	Yes
☐	No
☐	Unknown

25. Perineural Invasion:

☐	Yes
☐	No
☐	Unknown

26. Patient Enrolled in a clinical trial:

☐	Yes Please Specify: ______________________
☐	No
☐	Unknown

27. Oncologist(s): ☐ Not assessed

1.	3.
2.	4.

28. Chemotherapy given (If yes, pls. complete Treatment table below & attach all flow sheets):

Yes	Type	No (Pls. go to #32)	Unknown
☐	☐ Adjuvant ☐ Palliative	☐	☐

Height	**Weight**	**B.S.A.**
______.___ cm ☐ Unknown	______.___ kg ☐ Unknown	___.___ m2 ☐ Unknown

CHEMOTHERAPY TREATMENT (For cyclic chemo., pls. report each cycle *separately* e.g. 1, 2, 3, 4)

FOR BASELINE DIAGNOSIS

First Course Only. **Flow sheet attached Y/N:** ____________

Cycle #	Name	Drug Dosage	IV/PO	Days Given	Date Given	Palliative Therapy Response
_____	____________ ____________ ____________ ____________	________ ________ ________ ________	_____ _____ _____ _____	________ ________ ________ ________	________ ________ ________ ________	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	____________ ____________ ____________ ____________	________ ________ ________ ________	_____ _____ _____ _____	________ ________ ________ ________	________ ________ ________ ________	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	____________ ____________ ____________ ____________	________ ________ ________ ________	_____ _____ _____ _____	________ ________ ________ ________	________ ________ ________ ________	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	____________ ____________ ____________ ____________	________ ________ ________ ________	_____ _____ _____ _____	________ ________ ________ ________	________ ________ ________ ________	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

_____	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

32. Radiation given (*please attach all flow sheets, where available*):

Yes	Type	No	Unknown
☐	☐ Adjuvant ☐ Palliative	☐	☐

CLINICAL FOLLOW-UP SINCE BASELINE DIAGNOSIS

33. **New** cancer event in the four years following the initial diagnosis:

Yes	Check off as many that apply and complete the corresponding section.	None	Unknown
☐	☐ Locoregional Recurrence ☐ Distant Recurrence ☐ Other Non-Colorectal Primary ☐ Colorectal Primary ☐ Death	☐	☐

34. Patient Enrolled in a clinical trial since baseline:

☐	Yes Please Specify: ______________________________
☐	No
☐	Unknown

FIRST LOCOREGIONAL RECURRENCE

☐ None (go to #43)

If applicable, please attach copies of documentation (i.e. radiology reports, clinic notes, pathology reports, operative reports, etc.) with the date of first detection of site(s) of first locoregional recurrence(s).

35. Sites of involvement at time of first locoregional recurrence *(please check off all that apply):*

	Site	First Diagnosed Day	First Diagnosed Month	First Diagnosed Year
☐	Anastomosis			
☐	Mesentery			
☐	Abdominal Wall (not incisional)			
☐	Incisional			
☐	Pelvis			
☐	Other Please specify: _____			
☐	Unknown			

36. Surgery for locoregional recurrence:

☐	Yes Please specify: _____
☐	No
☐	Unknown

37. Treatment for locoregional recurrence:

☐	Yes
☐	No
☐	Unknown

38. Oncologist(s): ☐ Not assessed

1.	3.
2.	4.

39. Chemotherapy given (If yes, pls. complete Treatment table below & attach all flow sheets):

Yes	Type	No (Pls. go to #A6)	Unknown
☐	☐ Adjuvant ☐ Palliative	☐	☐

Height	**Weight**	**B.S.A.**
_____.___ cm ☐ Unknown	_____.___ kg ☐ Unknown	___.___ m2 ☐ Unknown

CHEMOTHERAPY TREATMENT (For cyclic chemo., pls. report each cycle *separately* e.g. 1, 2, 3, 4)

FOR FIRST LOCOREGIONAL RECURRENCE

First Course. **Flow sheet attached Y/N:**

____

Cycle #	Name	Drug Dosage	IV/PO	Days Given	Date Given	Palliative Therapy Response
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
	____	____	____	____	____	☐ Progression

_____	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____	_____ _____ _____	☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

40. Radiation given (*please attach all flow sheets, where available*):

Yes	Type	No	Unknown
☐	☐ Adjuvant ☐ Palliative	☐	☐

41. Other treatment given (*please attach all documents*):

☐	Yes
☐	No
☐	Unknown

42. Other Locoregional recurrence sites after the first site was identified *(please check off all that apply):*

	Site	Diagnosed Day	Diagnosed Month	Diagnosed Year
☐	Anastomosis			
☐	Mesentery			
☐	Abdominal Wall (not incisional)			
☐	Incisional			
☐	Pelvis			
☐	Other Please specify: _____ _____			
☐	Unknown			

FIRST DISTANT RECURRENCE

☐ None (go to #51)

If applicable, please attach copies of documentation (i.e. radiology reports, clinic notes, pathology reports, operative reports, etc.) with the date of first detection of site(s) of first distant recurrence(s).

43. Sites of involvement at time of first distant recurrence *(please check off all that apply):*

	Site	First Diagnosed Day	First Diagnosed Month	First Diagnosed Year
☐	Liver			
☐	Lung			
☐	Bone			
☐	Ascites			
☐	Non-mesenteric lymph nodes (except supraclavicular) Please specify: _____ _____			
☐	Supraclavicular nodes			
☐	Brain			

☐	Skin, except incision Please specify: _____			
☐	Adrenal gland			
☐	Other Please specify: _____			

44. Surgery for distant recurrence:

☐	Yes Please specify: _____
☐	No
☐	Unknown

45. Treatment for distant recurrence:

☐	Yes
☐	No
☐	Unknown

46. Oncologist(s): ☐ Not assessed

1.	3.
2.	4.

47. Chemotherapy given (If yes, pls. complete Treatment table below & attach all flow sheets):

Yes	Type	No (Pls. go to #B6)	Unknown
☐	☐ Adjuvant ☐ Palliative	☐	☐

Height	**Weight**	**B.S.A.**
_____.___ cm ☐ Unknown	_____.___ kg ☐ Unknown	___.___ m2 ☐ Unknown

CHEMOTHERAPY TREATMENT (For cyclic chemo., pls. report each cycle *separately* e.g. 1, 2, 3, 4)

FOR FIRST DISTANT RECURRENCE

First Course. **Flow sheet attached Y/N:**

_____

Cycle #	Name	Drug Dosage	IV/PO	Days Given	Date Given	Palliative Therapy Response
_____	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	____ ____ ____ ____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

48. Radiation given (*please attach all flow sheets, where available*):

Yes	Type	No	Unknown
☐	☐ Adjuvant ☐ Palliative	☐	☐

49. Other treatment given (*please attach all documents*):

☐	Yes
☐	No
☐	Unknown

50. Other Distant recurrence sites after the first site was identified *(please check off all that apply):*

	Site	Diagnosed Day	Diagnosed Month	Diagnosed Year
☐	Liver			
☐	Lung			
☐	Bone			
☐	Ascites			
☐	Non-mesenteric lymph nodes (except supraclavicular) Please specify: _____ _____			
☐	Supraclavicular nodes			
☐	Brain			
☐	Skin, except incision Please specify: _____			
☐	Adrenal gland			
☐	Other Please specify: _____			

OTHER NON-COLORECTAL PRIMARY(S)

☐ None (go to #55)

51. Hospital of Diagnosis:

Name	City or Town	MOH Code

52. Sites of new Non-Colorectal Primary Cancer(s) since the initial diagnosis of Colorectal cancer:

Cancer	Site	4-Digit ICD-9 Code
1.		
2.		
3.		
4.		
5.		

53. Date(s) of diagnosis of new Non-Colorectal Primary Cancer(s) (please use histological date):

Cancer	Day	Month	Year
1.			
2.			
3.			
4.			
5.			

54. Stage(s) of new Non-Colorectal Primary Cancer(s):

Cancer	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Unknown
1.	☐	☐	☐	☐	☐	☐
2.	☐	☐	☐	☐	☐	☐
3.	☐	☐	☐	☐	☐	☐
4.	☐	☐	☐	☐	☐	☐
5.	☐	☐	☐	☐	☐	☐

NEW COLORECTAL PRIMARY(S)

☐ None (go to #80)

55. Site of Cancer(s):

Cancer	Site Name	4-Digit ICD-9 Code	Diag. Day	Diag. Month	Diag. Year	Unknown
1.						☐
2.						☐
3.						☐
4.						☐
5.						☐

56. Preoperative symptoms (please check all that apply):

□	None, asymptomatic (detected by screening)
□	Bleeding
□	Constipation
□	Diarrhea
□	Pain
□	Weight Loss
□	Other Please Specify: _____
□	Unknown

57. Method of colorectal cancer diagnosis (check all that apply):

□	Colonoscopy
□	Rigid sigmoidoscopy
□	Flexible sigmoidoscopy
□	Sigmoidoscopy NOS
□	Barium enema
□	Chest x-ray
□	Chest CT scan
□	Abdominal CT scan
□	Ultrasound
□	Other Please Specify: _____
□	Unknown

58. Type of definitive surgery for colorectal cancer (SEER coding used) (please attach all pathology and operative reports for this colorectal cancer):

□	None (please go to #18)
□	Local tumour destruction, i.e. laser, electrocautery
□	Local surgical excision with specimen i.e. polypectomy, snare
□	Segmental resection, not hemi-colectomy i.e. cecectomy, appendectomy, sigmoidectomy, partial resection of transverse colon and flexures, iliocolectomy, enterocolectomy, partial colectomy, NOS □ Low Anterior
□	Hemi-colectomy, but not total. Right or left, must include a portion of transverse colon
□	Abdominoperineal resection
□	Total or subtotal colectomy, not rectum
□	Colectomy NOS
□	Segmental colectomy + other organs (*Please specify below)
□	Hemi-colectomy + other organs (*Please specify below)
□	Total or subtotal colectomy or + other organs (*Please specify below)
□	Abdominoperineal resection + other organs (*Please specify below)
□	Other Please Specify: _____
□	Unknown

*If Other Organs were removed:

□	Spleen
□	Gallbladder
□	Appendix (not a part of colon resection)
□	Stomach
□	Pancreas
□	Small intestine

☐	Liver
☐	Abdominal wall, Retroperitoneum
☐	Adrenal
☐	Kidney
☐	Bladder
☐	Urethra
☐	Ovary
☐	Uterus
☐	Vagina
☐	Prostate
☐	Other Please Specify: _____
☐	Unknown

59. If no surgery was performed, reason:

☐	Patient Refusal
☐	Antecedent Death
☐	Medical Contraindication
☐	Other Please Specify: _____
☐	Unknown

60. Summary of disease from pathology report only:

pT	
pN	
pM	
☐	Unknown

61. If pN1 or greater (*if pN0 pls. go to #D8*):

Number of Nodes Reported	
Number of Nodes Positive	

62. Pathological Stage of disease (from all information available):

T	
N	
M	
☐	Unknown

63. Stage of disease at initial diagnosis (from all information available)

☐	Stage 0
☐	Stage 1
☐	Stage 2
☐	Stage 3
☐	Stage 4
☐	Unknown

64. Other Pathology Identified:

Yes	**Type:**	**No**	**Unknown**
☐	☐ Crohn's Disease ☐ Ulcerative colitis ☐ Diverticulosis/it is ☐ Perforation ☐ Other Please Specify: _____	☐	☐

65. Preoperative CEA (carcinoembryonic antigen):

☐	Yes _____ ug/L
☐	No
☐	Unknown

66. Date of Blood Test for Preoperative CEA:

DD	
MM	
YYYY	
☐	Unknown

67. Date of surgery:

DD	
MM	
YYYY	
☐	Unknown

68. Primary surgery hospital:

Name	City or Town	MOH Code

69. Operating Surgeon:

70. Operative findings, local (residual tumour) (please obtain information from the operative report and/or the discharge summary)

☐	Tumour *not entirely* resected
☐	Tumour *entirely* resected
☐	Unknown

71. Operative findings, Distant (pls. obtain info. from the operative report &/or the discharge summary):

No Metastatic Disease	Metastatic Disease Found	Type of Metastatic Disease Found:	Unknown
☐	☐	☐ Ascites ☐ Mesenteric nodes, other than in mesentery of planned resection ☐ Liver ☐ Lung ☐ Omentum ☐ Abdominal wall ☐ Ovaries ☐ Bone ☐ Peritoneum ☐ Mesentery ☐ Other Please Specify: _____	☐

72. Margins:

Negative	Positive	Unknown
☐	☐ Proximal ☐ Distal ☐ Radial ☐ Other Please Specify: _____	☐

(CONCURRENT) PRIMARY DIAGNOSIS # _____ Please see Ques.#5 to identify Site #.
(Please complete a separate form for each primary diagnosis).

73. Grade of Primary:

Well Differentiated	Moderately Differentiated	Poorly Differentiated	Undifferentiated	Unknown
☐	☐	☐	☐	☐

74. Cell Type:

	Adenoca.
☐	NOS
☐	Mucinous
☐	Signet ring cell
☐	Other Please specify: _____
☐	Unknown

75. Vascular Invasion:

☐	Yes
☐	No
☐	Unknown

76. Lymphatic Invasion:

☐	Yes
☐	No
☐	Unknown

77. Perineural Invasion:

☐	Yes
☐	No
☐	Unknown

78. Oncologist(s): ☐ Not assessed

1.	3.
2.	4.

79. Chemotherapy given (If yes, pls. complete Treatment table below & attach all flow sheets):

Yes	Type	No (Pls. go to #D28)	Unknown
☐	☐ Adjuvant ☐ Palliative	☐	☐

Height	**Weight**	**B.S.A.**
______.___ cm ☐ Unknown	______.___ kg ☐ Unknown	___.___ m2 ☐ Unknown

CHEMOTHERAPY TREATMENT (For cyclic chemo., pls. report each cycle *separately* e.g. 1, 2, 3, 4)

FOR NEW CRC PRIMARY

First Course **Flow sheet attached Y/N:**

Cycle #	Name	Drug Dosage	IV/PO	Days Given	Date Given	Palliative Therapy Response
_____	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	______ ______ ______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

_____	____________ ____________ ____________ ____________	________ ________ ________ ________	_____ _____ _____ _____	________ ________ ________ ________	________ ________ ________ ________	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	____________ ____________ ____________ ____________	________ ________ ________ ________	_____ _____ _____ _____	________ ________ ________ ________	________ ________ ________ ________	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	____________ ____________ ____________ ____________	________ ________ ________ ________	_____ _____ _____ _____	________ ________ ________ ________	________ ________ ________ ________	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

79. Radiation given (*please attach all flow sheets, where available*):

Yes	Type	No	Unknown
☐	☐ Adjuvant ☐ Palliative	☐	☐

DEATH

80. Date of Death:

DD	
MM	
YYYY	

81. Cause of Death *(please attach copy of death certificate if available):*

☐	Colorectal cancer
☐	Other, No colorectal present Please specify: ______________________
☐	Other, colorectal present Please specify: ______________________
☐	Unknown

82. Autopsy performed *(please attach copy of report if available)*:

☐	Yes
☐	No
☐	Unknown

83. Location of Death:

☐	Hospital Please specify: ______________________
☐	Home
☐	Hospice Please specify: ______________________
☐	Other Please specify: ______________________
☐	Unknown

DATE OF FINAL CHART NOTE: _____

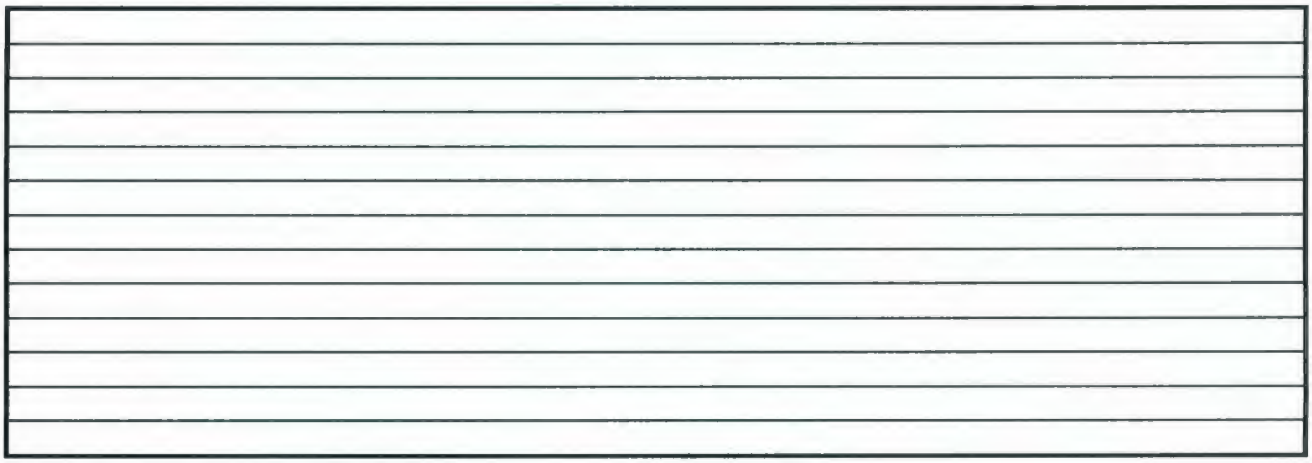
PATIENT HAS BEEN REFERRED TO THE CARE OF: DR. _____

ADDITIONAL FOLLOW-UP REQUIRED (Y/N): _____

Date form Completed: _____ _____ _____ (dd/mmm/yyyy)

Abstractor's Initials: _____ _____

ADDITIONAL NOTES:



A COMPARATIVE STUDY OF THE ADJUVANT MANAGEMENT OF AND SURVIVAL FROM COLON CANCER IN THE TWO CANADIAN PROVINCES OF NEWFOUNDLAND & LABRADOR AND ONTARIO

DEBRAH WIRTZFELD