Clinical issues in the surgical treatment of colon cancer
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Chapter 1:

General introduction and outline of the dissertation
Chapter 1

General introduction

Colorectal cancer is the third most diagnosed malignancy worldwide; with over 1,360,000 new cases diagnosed each year.\(^1\) About two thirds of these cases are cancers of the colon,\(^2\) which often have different disease biology than their rectal counterparts\(^3\) and subsequently have considerably different treatment regimens.\(^4,5\)

More than half of colon cancer patients will eventually die of their disease.\(^6\) Early detection is crucial to maximize chances of cure, as five-year survival can range from 97% to as low as 8% depending on disease stage at diagnosis.\(^7,8\) Since colon cancer is associated with both old age\(^9\) and obesity,\(^10\) nearly 60% of new cases come from the developed world,\(^11\) where many nationwide screening initiatives have been launched in the last two decades,\(^12,13\) in an effort to lower incidence rates and to provide early detection. Although successful,\(^14\) screening benefits are offset by an aging\(^15\) and increasingly obese\(^16\) and paradoxically malnourished\(^17\) population, and the fact that lower age thresholds exclude younger patients.\(^18\)

Surgical resection remains the only definitive therapy for colon cancer. Consequently, essentially all curable colon cancer cases will be treated surgically, thereby forming a large, heterogeneous and ever changing population. The clinical issues and challenges faced during the surgical treatment of colon cancer will therefore come in many forms, ranging from patient factors existing long before enrollment in surgical treatment, to factors specific to the surgical admission itself such as perioperative complications or the specifics of surgical pathology.

Setting of this dissertation

This dissertation is based around a cohort comprising all 1071 patients treated surgically for colon cancer at Massachusetts General Hospital in the 2004 through 2011 timeframe. Data on these patients was stored in an anonymized database after institutional review board approval, specifically for the purpose of the research topics described in this dissertation. Primary sources included the prospectively maintained MGH Research Patient Data Repository and MGH Cancer Registry, with the addition of further detailed information through retrospective review of admission records, pathology reports, operative reports, and all follow-up records, including those of affiliated hospitals including the Dana-Farber Cancer Institute, Brigham and Women’s Hospital, North Shore Hospital, Newton-Wellesley Hospital and the Spaulding Rehabilitation Network. The database was subsequently maintained prospectively starting 2011, frequently updating follow-up and survival status through the Social Security Death Index and patient records.
Outline of the dissertation

This dissertation navigates through clinical issues and challenges encountered during the surgical treatment of colon cancer in chronological order, looking at factors prior to surgery (parts I and II), issues surrounding surgery and the postoperative recovery period (part III) and lastly, the result of surgery which dictates further management of disease, the surgical pathology (part IV).

Part I: Baseline presentation and impact on outcomes

The first section of this dissertation discusses factors surrounding the baseline presentation of the surgically treated colon cancer patient, specifically exploring diagnosis modality, biomarker status and diagnosis-to-treatment delay. The respective interplay of these factors with outcomes is also highlighted, as they may serve as risk stratification tools prior to surgical treatment.

*Chapter 2* pays special attention to the impact of the introduction of recommended routine screening colonoscopy for patients 50 and over in the United States on the characteristics of surgically-treated colon cancer patients, assessing the magnitude of its influence on disease stage at presentation, and what this means for their eventual outcomes compared to patients diagnosed outside of screening.

On the opposite side of the spectrum, *Chapter 3* discusses patients who present in an emergency setting. These patients are by definition symptomatic, tend to have advanced disease and are examples of late detection. Emergency admissions may therefore lead to more complex and costly admissions, and worse outcomes, both in the immediate postoperative period and in the long term.

When patients do not present in an emergency situation and their status permits a complete preoperative assessment, an oft-used modality routinely included in the preoperative assessment is the measurement of serum Carcinoembryonic Antigen (CEA). CEA is a validated tumor marker that is used to detect recurrence, and *Chapter 4* explores whether the baseline CEA value can also be predictive of the eventual outcomes of colon cancer patients.

Because of the evaluation of newly diagnosed colon cancer patients, but also due to logistical reasons, a certain delay between diagnosis and surgical treatment is unavoidable and a controversial topic for colon cancer patients. *Chapter 5* aims to measure whether this treatment delay, as it currently prevails in a specialized tertiary clinical setting, has any influence on the eventual outcomes of patients.
Part II: Patient and Population Factors

There are multiple factors which impact outcomes when patients present for surgical treatment of colon cancer that are related to sociodemographic factors that can shape patient characteristics or disease presentation long before the surgeon ever sees the patient. The influence the surgeon has over these factors is therefore limited; the benefit will come mainly from identifying existing disparities in order to account for them in the future. Part II of the dissertation puts the emphasis on these population characteristics and their effect of individual patient characteristics, and the subsequent surgical management of colon cancer.

Chapter 6 focuses on the gender and ethnic disparities in this cohort, with specific interest to baseline disease on presentation and their effect on outcomes. It also analyzes the mutual interplay of gender and ethnic disparities, in the context of an ethnically mixed population in an American state that offers universal healthcare, which may serve as a case study for the nationwide transition towards universal healthcare.

Women are often seen as more compliant in screening efforts, yet for colorectal screening, early numbers show lower screening rates in women. Therefore, Chapter 7 deals with the magnitude of this gender disparity in screening compliance among women in the screening age range and how this influences staging and survival.

Another group that is subject to a widening disparity gap is the younger population, defined as patients aged under 50. This group with young-onset colon cancer is the only age group in the United States with rising incidence rates. Due to their often atypical disease and their relatively small numbers among a host of healthy peers, they present a diagnostic and therapeutic conundrum that is discussed in Chapter 8.

The last chapter in this section treats a notorious risk factor for countless malignancies: smoking. The effects of smoking are well established for the risk of developing colon cancer, but far less is known about its effects on metastatic spread when disease is already present, Chapter 9 discusses the possibility that not a history of smoking, but active smoking may be a risk factor for developing hematogenous colon cancer metastases.

Part III: Surgical Safety and Complications:

The third part of this dissertation treats aspects related to the index admission and the surgical procedure itself: as with any surgery, there are risks and there may be complications. This section is dedicated to the identification of factors that influence this risk of complications in the perioperative phase. The chapters in this section also pay special attention to the interplay of patient factors and surgical technique.
Patients who have abdominal adhesions are ubiquitous in the colon cancer population. These adhesions may lead to more complicated admissions, most likely due to primary difficulties during surgery, but also potentially due to higher rates of adhesion-related postsurgical complications. Chapter 10 therefore evaluates the impact of adhesions on both the operations and the postoperative recovery after colon cancer surgery.

One of the methods that may reduce the burden of adhesions for future procedures is the implementation of minimally invasive techniques,\textsuperscript{32} whose introduction often comes hand in hand with increasing use of surgical stapling. Laparoscopy and surgical staplers are now commonplace for countless abdominal surgeries. For colon cancer however, this introduction was delayed in many centers, owing to a reluctance towards the use of laparoscopy due to early reports of laparoscopic port metastasis,\textsuperscript{33,34} and the relatively higher learning curve with an initially high risk of conversion.\textsuperscript{35} This means that the routine use of laparoscopy is still relatively novel in the last decade and in many instances still far from standard. Chapter 11 presents the case of the introduction of laparoscopy and surgical stapling for colon cancer surgery at MGH and evaluates its effect on surgical efficiency, quality of resection, and complication rates.

The obesity epidemic in the western world raises pervasive issues in healthcare. Colon cancer is not an exception therein, and obesity is recognized as a risk factor to develop the disease.\textsuperscript{36} In addition, a high BMI will invariably complicate any abdominal surgery\textsuperscript{37} and can complicate postoperative recovery.\textsuperscript{38} For the resection of a colonic primary tumor, even minimally invasive approaches will still yield at least one larger surgical wound. Combined with the high median patient age, which leads to lower performance status and higher comorbidity rates, the added factor of obesity may create a combination that puts obese colon cancer patients at considerable risk of wound-related complications. Chapter 12 aims to shed light on this issue.

\textit{Part IV: Surgical Pathology}

Following surgery, the primary diagnosis and the baseline disease staging are determined by the surgical pathology report. Due to its decisive role in the further management of disease and prognosis, surgeons and patients alike await this verdict with great anticipation. In order to expand on known histopathological factors already in use, this last segment of the dissertation explores the prognostic value of certain elements that are already part of the recommended protocols\textsuperscript{39} for the examination of surgical specimens of the colon,
but are not actively in use as a separate factor that could play a role in subsequent treatment considerations.

One such factor is radial margin involvement (Chapter 13). While deemed an important and extensively studied prognostic factor in rectal cancer,\textsuperscript{40,41} little or no data exists on its effect on locoregional and distant recurrence in cancers of the colon.\textsuperscript{5} Similarly, the ratio of tumor-positive lymph nodes to total lymph node yield in a resection specimen, or lymph node ratio (LNR), is a pathological parameter adopted for colon cancer\textsuperscript{42-44} from primary resections with a relatively uniform field both in terms of size and nodal yield.\textsuperscript{45-49} Meanwhile, the overall length of resection and the lymph node yield vary greatly in resections for colon cancer,\textsuperscript{50,51} and it might therefore be necessary to account for variations in resection length in the calculation of LNR for colon cancer, Chapter 14 explores this by comparing the prognostic values of standard LNR values with resection length-adjusted LNR.

Variations in resection size also stem from differences in the anatomy and vascularization of different segments of the colon: primary disease can be located in very distinct lymphovascular drainage areas. Additionally, emerging evidence shows that tumor biology can also be significantly different for specific colonic segments. These variations could well mean that patterns of metastatic spread will also differ significantly for major resection regions. Chapter 15 therefore assesses whether patterns of metastatic spread are indeed different when comparing left colectomies, right colectomies and sigmoid resections.

The final chapter of this dissertation will address one last pathologic factor with a potentially important prognostic value: high-grade disease. Chapter 16 evaluates the prognostic value of the high/low grade disease dichotomy as defined in recommendations by the College of American Pathologists\textsuperscript{52} and the World Health Organization,\textsuperscript{53} which is to base this solely on a 50\% glandular formation threshold.
References


