Chapter 8
Colon Cancer

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Introduction

Globally, colorectal cancer is one of the leading causes of cancer morbidity and mortality. In the USA, it is the third leading cause of cancer and the second leading cause of cancer death; colorectal cancer will be diagnosed in approximately 141,210 Americans this year and in 1 of every 20 Americans in their lifetime [1]. More than two-thirds of these cases will originate from the colon vs. the rectum. For the purpose of this chapter, we will focus on the more common colon cancer.

Most patients present with early-stage colon cancer and are treated by surgery with curative intent. However, approximately 25% of patients present with advanced stage IV disease. A minority of these patients (20%) will be considered for surgical resection. Successful eradication of metastatic disease requires multidisciplinary management by a team of pathology, medical, surgical, and radiation oncology professionals. Although several developments in cancer biology, systemic chemotherapy, targeted therapy, surgery, diagnostic imaging, and radiation oncology have evolved over the past two decades, our purpose is not to discuss each individual entity or approach. We propose to describe here the overall impact of these

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M.A. Rodriguez et al. (eds.), *60 Years of Survival Outcomes at The University of Texas MD Anderson Cancer Center*, DOI 10.1007/978-1-4614-5197-6_8,

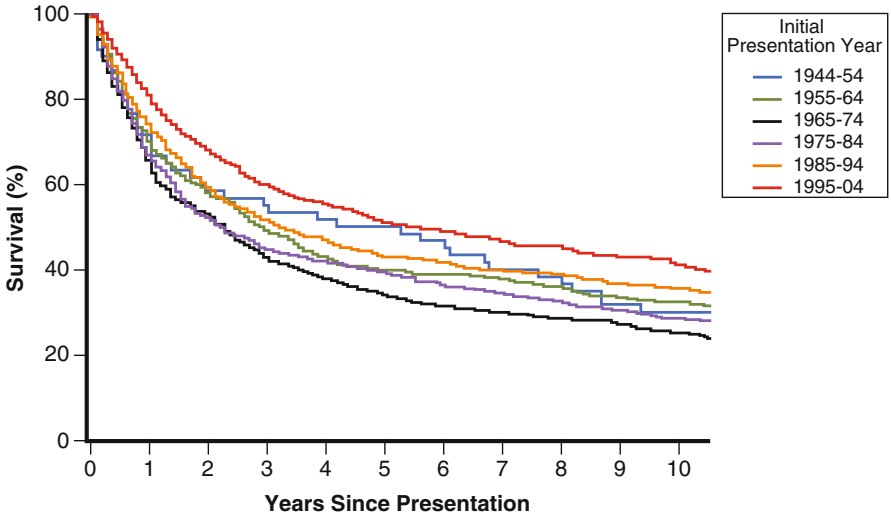

Fig. 8.1 Overall survival rates for patients with colon cancer (1944–2004) ($P < 0.0001$, log-rank test for trend).

developments on the outcome of patients with local, regional, or distant (advanced) colon cancer (Figs. 8.1, 8.2, 8.3, and 8.4) who were treated at MD Anderson Cancer Center over six decades.

Historical Perspective

An early diagnosis of colon cancer is imperative for optimal outcome. Patients with stage I disease have an excellent 5-year overall survival (OS) rate of 95% and remain on surveillance after surgical resection. Yet the majority of patients present with locally advanced disease (AJCC stage II or stage III), for which adjuvant chemotherapy is considered in order to reduce the risk of recurrence, the overall survival benefit for these patients is <10%. Patients with stage IV disease are rarely cured with chemotherapy alone and have a 5-year OS rate of 11%. However, advances in chemotherapy have dramatically improved response rates, allowing reduction in tumor burden and consideration of metastatic surgical resection. Hence, for these selected patients, the expected 5-year OS rate increases to 30–60% [2].

Risk Factors

In a minority of patients, colorectal cancer develops because of inherited genetic disorders including familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, as well as chronic inflammatory

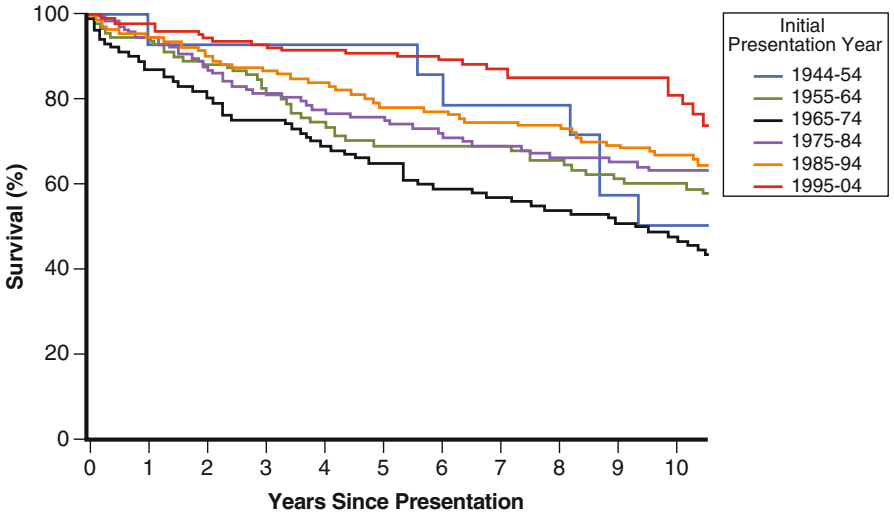

Fig. 8.2 Survival rates for patients with local (SEER stage) colon cancer (1944–2004) ($P < 0.0001$, log-rank test for trend).

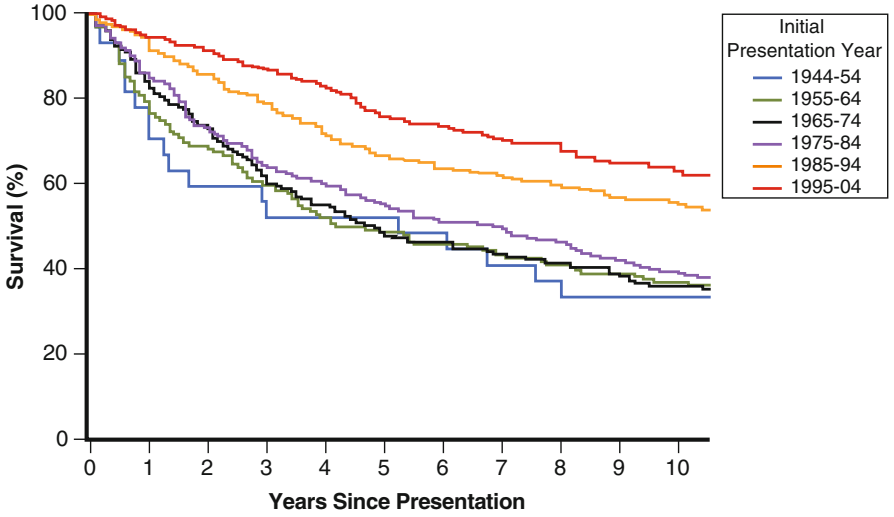

Fig. 8.3 Survival rates for patients with regional (SEER stage) colon cancer (1944–2004) ($P < 0.0001$, log-rank test for trend).

bowel diseases such as ulcerative colitis and Crohn's disease. However, in most cases, sporadic colorectal cancer is diagnosed, a multifactorial process attributed to both somatic and germline mutations. Recent literature indicates that a defect in the microsatellite DNA mismatch repair gene may result in a microsatellite instability (MSI) defect, commonly associated with HNPCC and sporadically

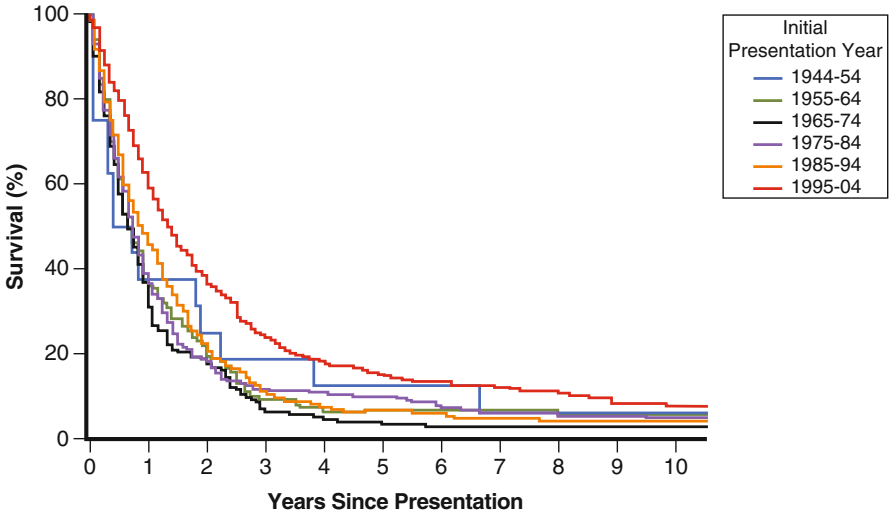

Fig. 8.4 Survival rates for patients with distant (SEER stage) colon cancer (1944–2004) ($P < 0.0001$, log-rank test for trend).

due to hypermethylation of the promoter region (associated with MSI-high or MSI-deficient mismatch repair protein).

The main limitation to use MSI testing is the fact that 12–15% of nonfamilial colorectal cancers exhibit somatically acquired MSI, generally seen in older patients with right-sided tumors. Despite this limitation in the use of MSI in predicting HNPCC, there is an important reason to consider the use of routine MSI testing. One characteristic that sporadic MSI shares with HNPCC is that patients with MSI-H tumors have improved prognosis and survival [3]. Oddly, this trend exists regardless of the relative insensitivity of MSI tumors to the agent most commonly used in the adjuvant chemotherapy setting, 5-fluorouracil (5-FU), and its analogs [4]. Retrospective studies have indicated that MSI status may affect the efficacy of 5-FU monotherapy and overall prognosis.

At MD Anderson, we have attempted to be one of the pioneers in addressing some of the limitations in the use of MSI tumor testing. We have recently begun performing MSI testing by immunohistochemical (IHC) analysis for mismatch repair protein expression in all new cases of colorectal cancer surgically resected at MD Anderson. We have not yet initiated MSI testing in patients who undergo surgical resection in outside institutions because of the logistic challenges encountered when requesting unstained slides. However, this will be an initiative in the near future.

Since sporadic MSI exists in 12–15% of all colorectal cancer, but HNPCC exists in only 1–2%, it would be very undesirable to conduct expensive germline mutation testing (>$2,000 just for hMSH2 and hMLH1 tests) in all cases of MSI. Furthermore, to do so would carry a predicted uninformative rate of >90%. Fortunately, assays are now in place that can distinguish sporadic MSI from HNPCC-associated MSI.

Polymerase chain reaction-based methylation assays and BRAF mutation testing also work very well in this regard and are routinely reported as a supplement to pathological testing in which MSI/IHC analysis has shown abnormalities warranting further evaluation [5, 6].

Treatment

Radical surgical resection with curative intent is appropriate for 80–90% of patients with colon carcinoma and is the only treatment required for most tumors limited to the bowel wall. In these cases, adequate surgical resection is the major treatment factor affecting local control and cure [7, 8].

The primary principles of surgical management in colon cancer are as follows:

- Removal of the primary tumor along with proximal, distal, and radial resection margins
- Treatment and drainage of lymphatics
- Restoration of function by anastomosis and avoidance of a permanent colostomy

These principles of surgical management have remained largely constant over the years. Surgical management must also include assessment for the presence of liver metastases. Although this is commonly accomplished by palpation and inspection, intraoperative ultrasonography of the liver has been observed to increase the likelihood of detecting small metastases. The extent of colonic resection is determined by the blood vessels that must be divided to remove the lymphatic drainage of the tumor-bearing portion of the colon with tumor-free margins. This is the primary treatment approach in patients with colon carcinoma. Resection of intermediate and principal nodes requires ligation and division of the main vascular trunks to the affected colon segment. Tumor-free margins are usually accomplished by resection of >5 cm of normal bowel proximal and distal to the tumor [9].

Excellent results have been obtained with wide mesenteric resection and adequate lymphadenectomy. In addition to the therapeutic benefits of this procedure, by prevention of local progression, lymphadenectomy is critical in the staging of colon carcinoma. In colon cancer, recovery of involved lymph nodes is the parameter most often used as an indicator of the need for adjuvant therapy within treatment guidelines applicable in the USA. Mesenteric resection should be extensive enough to harvest at least 12 lymph nodes for examination to allow for accurate staging. The number of examined lymph nodes is a process outcome that involves the patient and tumor characteristics, as well as the quality of the surgery and the pathology examination [10].

Laparoscopic techniques are widely used in the management of benign and malignant colorectal conditions. These techniques can be carried out safely and successfully, especially when conducted by an experienced laparoscopic surgeon. Laparoscopic techniques have been shown to reduce the duration of hospitalization and hasten recovery. The shortened stay associated with laparoscopic colectomy,

attributable to early postoperative feeding, has resulted in changes to the treatment of patients with colon cancer who undergo resection techniques. Available data on the extent of lymphadenectomy and resection margins achieved by oncologic laparoscopic resection indicate that this technique is comparable to open colectomy for cancer. Rates of recurrence in port sites after laparoscopic resection have ranged between 1.1% and 3.6%, similar to rates associated with laparotomy wounds in patients treated by open resection. Similarly, there are equivalent results in terms of local recurrence, distant metastases, and survival.

For those patients for whom chemotherapy must be considered, 5-FU has served as the foundation for chemotherapy for almost five decades in both adjuvant and metastatic settings, regardless of stage and purpose of therapy. Given the limited variety of treatment, modifications in intravenous 5-FU administration have been attempted, including bolus, continuous infusion (7 days), and most recently, the De Gramont method of continuous infusion over 46–48 h. The oral fluoropyrimidine capecitabine is an alternative to intravenous 5-FU, with similar toxic effects, and is currently approved in early- and advanced-disease settings. Therapeutic advances outside of 5-FU were not noted until 1998, when the topoisomerase-1 inhibitor irinotecan was the first drug for metastatic colorectal cancer administration as a single agent and in combination with 5-FU [IFL (bolus 5-FU) or FOLFIRI (infusional 5-FU)]. Multiple trials have determined that irinotecan has no role in the adjuvant setting but only in the metastatic setting.

FDA approval of the third-generation platinum analog oxaliplatin in 2004 added to the treatment armamentarium. Unlike irinotecan, it is inactive as a single agent and must be given in combination with either infusional 5-FU (FOLFOX), bolus 5-FU (FLOX), or the oral fluoropyrimidine capecitabine (XELOX). Oxaliplatin has been determined to be efficacious in both early and advanced disease. The most recent treatment advances (since 2006) have focused less on traditional cytotoxic agents and more on biologic "targeted" agents, specifically the monoclonal antibodies against the vascular endothelial growth factor (anti-VEGF) bevacizumab and the epidermal growth factor receptors (anti-EGFRs) cetuximab and panitumumab. These targeted therapies work best in combination with chemotherapy and are suited at this time for the metastatic disease setting [11, 12]. Overall, these therapeutic advances have improved the response, progression-free survival, and overall survival for patients with metastatic disease.

The MD Anderson Cancer Center Experience

The intent of this chapter is to discuss the historical outcome of patients who were treated at MD Anderson for all stages of colorectal cancer. Between 1944 and 2004, a total of 20,880 patients initially presented to MD Anderson with a diagnosis of colon cancer (Table 8.1); the number of patients presenting to our institution increased linearly over this interval. Of these patients, 3,182 had no other cancers and received their first course of treatment at MD Anderson (Table 8.1).

Table 8.1 Colon cancer population

Patient demographics	No. of patients
Patients with cancer of the colon initially presenting to MD Anderson Cancer Center on or before 12/31/2004	20,880
No previous treatment	5,073
Definitive MD Anderson treatment	4,176
No other primaries except superficial skin cancers[a]	3,182

[a]Survival calculated for this subgroup of 3,182 from initial presentation at MD Anderson

Table 8.2 Patients with colon cancer treated at MD Anderson, 1944–2004

	SEER stage at presentation					
	In situ	Local	Regional	Distant	Unstaged	Total
Decade	[No. (%) of patients]					
1944–1954	1 (1.7)	14 (23.3)	27 (45.0)	16 (26.7)	2 (3.3)	60 (100.0)
1955–1964	3 (0.8)	91 (25.6)	144 (40.4)	113 (31.7)	5 (1.4)	356 (100.0)
1965–1974	3 (0.7)	102 (22.7)	162 (36.1)	180 (40.1)	2 (0.4)	449 (100.0)
1975–1984	5 (0.8)	114 (18.9)	216 (35.8)	263 (43.6)	5 (0.8)	603 (100.0)
1985–1994	0 (0)	143 (18.5)	284 (36.7)	332 (42.9)	14 (1.8)	773 (100.0)
1995–2004	3 (0.3)	147 (15.6)	350 (37.2)	418 (44.4)	23 (2.4)	941 (100.0)
Total	*15 (0.5)*	*611 (19.2)*	*1,183 (37.2)*	*1,322 (41.5)*	*51 (1.6)*	*3,182 (100.0)*

SEER Surveillance, Epidemiology, and End Results program

Among these 3,182 patients over this 60-year period, 611 (19.2%) had local disease, 1,183 (37.2%) had regional disease, and 1,322 (41.5%) presented with metastatic disease. There is an evident trend from seeing more patients with locoregional disease (23.3% vs. 15.6%) to seeing those with more distant disease (26.7% vs. 44.4%), which probably reflects the fact that more patients with local disease are receiving treatment in outside institutions, resulting in our seeing the more advanced cases (Table 8.2).

For all stages, the 5-year OS rates appear to have remained fairly stagnant, but clear improvement was seen in 10-year OS (30–41.1%) for all patients. The greatest improvements in 5-year OS were notably in the past two decades for regional disease (51.9–75.6%) and distant disease (12.5–15.2%), likely due to modifications in adjuvant and distant chemotherapy as well as to surgical approaches.

It should be noted again that for the 60-year duration, from 1944 to 2004, innovations in chemotherapy for colon cancer were few. Thus, many significant chemotherapeutic developments of this past decade are not truly visualized in these data.

Conclusions

Over the past six decades, we have seen exponential growth in patients treated for colon cancer at our institution for both early and advanced disease. During this period, we have seen treatment developments expand beyond 5-FU alone to include

four other chemotherapy agents. We have also seen great advances in surgical techniques as well as in genetic and molecular testing. We have moved beyond the standard chemotherapeutic cytotoxic agents and are focused on biologic agents that are created as inhibitors of various receptors or ligands involved in colon carcinogenesis. We envision that this methodology will continue to evolve as various molecular markers are validated as predictive for efficacy of therapy. Colon cancer treatment has manifested as one of the most advanced fields in oncology. The landscape continues to change in its treatment, and it is presumed that MD Anderson Cancer Center will continue to evolve with all future methodology.

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