12-14-2012

Evaluation of the Survival Effect for Various Treatment Modalities Among Stage II and III Rectal Cancer Patients in California, 1994-2009

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EVALUATION OF THE SURVIVAL EFFECT FOR VARIOUS TREATMENT MODALITIES AMONG STAGE II AND III RECTAL CANCER PATIENTS IN CALIFORNIA, 1994-2009

By

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A Dissertation in Partial Fulfillment of the Requirements for the

Degree of Doctor of Public Health in Epidemiology

December 14, 2012

Each person whose signature appears below certifies that this dissertation, in his/her opinion, is adequate in the quality as a dissertation for the degree of Doctor of Public Health.

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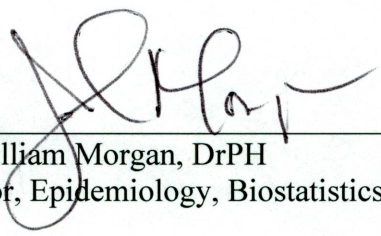

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ABSTRACT OF THE DISSERTATION

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Background: European trials evaluating the effect of preoperative (PreOP) versus postoperative chemoradiotherapy (PostOP CRT) found no survival benefit. However, the effect of a change from PostOP to PreOP CRT has not been evaluated in a population-based setting. We sought to evaluate multimodal treatment changes and overall survival for perioperative (PeriOP) CRT versus surgery alone and for PreOP versus PostOP CRT from 1994 through 2009 among patients receiving radical surgery for stage II and III rectal cancer (RC).

Patients and Methods: We conducted a nonconcurrent cohort study evaluating demographic predictors of multimodal therapy for stage II and III RC using the diverse California Cancer Registry population-based data. First, we compared patients who received only surgery versus those receiving surgery plus PeriOP CRT. Second, we compared patients who received PreOP CRT with those receiving PostOP CRT. Cox proportional hazards regression was used to assess survival over 192 months in both

study groups, adjusting for date of surgery, stage, age, gender, race/ethnicity, and socioeconomic status (SES).

Results: The Cox proportional hazards regression analysis showed that PeriOP CRT was associated with lower mortality, and the hazards ratio (HR) decreased with each time period (1994-1997: HR=0.73, 0.65-0.83; 1998-2001: HR=0.66,0.60-0.73; 2002-2005: HR=0.55, 0.49-0.61; and 2006-2009: HR=0.36, 0.31-0.43) ($p_{trend}<0.0001$). For PreOP versus PostOP CRT, our findings showed a stepwise increase (OR, 95% CI) in the use of PreOP CRT across three time-periods (1994-1997: OR=0.07, 0.06-0.08; 1998-2005: OR=0.33, 0.29-0.36; 2006-2009: OR=1) which was concomitant with publication of findings from European trials. However, we did not find a clear survival benefit for PreOP versus PostOP CRT.

Conclusions: Younger age-groups were more likely to receive PeriOP and PreOP CRT. The same was true for males compared to females. Survival was significantly better among patients receiving PeriOP CRT versus surgery alone, and the survival benefit increased over the time-period of our study, suggesting CRT procedures have been modified over time. Our study identified a clear shift in timing of PeriOP CRT from PostOP to PreOP. However, we found no clear support for a survival benefit associated with this shift. Our findings are in line with the results from clinical trials.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGMENTS

I could not have completed my dissertation without the support and encouragement of many people. First of all, I would like to express my gratitude to my dissertation committee: Dr. Kazanjian, a surgical oncologist who inspired me in choosing this topic; Dr. Morgan, an epidemiologist who gave me the opportunity to use the statewide California Cancer Registry data; and Dr. Raymond Knutsen, Chair of my committee: I am especially grateful for his invaluable guidance, unreserved commitment, and continued encouragement throughout my dissertation.

Secondly, I would express my thanks and appreciation to my co-authors: Prof. Oda and Prof. Shavlik who as biostatisticians explained the methodological intricacies of the study, and Dr. Synnove Knutsen, who as Department Chair gave me accurate advice, exposed me to the art of epidemiological analyses, and encouraged me to pursue excellence throughout my study.

Thirdly, I would like to thank to my friends in Loma Linda University who have given me their careful advice and thoughtful comments. Without their friendship I could not have enjoyable life in the United States where is far away from my home country.

Lastly and most importantly, I very much appreciate their unconditional love and prayers from my parents. Their belief in me gave me courage to persevere in my study. I am also immensely thankful to our heavenly Father for his constant love, guidance and protection against all kinds of difficulties. To these and many others who have supported me, once again I express my sincere gratitude. May all the praise and glory be to God who makes all things possible.

CHAPTER 1

INTRODUCTION

A. Statement of the Problem

In 2012, an estimated 40,290 new rectal cancer (RC) cases will be diagnosed among Americans (Siegel, Naishadham, & Jemal, 2012), while the estimate is 4,235 new diagnoses and 935 deaths for California (California Cancer Facts & Figures 2012). During the 1990's, the United States National Institutes of Health Consensus Conference (NIH Consensus Conference, 1990) and the German Cancer Society Consensus Conference (Junginger, Hossfeld, Sauer, & Hermanek, 1999) recommended the use of postoperative (PostOP) chemoradiotherapy (CRT) for Stage II and III RC. However, current National Comprehensive Cancer Network (NCCN) guidelines (National Comprehensive Cancer Network, 2012) recommend a series of multimodality therapies which consist of preoperative (PreOP) radiation therapy (RT) with concurrent chemotherapy, transabdominal resection, and PostOP chemotherapy within six months for stage II and III RC. These recommendations resulted from reports from several European trials during the last twenty years, particularly a Swedish rectal cancer trial (Swedish Rectal Cancer Trial, 1997) and a German rectal cancer study (Sauer, Becker, & Hohengerger, 2004).

B. Purpose of the Study

While it is reasonable to assume that outcome improvements along with current NCCN guidelines (National Comprehensive Cancer Network, 2012) have prompted changes in the treatment of stage II and III RC, survival benefits of these changes have not been adequately tested in a large-scale population-based setting. Thus, we sought to

conduct a non-concurrent cohort study to evaluate survival benefits of perioperative (PeriOP, PreOP and/or PostOP) CRT *versus* surgery alone and PreOP CRT *versus* PostOP CRT, adjusting for age, gender, race/ethnicity, and socioeconomic status (SES), from 1994 through 2009 among patients receiving radical operations for stage II and III RC using the diverse California population.

C. Hypotheses

1. Perioperative Chemoradiotherapy Versus Surgery Alone

a. Null hypothesis: There is no difference in survival between perioperative chemoradiotherapy (PeriOP CRT) and surgery alone among patients receiving radical surgery for stage II and III RC.

b. Alternative hypothesis: PeriOP CRT is associated with better survival than surgery alone among patients receiving radical surgery for stage II and III RC.

2. Preoperative Chemoradiotherapy Versus Postoperative Chemoradiotherapy

a. Null hypothesis: There is no difference in survival between preoperative (PreOP) CRT and postoperative (PostOP) CRT among patients receiving radical surgery for stage II and III RC.

b. Alternative hypothesis: PreOP CRT is associated with better survival than PostOP CRT among patients receiving radical surgery for stage II and III RC.

D. Research Questions

1. Perioperative Chemoradiotherapy Versus Surgery Alone

Two Research Questions are addressed:

a. What factors are associated with receiving perioperative chemoradiotherapy (PeriOP CRT) compared to surgery alone among stage II and III RC patients, adjusting for age, gender, race/ethnicity and socioeconomic status (SES)?

b. Is there a survival difference for PeriOP CRT *versus* surgery alone among stage II and III RC patients, adjusting for date of surgery, age, gender, race/ethnicity and SES?

2. Preoperative Chemoradiotherapy Versus Postoperative Chemoradiotherapy

Two research questions are addressed:

a. Are there any changes from postoperative (PostOP) to preoperative chemoradiotherapy (PreOP CRT) practices among stage II and III RC patients over the time-period 1994-2009 (i.e., 1994-1997, 1998-2005, and 2006-2009), and by age, gender, race/ethnicity and SES?

b. Is there a survival difference for PreOP *versus* PostOP CRT among stage II and III RC patients, adjusting for date of surgery, age, gender, race/ethnicity and SES?

E. Significance to Epidemiology

Colorectal cancer (CRC) incidence rates have increased in economically transitioning countries over the past decade (Center, Jemal, Smith, & Ward, 2009; Center, Jemal, & Ward, 2009) though, CRC mortality rates have decreased in long-standing developed countries, possibly because of effects of preventive measures like CRC screening (Center, Jemal, Smith, et al., 2009; Edwards et al., 2010). CRC is currently the third leading cause of cancer deaths among both females and males in the

United States with a 5-year survival rate of 68% nationally (Siegel, Naishadham, & Jemal, 2012).

NCCN guidelines (National Comprehensive Cancer Network, 2012) with standard treatments for cancer are different depending on TNM staging. TNM staging for colon and RC is defined together; however, there are outcome differences between colon cancer and RC. For example, the locoregional recurrence is more common for RC than colon cancer (Rajput & Bullard Dunn, 2007; Weiser et al., 2005; Wiig, Larsen & Giercksky, 2005), most likely because of the proximity to pelvic structures, absence of serosa, and technical challenges encountered in obtaining wide surgical margins.

RC incidence and mortality rates differ according to demographic factors like age, gender, race/ethnicity, and SES. These differences may, at least in part, be explained by demography associated treatment selections which in turn affect survival. It is, therefore, of interest to assess any association between demographic variables and multimodality treatment.

CHAPTER 2

LITERATURE REVIEW

A. Introduction

In 2008, more than 1.2 million new colorectal cancer (CRC) cases and 608,000 CRC deaths were estimated world-wide (Jemal, Bray, Center, Ferlay, Ward, et al., 2011). Incidence rates of CRC vary markedly worldwide, with rates per 100,000 for the 1998-2002 periods ranging from 3.6 and 4.1 among females and males, respectively, in Karunagappally, India to 39.5 for females in New Zealand and 59.1 for males in the Chech Republic (Center, Jemal, Smith, & Ward, 2009). Over the past decade, CRC incidence rates have been increasing in economically transitioning countries like the Czech Republic and Slovakia, and in several areas historically at low risk, including Spain and a number of countries in Eastern Asia and Eastern Europe (Center, Jemal, Smith, et al., 2009). The incidence rates in males in the Czech Republic and Japan have already exceeded the peak incidence observed in the United States and other long-standing developed nations like Canada and Australia where rates are stabilizing (Center, Jemal, Smith, et al., 2009; Center, Jemal, & Ward, 2009). These unfavorable trends are thought to reflect a combination of factors, including changes in dietary pattern, obesity, and an increased prevalence of smoking (Center, Jemal, Smith, et al., 2009; Center, Jemal, & Ward, 2009).

The United States is the only country in which CRC incidence has decreased significantly among both females and males in recent years, possibly due to favorable changes in risk factors/lifestyle habits as well as early detection of precancerous lesions

by CRC screening and removal of these (Center, Jemal, Smith, & Ward, 2009; Edwards et al., 2010).

CRC is projected to be the second leading cause of cancer death in the United States in 2012, ranking number three among both females and males, and producing an estimated 51,690 deaths (25,220 females and 26,470 males), nationwide. In the same year, it is estimated that there will be 143,460 (70,040 females and 73,420 males) new CRC diagnoses of which 40,290 (16,790 females and 23,500 males) are new rectal cancer (RC) diagnoses among Americans (Siegel, Naishadham, & Jemal, 2012). In California for 2012, the expected numbers of new CRC cases are 14,530 (7,000 females and 7,530 males), resulting an estimated 5,120 deaths (2,505 females and 2,615 males) (California Cancer Facts & Figures 2012). Of these, it is estimated that 4,235 will be RC (1,785 females and 2,450 males) and 935 (405 females and 535 males) will die from it (California Cancer Facts & Figures 2012). With a 66% five-year survival rate, CRC has a poorer prognosis than breast (91%) and prostate cancers (100%), respectively, in California (California Cancer Facts & Figures, 2012).

B. Character of Rectal Cancer

1. Anatomy of Rectum

Rectal cancer (RC) originates within 12 cm proximal from the anal verge (Graff, 2010; Kapiteijn et al., 2001; Nelson et al., 2001) on the same level as the superior rectal valve (i.e., valves of Houston). The colon and upper one third of the rectum are covered by serosa (i.e., intraperitoneal), however, the middle and lower portions of the rectum lack any serosa (i.e. extraperitoneal) (Koshinski, Habr-Gama, Ludwig, & Perez, 2012). Pelvic recurrence is more common for rectal than colon cancer (Rajput & Bullard

Dunn, 2007; Weiser et al., 2005; Wiig, Larsen, & Giercksky, 2005), in part because of the proximity to pelvic structures, the absence of serosa, and technical challenges encountered in obtaining wide surgical margins. The Dutch Colorectal Cancer Group (Kapiteijn et al., 2001) reported that the risk of recurrence of rectal cancer partly depends on tumor location relative to the anal verge; local recurrence rates were particularly low when the tumor was located more than 10.1 cm from the anal verge, and no significant difference was observed between patients who received radiation therapy (RT) and surgery, or those who received surgery alone. Thus, treatment for RC depends on determination of tumor location by rigid sigmoidoscopy (Schoellhammer, Gregorian, Sarkisyan, & Petrie, 2008).

2. Risk Factors

Dietary and lifestyle factors may play major roles in the etiology of RC. Studies have indicated that intake of high energy foods (Giovannucci & Goldin, 1997), red or processed meats (Larsson & Wolk, 2006; Norat et al., 2005), and alcohol (Moskal, Norat, Ferrari, & Riboli, 2007) are associated with an increased colorectal cancer (CRC) risk. Higher intake of fruit and vegetables, however, is associated with a moderately reduced risk (Koushik et al., 2007; Riboli & Norat, 2003). Other studies have indicated that insulin, iron, and refined sugars are possible risk factors for CRC, while whole grains, antioxidants, and phytochemicals may be protective, but the evidence is not conclusive, and further studies are needed (Boyle & Levin, 2008). Some studies have reported that obesity (Dai, Xu, & Niu, 2007; Larsson & Wolk, 2007; Moghaddam, Woodward, & Huxley, 2007; Renehan, Tyson, Egger, Heller, & Zwahlen, 2000) and cigarette smoking (Liang, Chen, & Giovannucci, 2009; Lüchtenborg, White, Wilkens,

Kolonel, & Le Marchand, 2007; Morrison et al., 2011) are associated with increased CRC risk, while both long term use and in higher doses of NSAIDS (non-steroidal anti-inflammatory drugs), particularly aspirin, may be associated with reduced CRC risk (Chan et al., 2005; Flossmann & Rothwell, 2007; Jacobs et al., 2007; Larsson, Giovannucci, & Wolk, 2006). However, the use of NSAIDS for patients with high CRC risk, such as familial adenomatous polyposis (FAP), requires supervision and close follow-up by physicians because of possible serious side effects. Current smoking has been found to increase the risk of colon cancer mortality by 50% and the risk of rectal cancer mortality by 100%, compared to never smoking (Liang, Chen, & Giovannucci, 2009; Morrison et al., 2011). The use of hormone replacement therapy (HRT) among females also is associated with reduced risk of CRC, but the risks of breast cancer and coronary heart disease are increased concomitantly (Boyle & Levin, 2008). Complex interactions between genetic, dietary, and environmental factors may modify CRC risk as well (Boyle & Levin, 2008).

3. TNM Staging for Rectal Cancer

According to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition (Edge et al., 2010), the TNM staging system for colorectal cancer (Stage 0-IV) is based on the depth of primary tumor invasion through the wall (Tis and T1-4), the number of regional lymph nodes involved (N0-2), and the absence or presence of distant metastasis (M0-1). The depth of primary tumor invasion (T) is defined as carcinoma in situ (i.e., intraepithelial or invasion of lamina propria; Tis), invasion of submucosa (T1), invasion of muscularis propria (T2), invasion through the muscularis propria into the pericolorectal tissue (T3), and penetration to the surface of the visceral

peritoneum (T4). Involvement of regional lymph nodes (N) is classified as no regional lymph node metastasis (N0), metastasis in one to three regional lymph nodes (N1), and metastasis in four or more regional lymph nodes (N2). Distant metastasis (M) is classified as no distant metastasis (M0) and distant metastasis (M1) (Edge et al., 2010). Thus, stage 0 is TisN0M0, stage I is T1 or T2N0M0, stage II is T3 or T4N0M0, stage III is T(any)N1 or N2M0, and stage IV is T(any)N(any)M1.

TNM staging for colon and rectal cancer (RC) are defined together which may pose a problem because of their outcome differences, such as the risk of local recurrence which is more common for rectal than colon cancer (Rajput & Bullard Dunn, 2007; Weiser et al., 2005; Wiig, Larsen, & Giercksky, 2005). Radiation therapy (RT) is applied to reduce local recurrence of RC, not of colon cancer. Thus, TNM staging for RC should be evaluated separately from colon cancer (Koshinski, Habr-Gama, Ludwig, & Perez, 2012).

4. Diagnostic Modalities

Precise preoperative (PreOP) evaluation (i.e., TNM staging) of rectal cancer (RC) is important in order to plan optimal treatment (Kim, N. K., Kim, M. J., Yun, Sohn, & Min, 1999). The extent of tumor spread is usually evaluated by endoscopic ultrasound (EUS), computed tomography (CT), and magnetic resonance imaging (MRI) (Kim, N. K. et al., 1999; Low et al., 2008). EUS assesses the depth of tumor invasion through the rectal wall, particularly superficial rectal cancer, and regional lymph node metastasis (Brown, 2008; Kim, N. K. et al.; Low et al., 2008); one limitation to this method is the possible over-staging of T2 lesion (Brown, 2008; Low et al., 2008). CT and MRI are used to detect the presence of distant metastasis (Kim, N. K. et al; Low et al.,

2008). Although CT has poor spatial and contrast resolution compared to MRI, CT is more practical and widely available (Low et al., 2008). Lately, multi-detector CT (MDCT) has been introduced as a new imaging modality with superior spatial resolution and a variety of imaging planes to visualize data (Low et al., 2008).

The use of endorectal coils offers high spatial resolution to MRI (Low et al., 2008). MRI is reliable to detect tumor spread into surrounding organs, particularly to mesorectal fascia which is a critical structure in total mesorectal excision (TME) for locally advanced RC (Brown et al., 2003). MRI has limitations compared to EUS due to over-staging for T1-T2 lesions, and in an attempt to solve this problem, diffusion weighted MR imaging (DWI) has been tried in a preliminary functional imaging study (Dzik-Jurasz et al., 2002; Hein et al, 2003).

EUS, CT, and MRI are unreliable in differentiating between lymph node positive or negative RC (Low et al., 2008). To address the problem, superparamagnetic iron oxide (SPIO) particles, that is, MRI contrast media, has been proposed to identify pathophysiological differences between malignant and normal lymph nodes (Low et al., 2008). SPIO have the property to selectively accumulate in the reticuloendothelial cells of normal lymph nodes when administered intravenously (Taupitz, Schmitz, & Hamm, 2003). On T2-weighted MRI images, SPIO is not taken up by malignant lymph nodes and appeared with high signal intensity, while SPIO is taken up by normal lymph nodes and appeared with low signal intensity (Koh et al., 2004).

C. Surgical Approaches for Rectal Cancer

Surgical resection is still the cornerstone of curative rectal cancer (RC) treatment method (Kosinski, Habr-Gama, Ludwig, & Perez, 2012). Although there are a variety of

surgical approaches, treatment of RC depends on the location and extent of the disease (Guillem & Cohen, 1999; Lindsetmo, Joh, & Delaney, 2008).

Abdominoperineal resection (APR) is the treatment of choice in cases in which the tumor has invaded the anal sphincter or the levator muscles. APR is *en bloc resection* (i.e., the removal of organs in one piece at one time) of the anal canal, the rectum, and the sigmoid colon, with surrounding mesentery, mesorectum and perianal soft tissue, followed by permanent end stoma (non-sphincter-preserving) (Marr et al, 2005). Low anterior resection (LAR, Hartmann's procedure) is radical proctectomy below the peritoneal reflection (mid or lower-rectum), sigmoid colectomy with colorectal or coloanal anastomosis (colon J-pouch or straight anastomosis, sphincter-preserving), or permanent colostomy (functionally non-sphincter-preserving). Thus, LAR is usually chosen for lesions in the mid to upper rectum (Kosinski, Habr-Gama, Ludwig, & Perez, 2012). Retrospective studies which compare the treatment outcomes for RC between APR and LAR reported that LAR has lower local recurrence and better overall survival rates (den Dulk et al., 2009; Pahlman et al., 2007).

In 1982, total mesorectal excision (TME) was utilized by R. J. Heald as a new fundamental principle of surgery to reduce local recurrence rates and improve function after proctectomy (Heald, Husband, & Ryall, 1982). The procedure was introduced globally in the early 1990's as the standard surgery for RC (Kapiteijn et al., 2001; Madsen & Christiansen, 1986; Martijn et al., 2003; Pahlman et al., 2007; Peeters et al., 2007). The TME approach is designed to radically dissect lymphatic drainage regions of the tumor above the levator muscles (Schrag, 1996). TME is an *en bloc resection* of the mesorectum with surrounding vascular and lymphatic vessels, fatty tissue, and mesorectal

fascia to spare the autonomic nerves (Baxter & Garcia-Aguilar, 2007; Heald, Husband, & Ryall, 1982; Lindsetmo, Joh, & Delaney, 2008), and is followed by coloanal anastomosis if anal function is intact.

D. Multimodal Therapy for Stage II and III Rectal Cancer

1. Adjuvant (Postoperative) Therapy

Until the mid 1980s, surgical resection without adjuvant therapy was the method used for locally advanced rectal cancer (RC) (Yorio, Bhadkamkar, Kee, & Garrett, 2012). However, it carried a high risk of local and distant recurrence (Gunderson et al., 2004). In 1985, the Gastrointestinal Tumor Study Group (GITSG) (Gastrointestinal Tumor Study Group, 1985) assessed the recurrence and survival rates of postoperative chemoradiotherapy (PostOP CRT) for locally advanced RC among four treatment groups (e.g., surgery alone as control, PostOP radation therapy [RT], PostOP chemotherapy, and PostOP CRT), and reported that PostOP CRT had the lowest local recurrence rate (33%), followed by PostOP chemotherapy (46%) and PostOP RT (48%), compared to surgery alone (55%), with no significant overall survival difference. In 1986, their seven year follow-up study concluded that PostOP CRT improved survival by 24% (p=0.005), compared to surgery alone (Douglas Jr., Moertel, & Mayer, 1986).

Even after the GITSG report, it was still questionable whether or not PostOP CRT was more effective in improving local recurrence rates and overall survival than PostOP RT alone, and a randomized clinical trial for T3, T4, or N1-2 RC assessed five-year recurrence rate and overall death rate between PostOP CRT *versus* PostOP RT alone (Engstrom, et al, 2010). The estimated five-year recurrence rate for PostOP CRT was 41.5% (p=0.0016), compared to PostOP RT alone (62.7%), with a 29% decrease in the

overall death rate. Thus, in 1990 the United States National Institutes of Health Consensus Conference and the German Cancer Society Consensus Conference (Junginger, Hossfeld, Sauer, & Hermanek, 1999) recommended the use of PostOP CRT for Stage II and III RC.

2. Neoadjuvant (Preoperative) Therapy

In the last 20 years, several European trial groups (Camma et al., 2000; Peeters et al., 2007; Swedish Rectal Cancer Trial, 1997; van Gijn et al., 2011) have also reported that a short-course of preoperative radiation therapy (PreOP RT) significantly reduced local recurrence and improved overall survival compared to surgery alone. For example, in early 1997, the Swedish rectal cancer trial (Swedish Rectal Cancer Trial, 1997) found that short-course PreOP RT (25 grey in five fractions in one week) reduced local recurrence and improved overall survival for RC among patients with resectable tumors compared to surgery alone. In 2005, their follow-up study (Birgisson, Pahlman, Gunnarsson, & Glimelius, 2005) reported that a short-course PreOP RT for resectable RC increased relative risk for PostOP hospitalization for subsequent bowel complications compared to surgery alone. A Dutch colorectal cancer group (Peeters et al., 2007; van Gijn et al., 2011) reported that short-course PreOP RT significantly improved 10-year survival, compared to surgery alone, among stage III RC patients showing negative resection margins (50% *versus* 40%, p=0.032). Some randomized trials reported no local recurrence and overall survival difference between short-course CRT (mainly preferred by European countries) and long-course RT (U.S. preference) (Bujko et al., 2006; Ngan et al., 2010).

Advantages of PreOP over PostOP RT include: (1) Reduced tumor volume, thereby enhancing preservation of anal sphincter and avoiding stoma (Sauer, Becker, & Hohengerger, 2004; Sauer et al., 2001; Wagman, Minsky, Cohen, Guillem, & Paty, 1998); (2) Avoidance of PostOP complications by substituting lateral lymph node dissection with PreOP RT (Cancer Support Information Center, 2004); (3) Better vascularization (oxygenation) of unaffected tissue before surgery yields superior RT response (Cancer Support Information Center, 2004; Kachnic, 2006; Sauer et al., 2004; Sauer et al., 2001; Wagman et al., 1998); and (4) Reduced radiation-induced injury from misplacement of the small bowel into the pelvis by surgical adhesions (Cancer Support Information center, 2004; Kachnic, 2006; Sauer et al., 2001; Wagman et al., 1998).

In contrast, significant disadvantage of PreOP RT include: (1) Delay of surgery by about 2 months (Cancer Support Information Center, 2004); (2) Surgical challenge because of tissue adhesion caused by RT (Cancer Support Information Center, 2004); (3) Increased probability of PostOP complications (i.e., infection) due to extended healing time of surgical scar (Cancer Support Information Center, 2004); and (4) The possibility of over-treating early-stage tumors, which otherwise would not have required adjuvant RT (Madoff, 2004; Sauer, Becker & Hohengerger, 2004).

In addition to comparing PreOP RT *versus* surgery alone, several studies have reported the effect of PreOP RT *versus* PostOP CRT and PreOP CRT *versus* PostOP CRT. The United Kingdom and Canada randomized trial group (Sebag-Montefiore et al., 2009; Stephens et al., 2010) found that short-course PreOP RT reduced local recurrence for RC, but did not improve overall survival, compared to PostOP CRT. In late 2004, a German rectal cancer study group (Sauer, Becker, & Hohengerger, 2004) reported that

PreOP CRT for stage II and III RC significantly reduced local recurrence (6% *vs.* 13%; p=0.006) and treatment-associated toxicity (27% *vs.* 40%; p=0.001) compared with PostOP CRT, although no difference was seen in overall survival. In April 2012, the 11 year follow-up of their study (Sauer et al., 2012) reported the unchanged conclusion from their first report: PreOP CRT for stage II and III RC significantly reduced local recurrence compared to PostOP CRT (7.1% *vs.* 10.1%; p=0.048). However, there was no effect on overall survival. An additional benefit of concurrent chemotherapy with RT is amplification of the tumoricidal effect (Bosset et al., 2005) and reduction of distant micrometastases (Ceelen, Van Nieuwenhove, & Fierens, 2009; Gérard et al., 2006; Sauer, Becker, & Hohengerger, 2004).

3. Additional Postoperative Chemotherapy After Preoperative Chemoradiotherapy

Current National Comprehensive Cancer Network (NCCN) guidelines (National Comprehensive Cancer Network, 2012) recommend a series of multimodality therapies which consist of preoperative radiation therapy (PreOP RT) (45-50 grey in 25-29 fractions) with concurrent chemotherapy, transabdominal resection, and postoperative (PostOP) chemotherapy within six months for stage II (T3-4, N0, M0) and III (Any T, N1-2, M0) RC (American Joint Committee on Cancer, 2002). NCCN guidelines (National Comprehensive Cancer Network, 2012) further recommend transabdominal resection and PostOP CRT only, as an alternative among patients having medical contraindications.

Current NCCN guidelines for stage II and III RC made reference to the adjuvant chemotherapy trials for stage II or III colon cancer; fluorouracil plus leucovorin with the

addition of oxaliplatin (FOLFOX4) as the standard adjuvant treatment (André et al., 2009), and capecitabine plus oxaliplatin (XELOX) as additional adjuvant therapy (Haller et al., 2011). Thus, there have been no evidence-based studies for stage II and III RC that show the effect of adjuvant (PostOP) chemotherapy after neoadjuvant (PreOP) CRT and surgical resection along with current NCCN guidelines (Yorio, Bhadkamkar, Kee, & Garrett, 2012).

E. Future Modality Approaches for Stage II and III Rectal Cancer

Future approaches of optimal treatment for RC will depend on dose and duration of PreOP RT, the combination of drugs, and treatment schedule. Recently, a four-stage modality approach (PreOP chemotherapy, CRT, surgery, and PostOP chemotherapy) has demonstrated that capecitabine/oxaliplatin (CAPOX) with cetuximub (i.e., monoclonal anti-epidermal growth factor [EGFR] therapy) as PreOP chemotherapy showed higher radiologic response and better overall survival than CAPOX alone (Dewdney et al., 2012). A study testing the effects of duration difference for PreOP chemotherapy *versus* PreOP CRT alone, PreOP CRT with two cycles of FOLFOX, and PreOP CRT with four cycles of FOLFOX found that more PreOP FOLFOX was associated with higher pathologic complete response rates with the same surgical complication rates (Garcia-Aguilar, Marcet, & Coutsoftides, 2011).

F. Association Between Demographic Variables and Multimodality Treatment

1. Age

Studies using Surveillance, Epidemiology, and End Results (SEER) Program data reported that elderly patients were less likely to receive a radical surgery and adjuvant therapy for RC (Chang, Skibber, Feig, & Rodriguez-Bigas, 2007; Schrag

et al., 2001). A study using the National Cancer Data Base also reported that younger patients were more likely to receive a surgical resection and adjuvant therapy even after adjusting for comorbidities (Esnaola, Stewart, Feig, Skibber, & Rodriguez-Bigas, 2008).

2. Gender

The incidence of RC is higher among males than females (California Cancer Facts & Figures, 2012; Siegel, Naishadham, & Jemal, 2012). According to Zutshi et al. (2012), males were more likely to receive preoperative radiation therapy (PreOP RT), even without significant differences in nodal or stage status compared to females (93% *vs.* 82%, p=0.002), and females were more likely to receive postoperative (PostOP) chemotherapy compared to males (39% *vs.* 20%, p=0.019). Other studies have found that female patients were less likely to receive any RT (including PreOP RT) for locally advanced RC (Baxter, Rothenberger, Morris, & Bullard, 2005; Mak et al., 2011).

Part of the gender difference in treatment modalities may be due to the anatomical differences between females and males. Generally speaking, males have a more narrow pelvis than females. Study findings indicate that a bulky tumor in the narrow male pelvis is harder for surgeons to remove because it is surrounded by structures such as blood vessels and organs, and instead of using medical instruments such as a stapler in males, surgeons will predominantly perform hand-sewn or straight anastomosis (23.9%), compared to females (10.8%) (p=0.018) (Zutshi, Hull, Shedda, Lavery, & Hammel, 2012).

3. Race and Ethnicity

Studies indicate that health disparities exist between race/ethnic groups that modify RC treatment modalities and thus survival (Morris, Billingsley, Baxter, &

Baldwin, 2004; Sankaranarayanan et al., 2010). Findings support the hypothesis that there are racial disparities in the treatment of gastrointestinal cancers, although most reports have been limited to comparison between non-Hispanic blacks (NHBs) and non-Hispanic whites (NHWs) (Morris, Billingsley, Baxter, & Baldwin, 2004; Morris, Wei, Birkmeyer, & Birkmeyer, 2006; Polite, Dignam, & Olopade, 2005). For example, a study group using the SEER Program data reported that African Americans patients with resectable RC were less likely to receive surgical resection with sphincter preservation and adjuvant RT compared to NHWs (Morris, Billingsley, Baxter, & Baldwin, 2004).

A recent study on RC using Los Angeles County Cancer Surveillance Program data (1988-2006) among four race/ethnic groups (Asians, Hispanics, NHBs, and NHWs) reported that Hispanic patients had highest percentage of young patients (22 %, ≤50 years of age), of immigrants (84%), and had the second highest percentage of patients in the lowest socioeconomic status (SES) (39%). Hispanic RC patients were more likely to receive RT (44%) and chemotherapy (49%), compared to NHB patients who were most likely to have distant metastasis (21%), least likely to receive radical surgery (75%), and had the highest proportion of patients in the lowest SES category (32%) (Kim, J. et al., 2011). Martinez, Chen, & Bilchik (2006) also found that Hispanics were significantly more likely to receive PreOP RT and were less likely to receive sphincter-preserving surgery than NHWs, even when adjusting for nodal status, tumor size, and T stage (1-4). At the time of diagnosis, Hispanics are more likely to present with more bulky and invasive tumors, and they may therefore need more aggressive treatment such as CRT, even at the same histopathologic stage as other race/ethnic groups.

According to our earlier findings, Hispanics are at higher risk of being diagnosed with stage II-IV colorectal cancer (CRC) compared to NHWs (Morgan et al., 2011). Since Hispanics have the lowest incidence of RC among all race/ethnic groups in California (Howlader et al., 2011), their later stage at diagnosis may indicate that RC among Hispanics is diagnosed late because access to healthcare is sub-optimal. The National Healthcare Disparities Report 2011 (U.S. Department of Health and Human Services, 2012) also indicated that Hispanics had worse quality health care and less access to health care than NHWs. These disparities may, at least partly, be explained by lack of communication skills caused by language barriers, and by lack of access to health care, including insurance and transportation problems (Martinez, Chen, & Bilchik, 2006).

Kim, J. et al. (2011) found that Asians had the highest overall RC survival among patients who received PreOP and PostOP CRT, followed by Hispanics, NHWs, and NHBs (7.7 *versus* 5.7, 5.5, and 3.4 years, respectively; $p<0.001$). Another study reported that Asians, Hispanics, and NHWs with RC had significantly better survival in multivariate analysis among patients who received PreOP RT compared to NHBs ($p=0.001$) (Lee et al., 2012).

4. Socioeconomic Status

Socioeconomic status (SES) has a great impact on life expectancy and mortality (Kim, J. M., 2012). According to the American Cancer Society, cancer mortality decreases as SES increases (Freeman, 1989). RC incidence rate ratio was 4% increased among low-income groups in Denmark (Egeberg, Halkjaer, Rottman, Hansen, & Holten, 2008), and was decreased among high-income groups in Canada and the United States (Boyd, Zhang-Salomons, Groome, & Mackillop, 1999; Mackillop, Zhang-

Salomons, Boyd, & Groome, 2000). Socioeconomic and cultural factors are associated with risk factors such as smoking and diet, and with outcomes like cancer (Nelson, 2003). Cancer screening and treatment are affected by health insurance status which is strongly associated with SES (Kim, J. M. et al., 2012).

Outcomes in race/ethnic groups will be modified when SES is included in the model, and race/ethnicity and SES may have a complex interaction (Krieger, Chen, Waterman, Rehkopf, & Subramanian, 2005). Thus, SES is a confounder of treatment outcomes that are directly dependent on access to health care (Doubeni et al., 2007; Harris et al., 2009; Le, Ziogas, Lipkin, & Zell, 2008).

G. Conclusion

According to literature review, it may be difficult for stage II and III RC patients in California to receive treatment as same as current NCCN guidelines because treatment may be given differently depending on age, gender, race/ethnicity, and SES. While it is reasonable to assume that the outcome improvements which were reported by the European trial groups have prompted changes in multimodality therapy of stage II and III RC from adjuvant (postoperative, PostOP) to neoadjuvant (preoperative, PreOP) therapy, survival benefits of these changes have not been adequately tested in a large-scale population-based setting. This dissertation therefore has attempted to assess the predictors (demographic variables) and the survival of stage II and III RC with various multimodality treatments using the California Cancer Registry data from 1994 to 2009.

CHAPTER 3

METHODS

A. Study Design

A non-concurrent cohort study design using the entire California population, 1994-2009, was used to assess demographic predictors and survival differences among stage II and III rectal cancer (RC) patients receiving multimodality therapies such as perioperative chemoradiation (PeriOP CRT) *versus* surgery alone, and preoperative chemoradiation (PreOP CRT) *versus* postoperative chemoradiation (PostOP CRT), adjusting for age, gender, race/ethnicity, and socioeconomic status. The statewide California Cancer Registry (CCR) includes cancers diagnosed among the approximately 33.9 million residents, and has a rich demographic diversity (SEER Data, 2011).

B. Study Population

Of the 46,236 RC cases (not including rectosigmoid junction) diagnosed in California during the 16 year study, 29,075 were unstaged, stage I or IV which were not eligible for our study, and 17,161 were stage II and III. Among stage II and III RC, 2,029 did not receive radical surgery and were therefore also excluded. Among the remaining 15,132 patients receiving radical surgery, 2,988 received radical surgery only without additional treatment (i.e. radiation therapy [RT] and/or chemotherapy), 8,852 received PeriOP CRT which included radiation given before and/or after surgery with concurrent chemotherapy, 4,280 patients received PreOP CRT, and 3,734 patients received PostOP CRT. CCR data provide information on the sequence (time) of RT with surgery during the first course of treatment such as PreOP RT, PostOP, and both, etc. while there is no similar information for chemotherapy. However, CCR data specifies the date when

chemotherapy was started. Therefore, to identify the time of chemotherapy given as first course of treatment such as PreOP and PostOP, we estimated this based on the date of first definitive surgery performed and the date when chemotherapy was started.

C. Data Analyses

Counts and percentages of PeriOP CRT *versus* surgery alone were assessed for categories of age at diagnosis (<50, 50–74, and ≥75 years), gender, race/ethnicity (Asian/Other [AO], Hispanic, non-Hispanic black [NHB], and non-Hispanic white [NHW]), and for socioeconomic status (SES) quintiles (1-5 highest). PreOP CRT *versus* PostOP CRT was also assessed for the same demographic variables as PeriOP CRT *versus* surgery alone. However, temporal variables such as Early (1994-1997, same as Swedish publication year), Middle (1998-2005, same as German publication year), and Late (2006-2009) were also added. The SES index was computed using a principle component analysis with seven census-derived economic and education variables measured for the 21,960 Year 2000 Census block groups of residence at diagnosis in California. Methods and variables used to compute the SES quintile index are described by Yost et al. (Yost, Perkins, Cohen, Morris, & Wright, 2001) and did not include age, sex, or race/ethnicity.

Using logistic regression, univariate odds ratios (OR) with 95% confidence intervals (CI) contrasting PeriOP CRT *versus* surgery alone and PreOP *versus* PostOP CRT were computed for each of these independent variables. Additionally, a final multivariable model was used where all independent variables were included. Interaction between race/ethnicity and SES (race/ethnicity×SES) was assessed in the multivariable model, however it was not significant ($p>0.05$).

Cox proportional hazards regression was used to assess the risk of mortality associated with PeriOP CRT *versus* surgery alone and PreOP CRT *versus* PostOP CRT adjusting for other covariates, such as date of surgery (continuous variable), stage (II and/or III), age (as categorical variable defined in logistic regression model), gender, race/ethnicity, and SES. Due to non-linearity, a quadratic term for date of surgery ([date of surgery]^2), and interaction terms [(PeriOP CRT/surgery alone)×(date of surgery) and (PeriOP CRT/surgery alone)×(date of surgery)^2] were added to the full model. For all of the independent variables, the proportional hazards (PH) assumption was evaluated using log-log survival plots with time-interactions included in the full model. No serious violations of the PH assumption were found. Statistical Analysis Software, version 9.3 (SAS, Cary, NC) was used for all analyses.

D. Limitations

Our data did not provide information on a second course of chemotherapy. We have identified the type of chemotherapy given as first course of treatment, such as single, multiple or not otherwise specified agents. Furthermore, we have no information on which specific chemotherapies were used. This prevents assessment of the exact NCCN treatment standard for stage II and III RC.

Although CCR data were not obtained in a randomized clinical trial, the data have other strengths in that they represent a 100% sampling of eligible patients from a long-standing statewide population-based cancer registry with immense diversity. As such, there is strong generalizability to the general population. However, our data provided no information on comorbidities which could contribute to survival differences, and may have also contributed to the choice of specific multimodality therapies. Our study

included no mechanisms to balance for these unmeasured effects, which may have differed in comparison groups.

CHAPTER 4

FIRST PUBLISHABLE PAPER

Outcomes of Multimodality Therapies for Stage II and III Rectal Cancer Patients in California, 1994-2009

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Short running head: Perioperative therapy for rectal cancer

Acknowledgements: The authors of this study acknowledge dedication to the challenging work of health professionals, scientists, and cancer registry staff which ensure high quality patient care, improved treatments, and the opportunity for evidence-based cancer research.

Source of support: There is no financial support.

For submission to the: Diseases of the Colon & Rectum

Keywords: Multimodality therapy, Perioperative chemoradiation, Rectal cancer, Survival

Note: The formatting and referencing style is not in accordance with dissertation guidelines and is according journal specifications.

Abstract

Background: Prior to the mid-1980s, surgical resection was the only accepted treatment of locally advanced rectal cancer (RC). More recently, chemoradiotherapy (CRT) before and after surgery has been used as a multimodality therapy for stage II and III RC, to reduce local and distant recurrence and to improve overall survival. Although several study groups have prompted these changes, survival benefits of CRT have not been adequately tested in a large-scale population-based setting.

Objective: To evaluate survival benefits of perioperative (PeriOP) CRT *versus* surgery alone from 1994 through 2009 for stage II and III RC using the diverse California population.

Design: A non-concurrent cohort study design of the entire California population, 1994-2009, was used to assess survival differences among RC patients receiving PeriOP CRT *versus* surgery alone, adjusting for age, gender, race/ethnicity, and socioeconomic status.

Settings: The statewide California Cancer Registry.

Patients: Patients with stage II and III RC receiving only radical surgery (N=2,988) or PeriOP CRT (N=8,852), among 46,236 RC cases.

Main Outcome Measures: Cox proportional hazards regression was used to assess the risk of mortality associated with PeriOP CRT *versus* surgery alone adjusting for month of surgery, stage, and selected demographic variables.

Results: In multivariable logistic regression, OR for receiving PeriOP CRT was higher among Hispanic (OR=1.17, 1.01-1.34), compared to non-Hispanic whites. Cox proportional hazards regression analysis showed that PeriOP CRT, relative to surgery alone, was associated with lower mortality during the entire study period with survival

benefit increasing over time (1994-1997: HR=0.73, 0.65-0.83; 1998-2001: HR=0.66, 0.60-0.73; 2002-2005: HR=0.55, 0.49-0.61; 2006-2009: HR=0.36, 0.31-0.43).

Limitations: Our data provided no information on comorbidities which could contribute to treatment and survival differences.

Conclusions: Compared to patients treated with surgery alone, PeriOP CRT is associated with significantly improved survival among stage II and III RC patients for the entire study period.

INTRODUCTION

Colorectal cancer (CRC) is currently the third leading cause of cancer deaths among both females and males in the US with a five-year survival rate of 68% nationally[1] and 66% in California.[2] It is estimated that there will be 40,290 (16,790 females; 23,500 males) new rectal cancer (RC) diagnoses among Americans in 2012.[1] An estimated 4,235 (1,785 females; 2,450 males) California residents will be diagnosed with RC during 2012, and approximately 935 (405 females; 535 males) will die from the disease.[2]

Until the mid-1980's, surgical resection without adjuvant therapy was the method used for locally advanced RC.[3] However, this single-modality treatment carried a high risk for local recurrence with a propensity for spread. In 1985, the Gastrointestinal Tumor Study Group (GITSG) reported that for stage II and III RC, adjuvant chemoradiotherapy (CRT) resulted in lower local recurrence (33%) than surgery alone (55%).[4] In 1986, their seven-year follow-up study found that surgery combined with CRT improved survival by 24% (p=0.005), compared to surgery alone.[5] The US National Institutes of Health Consensus Conference (1990)[6] and the German Cancer Society Consensus Conference (1999)[7] recommended the use of postoperative (PostOP) CRT for Stage II and III RC.

During the last 20 years, several European trial groups[8-11] have also reported that a short-course of preoperative (PreOP) radiation therapy (RT) significantly reduced local recurrence and improved overall survival for stage II and III RC, compared to surgery alone. Specifically, the Swedish rectal cancer trial[8] found that short-course PreOP RT (25 Gy delivered in five fractions in one week followed by surgery within one week) reduced local recurrence and improved overall survival for RC among patients with resectable tumors, compared to surgery alone. A Dutch colorectal cancer group[10,11] reported that

short-course PreOP RT significantly improved 10-year survival, compared to surgery alone, among stage III RC patients showing negative resection margins. In addition to comparisons of PreOP RT *versus* surgery alone, several studies have reported the effect of PreOP RT *versus* PostOP CRT and PreOP CRT *versus* PostOP CRT. The UK and Canada randomized trial group[12,13] found that short-course PreOP RT reduced local recurrence for RC, but did not improve overall survival, compared to PostOP CRT. A German rectal cancer study group[14,15] reported that PreOP CRT for stage II and III RC significantly reduced local recurrence compared with PostOP CRT, although no difference was seen in overall survival. Current National Comprehensive Cancer Network (NCCN) guidelines[16] for stage II (T3-4, N0, M0) and III (Any T, N1-2, M0) RC[17] recommend a sequence of treatment modalities such as PreOP CRT followed by transabdominal resection and PostOP chemotherapy within 6 months.

While it is reasonable to assume that the outcome improvements reported by European trial groups[8-15] have prompted changes in multimodality therapy of stage II and III RC, survival benefits of these changes have not been adequately tested in a large-scale population-based setting. We sought to evaluate survival changes according to use of perioperative (PreOP and/or PostOP) CRT *versus* surgery alone from 1994 through 2009 for stage II and III RC using the diverse California population.

MATERIALS AND METHODS

Study population: A non-concurrent cohort study design was used to assess demographic predictors and outcomes of perioperative (PeriOP) CRT *versus* surgery alone, for stage II and III RC using the entire California population from 1994 through

2009. The statewide California Cancer Registry (CCR) includes cancers diagnosed among the approximately 33.9 million residents, and has a rich demographic diversity.[18]

Of the 46,236 RC cases (not including recto-sigmoid junction) diagnosed in California during the 16 year study, 17,161 were stage II and III, among which 2,029 did not receive radical surgery and were ineligible for our study. The remaining 15,132 patients received radical surgery, with 3,292 excluded because they received RT or chemotherapy only, either before or after surgery. Among the remaining 11,840 patients that constitute our study population, 2,988 received radical surgery only without additional treatment (i.e. RT and/or chemotherapy), while 8,852 received PeriOP CRT which included RT given before and/or after surgery with concurrent chemotherapy (Figure 4.1).

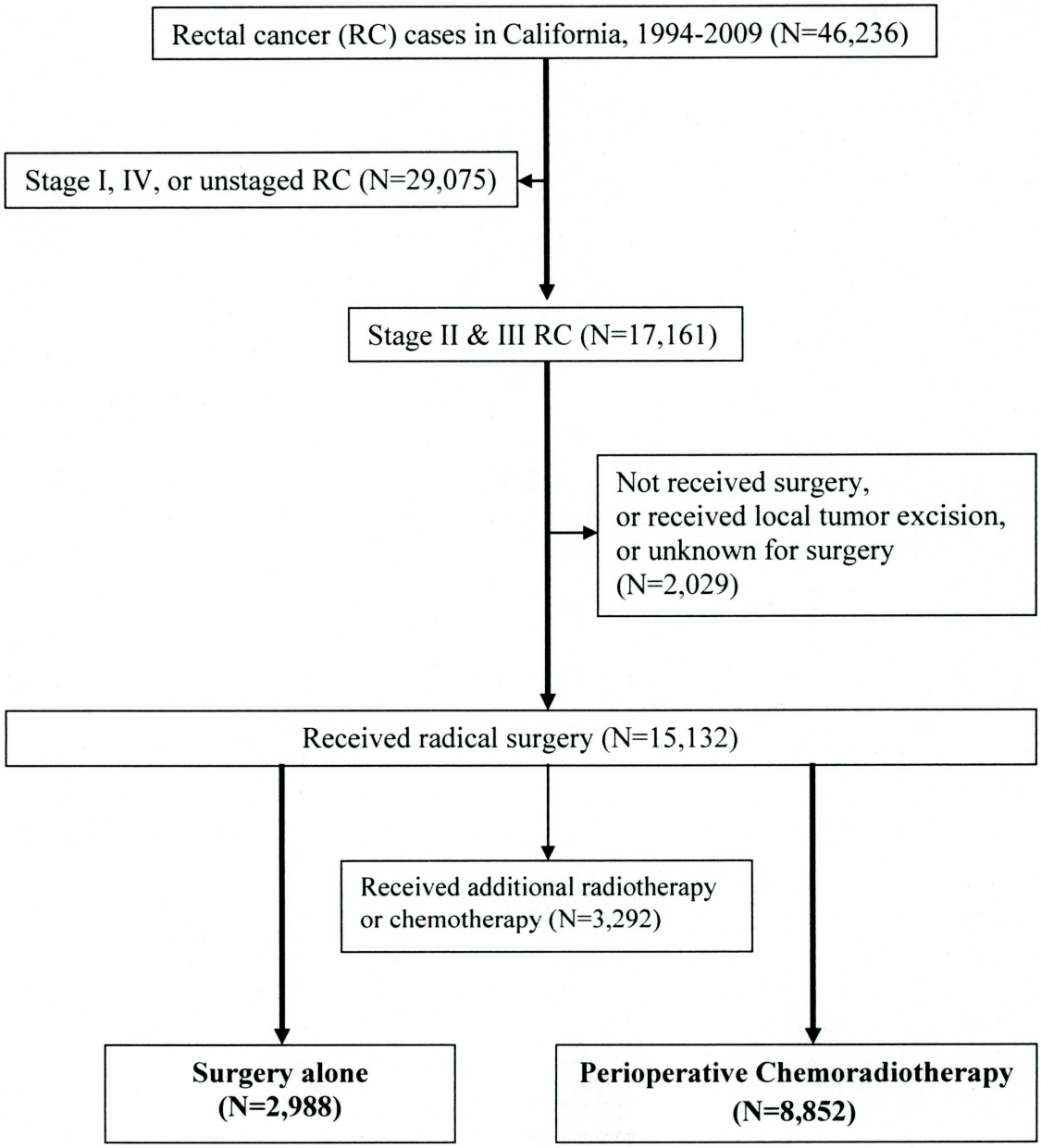

Figure 4.1. CONSORT diagram for patient's selection in our study.

Statistical Analyses: Counts and percentages (%) of surgery alone and PeriOP CRT were assessed for categories of age at diagnosis (<50, 50–74, and ≥75 years), gender, race/ethnicity (Asian/Other [AO], Hispanic, non-Hispanic black [NHB], and non-Hispanic white [NHW]), and for socioeconomic status (SES) quintiles (1-5 highest). The SES index was computed using a principle component analysis with seven census-derived economic and education variables measured for the 21,960 Year 2000 Census block groups of residence at diagnosis in California. Methods and variables used to compute the SES quintile index are described by Yost et al.[19]

Using logistic regression, univariate odds ratios with 95 % confidence intervals (OR, CI) for the use of PeriOP CRT versus surgery alone were computed for each of the independent variables. The final multivariable model included all independent variables. Interaction between race/ethnicity and SES (race/ethnicity×SES) was assessed in the multivariable model, and it was not significant (p=0.22) and therefore not included in the final model.

Cox proportional hazards regression was used to assess risk of mortality associated with PeriOP CRT *versus* surgery alone adjusting for other covariates, including date of surgery, stage (II and/or III), age (as categorical variable defined in logistic regression model), gender, race/ethnicity, and SES. Due to non-linearity of date of surgery, we ran two models. In the first model we categorized this variable into four time periods (1994-1997, 1998-2001, 2002-2005, and 2006-2009). In the second model we used a quadratic term for date of surgery [(date of surgery)^2]. Interaction terms [(PeriOP CRT/surgery alone)×(date of surgery) and (PeriOP CRT/surgery alone)×(date of surgery)^2] were also included in the full model. For all of the independent variables,

the proportional hazards (PH) assumption was evaluated using log-log survival plots with time-interactions included in the full model. No serious violations of the PH assumption were found. The Statistical Analysis Software (SAS), version 9.3[20] was used for all analyses.

RESULTS

Counts, proportions, univariate and adjusted ORs with 95% CI for stage II and III RC patients receiving PeriOP CRT *versus* surgery alone for demographic variables are presented in Table 1. In univariate analyses, age was a determinant of PeriOP CRT with decreasing use as age increased. Compared to the 50-74 age-category, the <50 age group was more likely (OR=2.37, 1.98-2.84) to receive PeriOP CRT while the ≥75 age group was less likely (OR=0.17, 0.15-0.18) to receive this treatment. Females were less likely to receive PeriOP CRT (OR=0.68, 0.63-0.74) than males. AO and Hispanic patients were 19% and 35% more likely to receive PeriOP CRT, respectively, compared to NHW. ORs for receiving PeriOP CRT increased monotonically from lowest (OR=0.65) to highest SES (referent group).

The association between PeriOP CRT and demographic variables remained virtually unchanged in the multivariable analysis, except for the association with race/ethnicity. The higher odds of PeriOP CRT among the AOs was no longer present (OR=0.98) and the finding for Hispanic ethnicity was attenuated, but still statistically significant (OR=1.17) (Table 4.1).

Table 4.1. Counts, proportions, univariate, and adjusted odds ratios (OR) with 95% confidence intervals (CI) for Stage II and III rectal cancer cases receiving perioperative chemoradiotherapy (PeriOP CRT) versus surgery alone by demographic variables, 1994-2009. Data from the California Cancer Registry.

Independent Variables	Counts[¥] (N=11,840)	%Surgery alone	%PeriOP CRT[†]	PeriOP CRT/Surgery alone		PeriOP CRT/Surgery alone	
				OR	95% CI	Adjusted OR[‡]	95% CI
Age							
<50	1,832	8.02%	91.98%	**2.37**	1.98-2.84	**2.41**	2.01-2.89
50-74	7,071	17.13%	82.87%	**1**	-	**1**	-
≥75	2,937	55.50%	44.50%	**0.17**	0.15-0.18	**0.17**	0.15-0.18
							p*<0.0001
Sex							
Female	4,769	29.59%	70.41%	0.68	0.63-0.74	**0.76**	0.69-0.83
Male	7,071	22.30%	77.70%	1		**1**	-
Race/Ethnicity							
Asian/Other (AO)	1,565	23.13%	76.87%	1.19	1.05-1.35	**0.98**	0.85-1.13
Hispanic	1,895	21.00%	79.00%	1.35	1.19-1.52	**1.17**	1.01-1.34
Non-Hispanic black (NHB)	598	29.43%	70.57%	0.86	0.72-1.03	**0.83**	0.67-1.02
Non-Hispanic white (NHW)	7,782	26.37%	73.63%	1	-	**1**	-
Socioeconomic status (SES)[#]							
1Lowest	1,661	28.36%	71.64%	0.65	0.56-0.75	**0.54**	0.46-0.64
2	2,340	28.50%	71.50%	0.64	0.56-0.73	**0.57**	0.50-0.66
3	2,561	24.87%	75.13%	0.77	0.68-0.88	**0.72**	0.62-0.83
4	2,644	25.57%	74.43%	0.75	0.66-0.85	**0.72**	0.63-0.83
5 Highest	2,634	20.39%	79.61%	1	-	**1**	-
							p*<0.0001

[¥]Counts of surgery alone and PeriOP CRT.

[†]PeriOP CRT includes patients receiving radical surgery with preoperative and/or postoperative CRT.

[‡]OR adjusting by demographic variables.

*p-value for trend.

[#]SES is measured using a Census derived index based on place of residence [19].

Multivariable survival analysis showed a time dependent association between PeriOP CRT *versus* surgery alone. The hazard for all-cause mortality among those receiving PeriOP CRT, compared to surgery alone, was reduced by 27% (HR=0.73, 0.65-0.83) for those treated during the 1994-1997 time period. This hazard continued to decrease during later time periods, with a 64% reduction (HR=0.36, 0.31-0.43) for those treated with PeriOP CRT between 2006 and 2009 (p_{trend}<0.0001) (Table 4.2). When using surgery date as a continuous variable in the Cox model (Figure 4.2), the time dependent HR is even more apparent.

Table 4.2. Mortality hazard ratios (HR)[†] with 95% confidence interval (CI) for perioperative chemoradiotherapy (PeriOP CRT) *versus* surgery alone among stage II and III rectal cancer cases over years of surgery date (four categories), 1994-2009. Data from the California Cancer Registry.

Year of Surgery	HR[†]	95% CI
1994-1997	**0.73**	0.65-0.83
1998-2001	**0.66**	0.60-0.73
2002-2005	**0.55**	0.49-0.61
2006-2009	**0.36**	0.31-0.43
	*p**<0.0001	

[†]HR adjusted for age, gender, race/ethnicity, and socioeconomic status variables.

*p-value for trend.

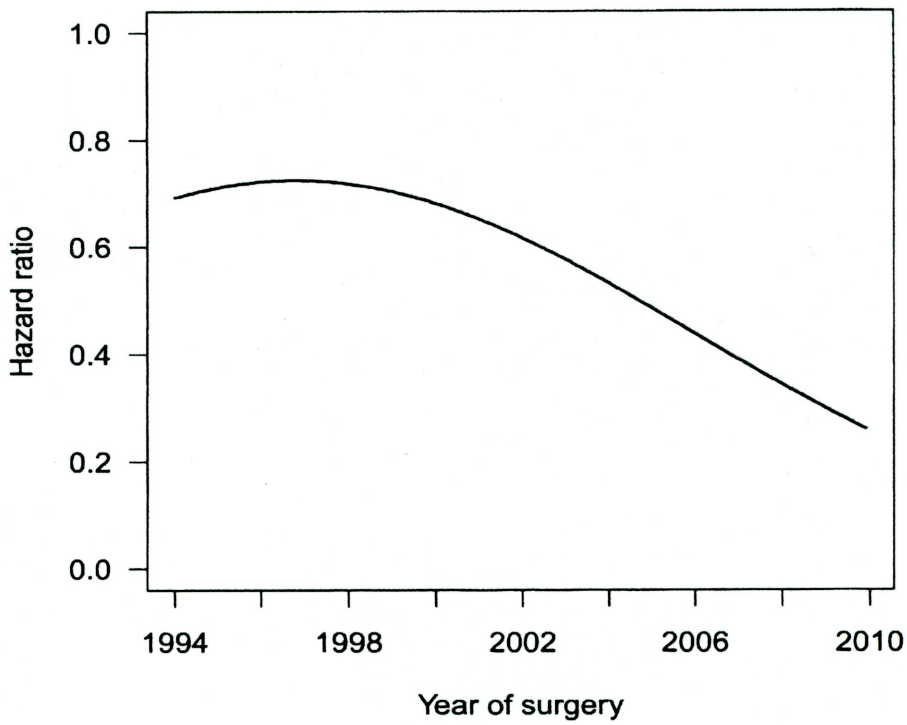

Figure 4.2. Mortality hazard ratios with 95% confidence interval for Perioperative chemoradiotherapy *versus* surgery alone adjusted for demographic variables (age, gender, race/ethnicity, and socioeconomic status) among stage II and III rectal cancer cases over years of surgery date (continuous variable), 1994-2009.
Data from the California Cancer Registry

DISCUSSION

Older patients (≥75 years) with stage II and III RC were less likely to receive PeriOP CRT during the study period, while patients younger than age 50 more frequently received the adjuvant therapy. Older patients, especially those 80 years and older, may have more co-morbidities, weaker immune system, and other medical contraindications for CRT, while younger patients may be considered more hardy, with fewer co-morbidities, and therefore suitable for the more aggressive PeriOP CRT treatment. Additionally, there may also be self-selection of limited treatment among the oldest study subjects, some of whom may not believe they are able to handle the side effects of CRT, or may have other reasons for not wanting the multimodality treatment.

We observed lower utilization of PeriOP CRT among females than males. The explanation for this finding is unclear and should be explored further in studies with cohort design where more information is available from surgery and pathology records as well as imaging findings (CT, MRI, etc.). However, it is possible that RC in males tends to have a more advanced presentation within the same histopathologic stage/category. This could be due both to the fact that males may be more likely to delay seeking medical care than females, and because a bulky tumor in the narrow male pelvis may be more difficult to remove.[21]

Our finding that the use of PeriOP CRT was significantly more common among Hispanics, and tended to be less common among NHBs, compared to NHW patients, is in line with a report from Martinez et al.[22] Even after adjustment for nodal status, tumor size and T stage (1-4), Martinez et al. found that Hispanics were significantly more likely to receive PreOP RT and were less likely to receive sphincter-preserving surgery than

NHWs. Our findings may reflect different compliance with NCCN guidelines according to race/ethnicity, and is supported by our earlier findings that Hispanics are at higher risk of diagnosis with stage II-IV CRC, compared to NHWs[23]. Since Hispanics have the lowest incidence of RC among all race/ethnic groups assessed in California[24], their later stage at diagnosis may indicate that RC among Hispanics is diagnosed at a more advanced stage because access to healthcare in this ethnic group may be sub-optimal. This supposition is supported by the National Healthcare Disparities Report 2011[25] which shows that Hispanics tended to receive lower quality health care and have less access to health care compared to NHWs. These disparities may, at least partly, be explained by communication problems resulting from language barriers, and by lack of access to insurance and transportation[22]. Our findings are consistent with Martinez et al.[22] who reported that Hispanics, compared to NHWs, are more likely to present with more bulky and invasive tumors and may require more aggressive treatment such as CRT, even at the same histopathologic stage.

Our analyses reveal significant differences across SES quintiles, indicating that subjects in lower SES groups are less likely to receive PeriOP CRT, compared to those in higher SES groups. Among stage II and III RC cases, SES is an independent selection criterion for receiving PeriOP CRT as opposed to surgery alone. Our findings of a survival benefit for PeriOP CRT versus surgery alone translates into a significantly reduced survival for members of lower SES categories. Our observation of an association between RC outcomes and SES are in line with a report by Kim et al.,[26] who found that the highest SES group had the best overall median survival (8.4 years) followed by the middle (5.1 years) and lowest (3.8 years) group among residents of Los Angeles County.

The time dependent improvement in survival among those receiving PeriOP CRT is consistent with improved CRT methodology during the time period of our study. These include improvements in medical technology such as advances in radiation techniques (e.g. 3-dimentional conformal radiation therapy [3DCRT])[27], intensity-modulated radiation therapy (IMRT)[27,28] and development of new drugs, particularly cetuximab[29,30] and bevacizumab[31] which were added to fluorouracil (5-FU) and/or leucovorin (LV) during the time period assessed.

Our data provided no direct information on comorbidities which could contribute to survival differences. Although CCR data were not obtained in a randomized clinical trial, our data have other strengths in that they represent a 100% sampling of eligible patients from a long-standing statewide population-based cancer registry with immense diversity. As such, there is strong generalizability to the general population. In conclusion, PeriOP CRT reveals significantly improved survival among stage II and III RC patients throughout the entire study period, compared to patients receiving surgery alone. The survival benefit increased over the time-period of our study suggesting that changes in CRT procedures have been modified over time.

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CHAPTER 5

SECOND PUBLISHABLE PAPER

Is There a Survival Difference for Preoperative *versus* Postoperative Chemoradiotherapy among Stage II and III Rectal Cancer Patients?

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Short running head: Pre- *versus* postoperative chemoradiotherapy for rectal cancer

Acknowledgements: The authors of this study acknowledge dedication to the challenging work of health professionals, scientists, and cancer registry staff which ensure high quality patient care, improved treatments, and the opportunity for evidence-based cancer research.

Source of support: There is no financial support.

For submission to the: Journal of Clinical Oncology

Keywords: Multimodality therapy, Perioperative chemoradiation, Rectal cancer, Survival

Note: The formatting and referencing style is not in accordance with dissertation guidelines and is according journal specifications.

Abstract

Background: National Comprehensive Cancer Network guidelines recommend preoperative (PreOP) chemoradiotherapy (CRT), transabdominal resection, and postoperative (PostOP) chemotherapy for stage II and III rectal cancer (RC). European trials evaluating the effect of PreOP *versus* PostOP CRT found no survival benefit. However, the effect of a change from PostOP to PreOP CRT has not been evaluated in a population-based setting.

Patients and Methods: We conducted a nonconcurrent cohort study evaluating demographic predictors of multimodal therapy for stage II and III RC using the diverse California Cancer registry population-based data. 4,280 patients received PreOP CRT and 3,734 patients receiving PostOP CRT. Cox proportional hazards regression was used to assess survival over 192 months among PreOP and PostOP CRT patients, adjusting for date of surgery, stage, age, gender, race/ethnicity, and socioeconomic status.

Results: Our findings showed a stepwise increase in the use of PreOP CRT across three time-periods (1994-1997, 1998-2005, and 2006-2009) which was concomitant with publication of findings from European trials. However, we did not find a clear survival benefit for PreOP *versus* PostOP CRT.

Conclusions: Our study identified a clear shift in timing from PostOP to PreOP CRT. However, we found no clear support for a survival benefit associated with this shift.

INTRODUCTION

Colorectal cancer (CRC) is projected to be the second leading cause of cancer death in the US during 2012, ranking number three among both females and males, producing an estimated 51,690 deaths, nationwide. In the same year, it is estimated that there will be 143,460 new CRC diagnoses among Americans, of which 40,290 are expected to be rectal cancers [1]. In 2012, it is estimated that 4,235 rectal cancers will be diagnosed among California residents, and that 935 persons with rectal cancer will die [2].

Rectal cancer originates within 12 cm proximal from the anal verge [3]. Risk of recurrence of rectal cancer partly depends on tumor location relative to the anal verge [4]. Pelvic recurrence is more common for rectal than colon cancer [5-7], in part, because of the proximity to pelvic structures, absence of serosa, and technical challenges encountered in obtaining wide surgical margins. Current National Comprehensive Cancer Network (NCCN) guidelines [8] recommend a series of multimodality therapies which consist of preoperative (PreOP) radiation therapy (RT) (45-50 Gy in 25-29 fractions) with concurrent chemotherapy, transabdominal resection, and postoperative (PostOP) chemotherapy, within six months for stage II (T3-4, N0, M0) and III (Any T, N1-2, M0) rectal cancer [9]. NCCN guidelines [8] further recommend transabdominal resection and PostOP chemoradiotherapy (CRT) only, as an alternative among patients having medical contraindications.

Reports from the US National Institutes of Health Consensus Conference (1990) [10] and the German Cancer Society Consensus Conference (1999) [11] recommended use of PostOP CRT for Stage II and III rectal cancer. In early 1997, a report from the

Swedish rectal cancer trial [12] found that short-term, high-dose PreOP RT (25 Gy in five fractions in one week) reduced local recurrence and improved overall survival for rectal cancer among patients with resectable tumors, compared to surgery alone. In late 2004, the German rectal cancer study group [13] reported that PreOP CRT for Stage II and III rectal cancer reduced local recurrence (6% *vs.* 13%; p=0.006) and treatment-associated toxicity (27% *vs.* 40%; p=0.001), but did not improve overall survival, compared to PostOP CRT.

Advantages of PreOP over PostOP RT include: (1) Reduced tumor volume, thereby enhancing preservation of anal sphincter and avoiding stoma [13-15]; (2) Avoidance of PostOP complications by substituting PreOP RT for lateral lymph node dissection [16]; (3) Better vascularization (oxygenation) of unaffected tissue before surgery yields superior RT response [13-17]; and (4) Reduced radiation-induced injury from misplacement of small bowel into the pelvis by surgical adhesions [14-17]. An additional benefit of concurrent chemotherapy with RT is amplification of tumoricidal effect [18] and reduction of distant micrometastases [13,19,20]. In contrast, a significant disadvantage of PreOP RT is: (1) Delay of surgery by about two months [16]; (2) Surgical challenge for tissue adhesion caused by RT [16]; (3) Increased probability of postoperative complications (i.e. infection) due to extended healing time of surgical scar [16]; and (4) The possibility of over-treating early-stage tumors, which otherwise, would not have required adjuvant RT [13,21].

In 2005, a follow-up study from the Swedish rectal cancer trial [22] reported that a short-course PreOP RT for resectable rectal cancer increased relative risk for PostOP hospitalization for subsequent bowel complications, compared to surgery alone. Recently,

the Dutch colorectal cancer group [23] reported that short-course PreOP RT significantly improved 10-year survival, compared to surgery alone, among stage III rectal cancer patients showing negative resection margins [24]. A multicenter, randomized trial in the UK and Canada [25,26] found that short-course PreOP RT alone, compared with PostOP CRT, reduced local recurrence for rectal cancer, although no difference was seen in overall survival. In April 2012, the German rectal cancer study group [27] reported the 11-year follow-up of their study. The conclusion was unchanged from their first follow-up report: PreOP CRT for stage II and III rectal cancer significantly reduced local recurrence compared to PostOP CRT (7.1% *vs.* 10.1%; p=0.048), however, there was no effect on overall survival.

While it is reasonable to assume that the outcome improvements which were reported by the Swedish [12] and German trials [13] have prompted changes in multimodality treatment of stage II and III rectal cancer, survival benefits of these changes have not been adequately tested in a large-scale population-based setting. We sought to evaluate treatment changes from PostOP to PreOP CRT practices and the effect on overall survival from 1994 through 2009 among patients receiving radical operations for stage II and III rectal cancer using the diverse California population.

PATIENTS AND METHODS

Study population: A non-concurrent cohort study design was used to evaluate temporal and demographic predictors of multimodal therapy for stage II and III rectal cancer using the entire California population for 1994-2009. The statewide California Cancer Registry (CCR) includes approximately 31.5 million residents and rich demographic diversity [28]. PreOP and PostOP chemotherapy timing (dependent

variable) was computed based on dates of primary surgery and initial chemotherapy, while RT was classified as PreOP or PostOP.

Of the 46,236 rectal cancer cases (not including rectosigmoid junction, RC) diagnosed in California during the 16 year study, 29,075 were unstaged, stage I or IV which were not eligible for our study, and 17,161 were stage II and III. Among stage II and III RC, 2,029 did not receive radical surgery and were therefore also excluded. The remaining 15,132 patients received radical surgery, and of these 5,364 did not receive additional RT and/or chemotherapy, and for 1, 754 the timing for CRT was unknown which render them ineligible for the study. Among the remaining 8,014 patients who constitute our study populations, 4,280 patients received PreOP CRT and 3,734 patients received PostOP CRT (Figure 5.1).

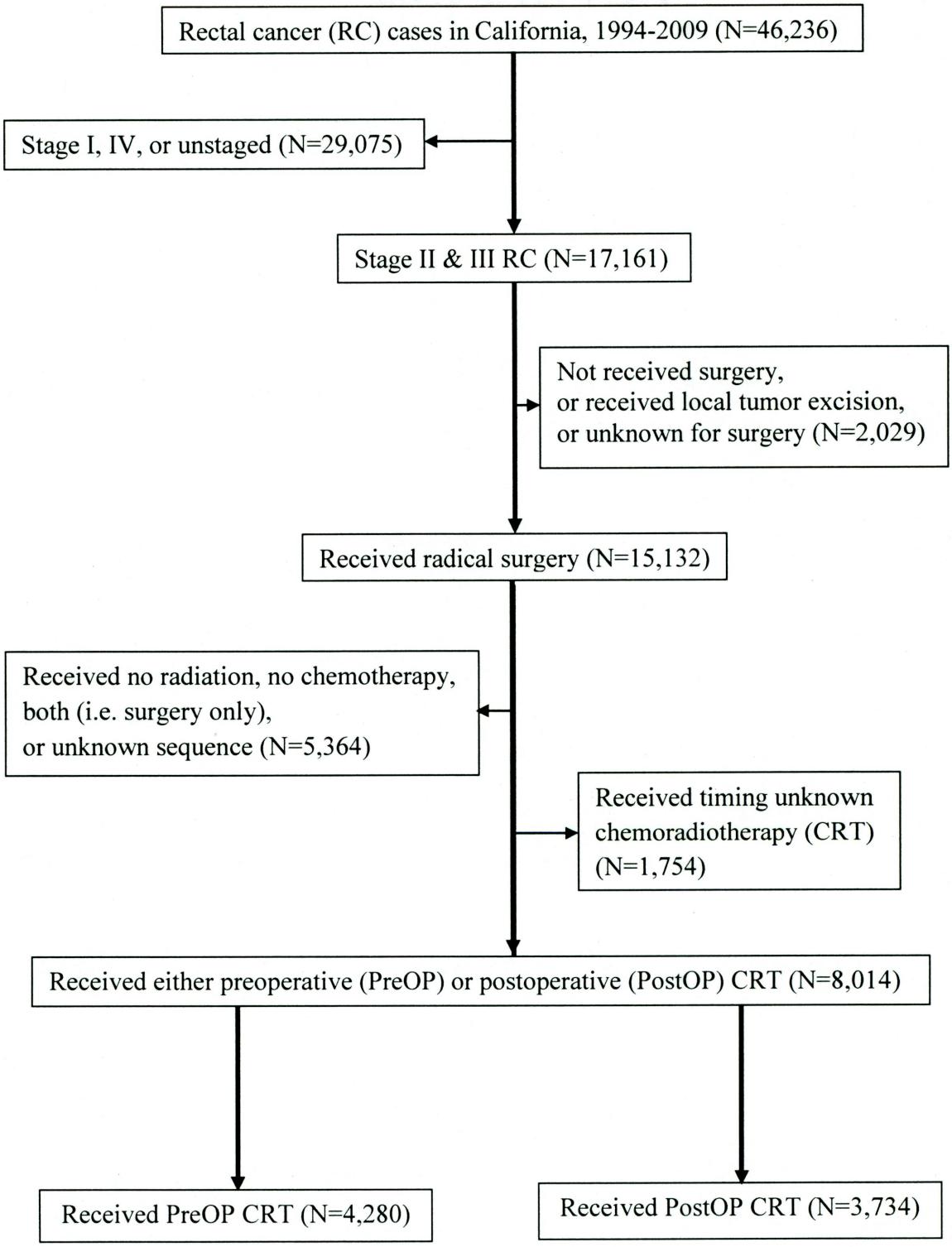

Figure 5.1. CONSORT diagram for patient's selection in our study.

Statistical Analyses: In the univariate analysis, counts and percentages (%) of PreOP and PostOP CRT were assessed for three time periods at diagnosis: Early (1994-1997, same as Swedish publication year), Middle (1998-2005, same as German publication year), and Late (2006-2009), for categories of age at diagnosis (<50, 50–74, and 75+ years), gender, race/ethnicity (Asian/Other [AO], Hispanic, non-Hispanic black [NHB], and non-Hispanic white [NHW]), and for socioeconomic status (SES) quintiles (1-5 highest). The SES index was computed using a principle component analysis with seven census-derived economic and education variables measured for the 21,960 Year 2000 Census block groups of residence at diagnosis in California. Methods and variables used to compute the SES quintile index are described by Yost et al. [29] and did not include age, sex, or race/ethnicity.

Univariate odds ratios with 95% confidence intervals (OR, CI) contrasting PreOP *versus* PostOP CRT were computed for each of these independent variables. The association between PreOP *versus* PostOP CRT and independent variables (time-period and demographic variables) was further evaluated using multivariable logistic regression. Multiplicative interaction between race/ethnicity and SES (race/ethnicity×SES) was assessed in the multivariable model, and it was not significant (p=0.46).

In the multivariable survival analysis, Cox proportional hazards regression was used to assess the risk of mortality associated with PreOP *versus* PostOP CRT adjusting for other covariates, such as date of surgery (continuous variable), stage (II and III), age (as categorical variable defined in logistic regression), gender, race/ethnicity, and SES. Due to non-linearity, a quadratic term for date of surgery [(date of surgery)^2] and interaction terms [(PreOP/Post OP CRT)×(date of surgery) and (PreOP/Post OP

CRT)×(date of surgery)^2], were added to the full model. For all of the independent variables, the proportional hazards (PH) assumption was evaluated using log-log survival plots and including time-interactions into the model. No serious violation of the PH assumption was found. The Statistical Analysis Software (SAS), version 9.3 [30] was used for all analyses.

RESULTS

Table 5.1 presents counts and proportions of stage II and III RC patients receiving PreOP and PostOP CRT for three time-periods and demographic variables. Univariate ORs with 95 percent CI for PreOP *versus* PostOP CRT are also presented. The proportions of PreOP CRT increased sequentially from Early to Late time-periods (Early: OR=0.07, 0.06-0.08; Middle: OR=0.33, 0.29-0.37), compared to the latest time period. Compared to the 50-74 age category, the younger age group was more likely to receive PreOP CRT (OR=1.31, 1.17-1.47), while there was no difference for the older age group. Females were less likely to receive PreOP CRT (OR=0.84, 0.77-0.92) than males, which persisted when age was controlled for both as a continuous variable and with nine different age categories. No significant difference was found in PreOP *versus* PostOP CRT among race/ethnicity and SES groups, although the NHW and highest SES groups tended to be somewhat more likely to have been treated with PreOP CRT.

Table 5.1. Counts, proportions (%), and univariate odds ratios (OR) with 95% confidence intervals (CI) for stage II and III rectal cancer cases receiving perioperative chemoradiotherapy (CRT) by time-period and demographic variables, 1994-2009. Data from the California Cancer Registry.

Variables	Counts of CRT[$] (N=8,014)	% PreOP CRT[†]	% PostOP CRT[‡]	OR	95% CI
Time-Period					
Early (1994-1997)	1,445	17.7%	82.4%	**0.07**	0.06-0.08
Middle (1998-2005)	4,038	51.7%	48.3%	**0.33**	0.29-0.37
Late (2006-2009)	2,531	76.6%	23.4%	**1**	-
Age					
<50	1,507	58.9%	41.1%	**1.31**	1.17-1.47
50-74	5,302	52.2%	47.8%	**1**	-
75+	1,205	52.0%	48.0%	**1.00**	0.88-1.13
Gender					
Female	3,043	50.8%	49.2%	**0.84**	0.77-0.92
Male	4,971	55.0%	45.0%	**1**	-
Race/Ethnicity					
Asian/Other (AO)	1,091	54.5%	45.6%	**1.06**	0.93-1.21
Hispanic	1,342	54.5%	45.5%	**1.06**	0.94-1.19
Non-Hispanic black (NHB)	384	51.6%	48.4%	**0.94**	0.77-1.16
Non-Hispanic white (NHW)	5,197	53.1%	47.0%	**1**	-
Socioeconomic status (SES)[#]					
1	1,069	52.1%	47.9%	**0.87**	0.75-1.01
2	1,501	52.0%	48.0%	**0.86**	0.75-0.99
3	1,746	53.4%	46.6%	**0.91**	0.80-1.04
4	1,788	53.0%	47.0%	**0.87**	0.79-1.02
5 Highest	1,910	55.7%	44.4%	**1**	-

[$] CRT includes patients receiving radical surgery with preoperative and postoperative chemoradiotherapy

[†] PreOP CRT includes patients receiving radical surgery with preoperative chemoradiotherapy.

[‡] PostOP CRT includes patients receiving radical surgery with postoperative chemoradiotherapy.

[#] SES is measured using a Census derived index based on place of residence [29].

The association between PreOP CRT and time-periods remained virtually unchanged in the multivariable analysis (p *trend* <0.0001) (Table 5.2). Likewise, the associations with age (p *trend* <0.0001), gender, and SES (p *trend* =0.08) remained consistent. However, compared to the univariate model, ORs for receiving PreOP *versus* PostOP CRT were markedly lowered, although not statistically significant, among AO and Hispanic patients in the multivariable model (AO: OR=0.89, 0.77-1.03; Hispanic: OR=0.92, 0.80-1.06).

Table 5.2. Adjusted[$] odds ratios (OR) with 95 % confidence intervals (CI) for stage II and III rectal cancer cases receiving perioperative chemoradiotherapy (CRT) by time-period and demographic variables, 1994-2009.
Data from the California Cancer Registry.

Independent Variables	PreOP CRT[†]/PostOP CRT[‡]	
	OR	95% CI
Time-Period		
Early (1994-1997)	**0.07**	0.06-0.08
Middle (1998-2005)	**0.33**	0.29-0.36
Late (2006-2009)	**1**	-
	p*<0.0001	
Age		
<50	**1.31**	1.15-1.48
50-74	**1**	-
75+	**0.95**	0.83-1.09
	*p**<0.0001	
Gender		
Female	**0.83**	0.75-0.92
Male	**1**	-
Race/Ethnicity		
Asian/Other (AO)	**0.89**	0.77-1.03
Hispanic	**0.92**	0.80-1.06
Non-Hispanic black (NHB)	**0.98**	0.78-1.23
Non-Hispanic white (NHW)	**1**	-
Socioeconomic status (SES)[#]		
1	**0.88**	0.74-1.04
2	**0.86**	0.74-1.00
3	**0.86**	0.74-0.99
4	**0.87**	0.76-1.01
5 Highest	**1**	-
	*p**=0.08	

[$]Adjusted for time-period and demographic variables (age, gender, race/ethnicity, and socioeconomic status).
[†]PreOP CRT includes patients receiving radical surgery with preoperative chemoradiotherapy.
[‡]PostOP chemoRT includes patients receiving radical surgery with postoperative chemoradiotherapy.
**p*-value for trend.
[#]SES is measured using a Census derived index based on place of residence [29].

The Cox proportional hazards regression analysis showed that PreOP *versus* PostOP CRT from 1994 through 2005 was associated with higher mortality (1994-1997: HR=1.44, 1.20-1.71; 1998-2001: HR=1.35, 1.19-1.54; 2002-2005: HR=1.15, 0.99-1.34), while mortality was lower from 2006 to 2009 (HR=0.81, 0.63-1.04) (Table 5.3, Figure 5.2).

Table 5.3. Hazard ratios (HR) with 95% confidence intervals (CI) for preoperative *versus* postoperative chemoradiotherapy among stage II and III rectal cancer cases over years of surgery date (four categories), 1994-2009.

Data from the California Cancer Registry.

Year of Surgery	HR[†]	95% CI
1994-1997	**1.44**	1.20-1.71
1998-2001	**1.35**	1.19-1.54
2002-2005	**1.15**	0.99-1.34
2006-2009	**0.81**	0.63-1.04
	p*<0.0001	

[†]HR adjusted for age, gender, race/ethnicity, and socioeconomic status (SES) variables.

*p-value for trend.

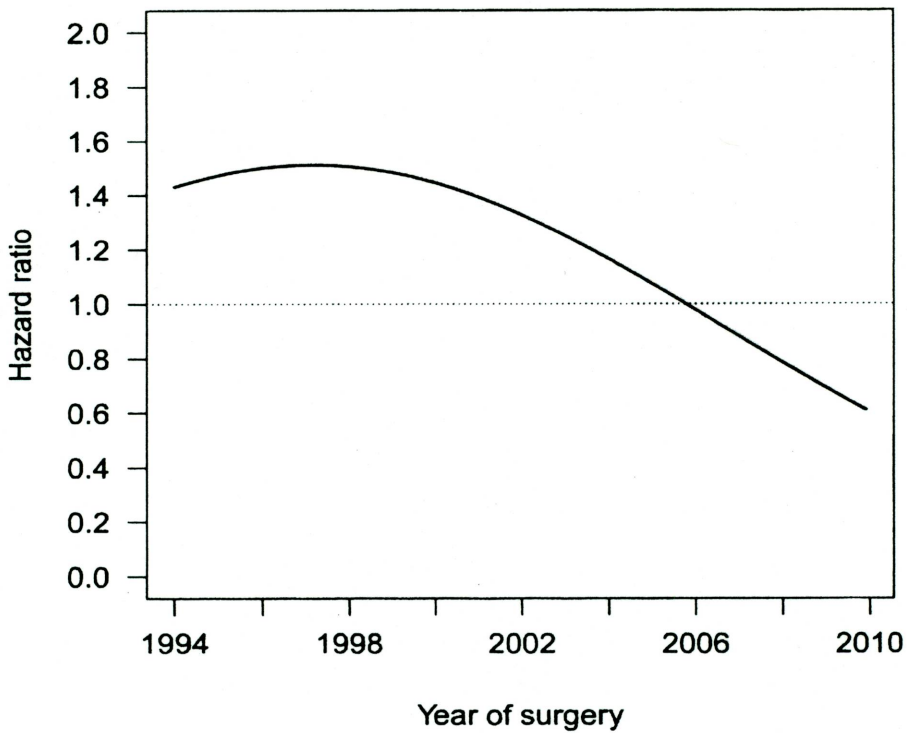

Figure 5.2. Hazard ratios with 95% confidence interval for preoperative *versus* postoperative chemoradiotheapy adjusted for demographic variables (age, gender, race/ethnicity, and socioeconomic status) among stage II and III rectal cancer cases over years of surgery date (continuous variable), 1994-2009.
Data from the California Cancer Registry.

DISCUSSION

Our population-based findings provide direct evidence of a stepwise increase in the ratio of PreOP to PostOP CRT over the three time-periods, Early (1990-1997), Middle (1998-2005), and Late (2006-2009), among stage II and III RC patients in the diverse California population consistent with current NCCN guidelines. This relatively rapid shift was most likely propelled by findings from the European rectal cancer treatment trials [12,13].

Younger age predicted more substantial shift from PostOP to PreOP CRT, compared to age 50-74 years, while patients older than age 74 showed no change in perioperative CRT during the study period. This difference may reflect a tendency for more aggressive treatment of younger patients who may be hardier and experiencing fewer co-morbidities than older patients who may have more medical contraindications to treatment with PreOP CRT, particularly with regard to the immunosuppressive status of those 80 years or older.

We observed a lower OR of PreOP to PostOP CRT among females than males. The explanation for this is unclear. Since PreOP CRT reduces tumor sizes before surgery, one possibility is that RC in males, even at the same histopathologic stage, are more often adjacent to structures such as large blood vessels. The higher PreOP CRT may also reflect later diagnosis and more serious presentation among males who in general are less prone to seek medical assistance than females. This observed gender difference needs further study in cohorts where more detailed information on surgery records, computed tomography or magnetic resonance imaging is available.

Our findings of lower ratios of PreOp to PostOp CRT among AO and Hispanic, compared to NHW patients (Table 5.2), may reflect different compliance with NCCN guidelines according to race/ethnic group. Although not significantly lower, these findings may result from differences in hospital surgery services or quality of care differences in various hospitals, including surgical volume and demographic characteristics of populations served by various facilities. Hospitals with the best treatment results for RC may have high surgical volume, be more likely to use the latest treatment and methodology, be the first to follow new NCCN guidelines, and be located in areas with mainly NHW populations. However, our analyses did not reveal any significant differences in compliance with NCCN guidelines across SES quintiles, indicating that SES does not by itself constitute a selection criterion for receiving PreOP *versus* PostOP CRT among stage II and III RC patients.

According to our survival analysis, there is a significant difference in HR for PreOP *versus* PostOP CRT depending on time of surgery ($p<0.0001$) (Table 5.3 and Figure 5.1). PreOP CRT is associated with higher mortality from 1994 to 2005, and with lower mortality from 2006 to 2009. It is unlikely that this is related to the timing of CRT (i.e. before or after surgery), because the outcome of this treatment modality is not expected to be time dependent. Our findings are in line with the results from the German randomized study [13,27] which found no difference in overall survival between PreOP and PostOP CRT. The shift in survival over time from PostOP to PreOP CRT could possibly be explained by factors associated with improvements in medical technology. These include: (1) Advances in radiation techniques, such as 3-dimentional conformal radiation therapy (3DCRT) [31], and intensity-modulated radiation therapy (IMRT)

[31,32]; (2) Development of new drugs, such as cetuximab [33,34] approved by FDA in 2004, and bevacizumab [35] approved by FDA in 2004 as first line, in 2006 as second line. Results from randomized clinical trials [33,34,35] indicate that survival in rectal cancer patients has improved further after these new drugs were added to a standard regimen of fluorouracil and/or leucovorin as PreOP CRT. Specifically, these new drugs seem to improve survival by preventing distant metastasis. Increased use of PreOP *versus* PostOP CRT after 2006 coincides with adoption of these new advances in both RT and chemotherapy resulting in improved survival. Today, the main purpose of PreOP CRT is to shrink the tumor size before surgery among stage II and III RC patients, and to reduce complications during surgery and postoperatively, particularly if the tumor is located very close to surrounding tissues. This may also have caused a selection bias in our study population regarding which patients received PreOP *versus* PostOP CRT after 2006.

In conclusion, according to our findings, a stepwise change from PostOP to PreOP CRT has taken a place in the treatment of stage II and III RC from 1994-2009. Although our findings for 2008-2009 reveal significantly improved survival among patients receiving PreOP *versus* PostOP CRT (Figure 5.2), this observation is most likely due to other factors associated with the use of PreOP CRT. Those surgeons/hospitals practicing PreOP CRT may be more likely to readily adopt newer radiation techniques and use of newer chemotherapy, both of which have shown improved survival.

Limitations: Our data do not provide information on second course of chemotherapy. We have identified the type of chemotherapy given as first course of treatment, such as single, multiple or not otherwise specified agents. However, we have no information about which specific drugs were used. This prevents assessment of the

exact NCCN treatment standard for stage II and III rectal cancer. Because short-course RT is not an NCCN treatment standard, we did not assess this perioperative RT practice. Although CCR data were not obtained in a randomized clinical trial, our data have other strengths in that they represent a 100 percent sampling of eligible patients from a long-standing statewide population-based cancer registry with immense diversity. As such, there is strong generalizability to the general population. However, our data provided no information on comorbidities which could contribute to survival differences, and may have also contributed to perioperative CRT timing. Our study included no mechanisms to balance for these unmeasured effects, which may have differed in comparison groups.

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CHAPTER 6

CONCLUSION

Firstly, PeriOP CRT is associated with significantly improved survival among stage II and III RC patients throughout the entire study period, 1994-2009, compared to patients receiving surgery alone (Figure 4.2). The survival benefit increased over the time-period of our study, suggesting that changes in CRT procedures have been modified over time. These changes in CRT methodology include improvements in medical technology such as advances in radiation techniques (e.g., 3-dimentional conformal radiation therapy [3DCRT; Zutshi, Hull, Shedda, Lavery, & Hammel, 2012], and intensity-modulated radiation therapy [IMRT; Pazdur, Wagman, Camphausen, & Hoskins, 2009; Zutshi, Hull, Shedda, Lavery, & Hammel, 2012]) and development of new drugs, particularly cetuximab (Galvin et al., 2004; Jonker et al., 2007) and bevacizumab (Karapetis et al., 2008) which were added to fluorouracil (5-FU) and/or leucovorin (LV) during the time period assessed.

Secondly, a stepwise change from PostOP to PreOP CRT has taken a place in the treatment of stage II and III RC from 1994-2009. Although our findings for 2008-2009 show a significantly improved survival among patients receiving PreOP *versus* PostOP CRT (Figure 5.2), this observation is most likely due to other factors associated with the use of PreOP CRT. Those surgeons/hospitals practicing PreOP CRT may be more likely to readily adopt newer radiation techniques and use of newer chemotherapy, both of which have shown improved survival.

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