Ann Surg Oncol (2013) 20:4063–4066
DOI 10.1245/s10434-013-3267-0

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEALTHCARE POLICY AND OUTCOMES

Association Between Postoperative Complications and Clinical Cancer Outcomes

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ABSTRACT

Introduction. The treatment for a majority of solid organ tumors is surgical resection; 10–20 % of patients suffer a perioperative complication. Perioperative complications may contribute to cancer recurrence. This study examined the relationship between postoperative complications and risk-adjusted patient overall survival.

Methods. Data from 2003 to 2009 were linked from our clinical cancer registry, the National Surgery Quality Improvement Project (NSQIP), and medical records. Patients who had tumor extirpation for cure were included. The NSQIP was used to identify complications. Patients with a complication were matched to patients without a complication. χ^2 tests and Cox proportional hazard regression models were used.

Results. A total of 415 patients were included for survival analysis. The hazard ratio (HR) for mortality associated with having a complication was 2.17. The HR for mortality after 200 days postoperatively was 2.47. Infectious complications were associated with the highest association with increased mortality (HR = 3.56). Noninfectious complications were not associated with an increased risk of mortality.

Conclusions. This study investigated the relationship of surgical infectious complications in cancer patients with long-term survival for patients who had a number of different types of cancer. After taking into account the site, histology, and stage of the cancer, we found that patients with infectious complications had earlier death.

Presented in abstract form at the Association of Academic Surgeons, February 1–3, 2011, Huntington Beach, CA.

First Received: 4 February 2013;
Published Online: 20 September 2013

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The primary treatment for the majority of solid organ tumors remains surgical tumor extirpation. The complex nature of these surgeries leads to a high rate of perioperative complications, occurring in 5–30 % of all cases.[1–3] The inflammatory state caused by complications of cancer therapy has been implicated in the progression of disease. Surgical morbidities, specifically, may contribute to subsequent cancer recurrence and progression.[4,5] Evidence to this effect in the surgical setting has been shown in colorectal and esophageal cancer resections, in which patients who suffered a postoperative complication had poorer outcomes.[6–8] The present study is the first published report to review a diverse group of malignant diagnoses, and attempts to examine whether postoperative complications are associated with decreased risk-adjusted survival across this broad spectrum of cancer resection surgeries.

METHODS

With approval from the institution's research protocol review board, data were obtained from three sources at the University of Utah Hospitals: (1) the Cancer Clinical Research (CCR) database, (2) the National Surgery Quality Improvement Project (NSQIP) database, and (3) patient medical records. The CCR securely links clinical and research data from various patient care and research groups throughout the University of Utah Healthcare System. It was used to identify patients who had tumor extirpation for cure, patient age, and survival information. The NSQIP data elements and methods for abstraction were initially developed by the Department of Veterans Affairs. NSQIP has been

extended to non-VA hospitals with the support of the American College of Surgeons and used at the University of Utah Hospitals since 2003. For this study, utilizing data from 2003 to 2009, the NSQIP database provided information about infectious (sepsis, wound infection, pneumonia, urinary tract infection, and anastomotic leak) and noninfectious surgical complications (bleeding requiring transfusion, cardiac arrest, deep vein thrombosis, myocardial infarction, ventilator greater than 48 h, progressive renal insufficiency, and unplanned intubation).

Patient Selection

There were 1,580 patients in the CCR database that could be linked to data in the NSQIP database. These patients were divided into groups that had the same site of primary disease, histology, and tumor staging. Patients were excluded from the analysis if they were in groups that did not contain at least one patient with a complication, one patient without a complication, and one patient who died. They were also excluded if the cancer stage was unknown or stage 4. After these exclusions, there were 10 groups containing 493 patients, included in the survival analysis.

Statistical Analysis

We used Cox proportional hazard regression model to test whether a postoperative complication was associated with time to outcome (death). Hazard ratios (HRs) are reported with the associated 95 % CIs. The association between complication and outcome was measured by the HR, which is similar to relative risk. All analyses were adjusted for age and for group determined by site, histology, and stage. Analyses were performed on all patients and again after excluding patients who were loss to follow-up or had the outcome less than 200 days after the operation. This outcome of 200 days was chosen to eliminate all extended postoperative complications resulting in eventual death and to exclude early aggressive tumor progression, which would indicate a failed curative surgical effort. These patients were excluded to reduce the likelihood of alternative explanations for the outcome, i.e., short-term deaths may have been due to factors independent of cancer recurrence, and short-term cancer recurrence may have been due to large amounts of residual disease present at the time of surgery.

RESULTS

The median overall follow-up time for survivors was 921 days. The overall survival of the study population was 87 %, the 2-year survival rate computed from the Kaplan–Meier survival analysis was 92 %. Table 1 demonstrates the disease histology included in the analysis, the mean age, the number of patients in each stage with or without a postoperative complication, as well as the site specific mortality rate. The overall median follow-up for survivors in the population who suffered any complication ($n = 72$) was 852.5 days (mortality 31.5 %) versus 929 days (mortality 8.7 %) for those who did not suffer a complication ($n = 421$; $P < 0.001$). Cox Proportional Hazard Regression Analysis was used to test the association of complications with survival outcome, calculated in mortality, adjusting for patient age, site of disease, and stage. The Cox regression confirmed a 2.17-fold increased risk of a mortality having suffered a postoperative complication. In order to eliminate operative mortality from the analysis, a Cox regression adjusted for a combination of age, site, and stage was performed, including only mortalities that occurred longer than 200 days from the date of surgery (1.2 and 2.2 % of the no-complications and complications groups respectively suffered a mortality within the first 200 days; Table 2). The longer than 200 days postsurgery Cox regression demonstrated a 2.47-fold increase in mortality, having suffered a postoperative complication. Table 2 also demonstrates the difference between infectious and noninfectious complications and association with survival, with a 3.56-fold increase risk of mortality longer than 200 days after surgery, if an infectious complication occurred. There was no significant correlation with whether a patient suffered sepsis from the infectious complication (by the NSQIP definition of sepsis) or the type (location) of the infectious complication and overall mortality. Noninfectious complications did not increase the risk of overall mortality or the longer than 200 days postoperative mortality.

DISCUSSION

This study investigated the association between postoperative complications following solid organ cancer surgery and the overall survival of the patient, in a broad group of cancer diagnoses. We have shown that after taking into account patient's age, the site of disease, histology, and stage of the cancer; the occurrence of any postoperative complication decreases overall survival. Allowing that a postoperative complication incites an increased systemic inflammatory response and altered local inflammatory response to wound healing, we believe this result is evidence that an altered immune response in the setting of postoperative complications increases the risk for cancer progression and decreases survival.

This study verifies, in a broader population, independent studies that found surgical complications were associated with a worse prognosis for patients who had colorectal, hepatocellular, and esophageal cancers. The relationship between perioperative inflammation and poorer prognosis

TABLE 1 Characteristics of patients included in survival analysis

Cancer site and histology	*N*	Mean age (range)	Mortality rate (% dead)	Complications (N in each stage)		No complications (*N* in each stage)	
				All	Count by stage IS/I/II/ III	All	Count by stage IS/I/II/III
Breast	176	58.5 (29–91)	3.4	5	2/3/0/0	171	37/134/0/0
Colorectal	205	60.0 (21–92)	11.7	53	0/13/19/21	152	0/42/38/72
Liver (hepatocellular carcinoma)	3	66.0 (50–76)	33.3	2	0/0/2/0	1	0/0/1/0
Ampulla of vater (adenocarcinoma)	10	65.9 (40–81)	40	6	0/0/5/0	4	0/0/5/0
Pancreas	27	66.3 (48–91)	44.4	11	0/0/11/0	16	0/0/16/0
Retroperitoneum	2	51.5 (43–60)	50	1	0/0/0/1	1	0/0/0/1
Endometrium	13	60.8 (36–83)	30.8	2	0/2/0/0	11	0/7/0/4
Ovary	7	61.4 (46–75)	14.3	1	0/0/0/1	6	0/0/0/6
Prostate	43	67.1 (52–85)	14	7	0/3/4/0	36	0/4/32/0
Bladder	7	68.7 (55–79)	71.4	4	0/2/1/1	3	0/2/1/0
Total	493	60.7 (21–92)	13	92	2/16/33/21	401	37/196/102/86

TABLE 2 Hazard ratio of mortality associated with types of surgical complications after 200 days

Complication type	Frequency ($n = 472$)	Deaths	HR for mortality[e,f] (95 % CI)
No complication	81 % (383)	30	1 (REF)
Any[a]	19 % (89)	27	2.47 (1.41–4.34)
Infectious[b]	15 % (69)	23	3.56 (1.94–6.53)
Sepsis[c]			
Yes	5 % (24)	9	3.42 (1.52–7.71)
No	10 % (45)	14	3.68 (1.783–7.58)
Location[d]			
SSI	10 % (48)	16	3.5 (1.79–6.85)
UTI	3 % (12)	3	4.43 (1.21–16.2)
Other	2 % (9)	4	3.37 (1.05–10.76)
Noninfectious[b]	4 % (20)	4	0.88 (0.29–2.67)

[a] Cox PH model compares the groups No complications versus any complication

[b] Cox PH model compares the groups No complication, infectious complication, noninfectious complication

[c] Cox PH model compares the groups No complication, infectious sepsis complication, infectious non-sepsis complication, and noninfectious complication

[d] Cox PH model compares the groups No complication, infectious SSI complication, infectious UTI complication, other infectious complication and noninfectious complication

[e] All models adjust for age and disease group effects

[f] All HRs are based on "no complication" as the referent group

in colorectal cancers has been studied by Roxburgh et al.[9,10] More specifically, several studies also have correlated an increased local tumor recurrence and decreased recurrence-free survival of colorectal adenocarcinomas with an anastomotic leak, independent of AJCC TNM staging.[11–13] Additional studies have shown poorer long-term survival in the setting of increased blood transfusion requirements for esophagectomy with esophageal cancers owing in part to the relative immune suppression associated with blood transfusion.[14,15] Postoperative complications have been implicated in decreasing overall survival and increasing overall recurrence in colorectal and esophageal cancer surgeries, and hepatectomies for colorectal metastases, as well.[7,11,16–20] This study suggests that a similar relationship between complications and poorer oncologic outcome exists for breast, gynecologic, and urologic cancer operations as well.

A possible explanation for these results could be an innate immune system "distraction." The association between cancers and innate immune response is dichotomous. There is extensive evidence that chronic innate immune surveillance may inhibit tumor growth and progression. Yet, there also is evidence that proinflammatory cytokines promote tumor growth, angiogenesis, and invasion. The clinical impact of this dichotomy is difficult to interpret at a cellular level. Yet, we believe that both scenarios may explain the poor prognostic effect of a postoperative complication in a cancer surgery. We hypothesize that cytokines released in the setting of an infectious, thrombotic, ischemic, or hypotensive event may all contribute to a protumorigenic environment, as has been previously shown at the molecular level.[5,21] Conversely, we suspect that the innate immune surveillance that chronically inhibits tumor progression may be diverted to the healing or inflammatory state, which may allow uninhibited tumor cell progression.[22] Two recent reviews on inflammation and cancer propose similar relationships between acute inflammation and poor cancer prognosis.[23,24]

Considering these two collaborative hypotheses of a possible "immune system distraction," the accelerated inflammatory state resulting from a postoperative complication compared with an uncomplicated recovery could explain the age, site of disease, and stage independent poorer prognosis of patients suffering a complication. This is the first study to show a significant correlation between any postoperative complication and poorer cancer prognosis for a broad range of sites of solid organ disease, unrelated to patient age, stage of disease, and tumor type at presentation. This study stresses the relevance of strategies to mitigate postoperative complications in surgical oncology as a means of minimizing perioperative morbidity and mortality associated with these procedures and, perhaps more importantly, to improve upon the ultimate goal of a cancer operation in the first place, to improve cancer-specific survival.

ACKNOWLEDGMENT This study was supported in part by the Huntsman Cancer Foundation support of the Clinical Cancer Research database.

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