Cancer Mortality Among Recipients of Solid-Organ Transplantation in Ontario, Canada

Sergio A. Acuna, MD; Kimberly A. Fernandes, MSc, Astat; Corinne Daly, MSc; Lisa K. Hicks, MD, MSc; Rinku Sutradhar, PhD; S. Joseph Kim, MD, PhD, MHS; Nancy N. Baxter, MD, PhD

**Importance**
Solid-organ transplant recipients (SOTRs) are at greater risk of developing some cancers than the general population; however, because they are also at increased risk of mortality from noncancer causes, the effect of transplantation on cancer mortality is unclear.

**Objective**
To describe cancer mortality in SOTRs and to assess whether SOTRs are at increased risk of cancer mortality compared with the general population.

**Design, Setting, and Participants**
Population-based cohort study of patients who underwent solid-organ transplantation in Ontario, Canada, between 1991 and 2010 with 85,557 person-years of follow-up through December 31, 2011. Solid-organ transplantation was identified using the national transplant register and linked to the provincial cancer registry and administrative databases. The analysis was conducted between November 2013 and February 2015.

**Exposure**
Solid-organ transplantation.

**Main Outcomes and Measures**
Cancer mortality for SOTRs was compared with that of the general population using standardized mortality ratios (SMRs). Mortality and cause of death were ascertained by record linkage between the Canadian Organ Replacement Register, the Ontario Cancer Registry, and the Office of the Registrar General of Ontario death database.

**Results**
A total of 11,061 SOTRs were identified, including 6,516 kidney, 2,606 liver, 929 heart, and 705 lung transplantations. Recipients had a median (interquartile range) age of 49 (37-58) years, and 4,004 (36.2%) were women. Of 3,068 deaths, 603 (20%) were cancer related. Cancer mortality in SOTRs was significantly elevated compared with the Ontario population (SMR, 2.84 [95% CI, 2.61-3.07]). The risk remained elevated when patients with pretransplant malignant neoplasms (n = 1,124) were excluded (SMR, 1.93 [95% CI, 1.75-2.13]). The increased risk was observed irrespective of transplanted organ. The SMR for cancer death after solid-organ transplantation was higher in children (SMR, 84.61 [95% CI, 52.00-128.40]) and lower in patients older than 60 years (SMR, 1.88 [95% CI, 1.62-2.18]) but remained elevated compared with the general population at all ages.

**Conclusions and Relevance**
Cancer death rate in SOTRs was increased compared with that expected in the general population; cancer was the second leading cause of death in these patients. Advances in prevention, clinical surveillance, and cancer treatment modalities for SOTRs are needed to reduce the burden of cancer mortality in this population.
Solid-organ transplant recipients (SOTRs) are known to have an increased incidence of malignant neoplasm after transplantation compared with the general population, but the few population-based studies that have explored cancer mortality after transplantation report disparate findings.\(^1\) An increased cancer incidence may not necessarily result in increased cancer mortality in this population; SOTRs have decreased survival rates and are at higher risk of dying of noncancer causes relative to the general population.\(^4\),\(^6\),\(^7\) In addition, common malignant neoplasms in SOTRs, such as nonmelanoma skin cancer (NMSC), are typically curable in the general population and have low mortality in the transplant population.\(^8\),\(^9\) Once a malignant neoplasm is diagnosed, transplant recipients have worse outcomes than patients with cancer who have not undergone transplantation.\(^10\)\(^-\)\(^13\) There are several explanations for this observation: malignant neoplasms arising in an immunosuppressed environment may be more biologically aggressive,\(^12\)\(^,\)\(^24\) and patients may receive less aggressive cancer treatment due to comorbidities and the fear that transplant rejection may occur.\(^11\)

Improving our understanding of the burden of cancer in this population is important. If SOTRs are at a high risk of dying of cancer, different screening and treatment strategies may be needed for this population. We therefore designed this study to determine the overall and site-specific risk for cancer mortality in a population-based cohort of SOTRs in Ontario, Canada, over a 20-year period.

**Methods**

**Study Population**

We designed a retrospective population-based cohort study including all SOTRs from January 1, 1991, through December 31, 2010, in the province of Ontario, Canada. The cohort was assembled using the Canadian Organ Replacement Register, a national registry that contains information on approximately 98% of all Canadian SOTRs since 1981.\(^15\) Transplants of the same organ occurring within 1 week of each other were combined into a single episode because they likely represent duplicate records. Non-Ontarian residents were excluded from the study population (n = 1253) because these patients could not be linked to the provincial registries and databases in Ontario. Patients who died within 30 days of transplantation were also excluded (n = 311) because these deaths were assumed to reflect perioperative mortality and were unlikely due to cancer. Patients were observed from the date of transplantation until death or December 31, 2011, to allow a minimum of 1 year of follow-up for all cohort members. The Research Ethics Board of St Michael’s Hospital, Toronto, Canada, approved the study and waived the need for informed consent due to the retrospective nature of the study.

To determine whether patients had a preexisting malignant neoplasm or developed a malignant neoplasm after transplantation (de novo malignant neoplasm), we linked members of our cohort to the Ontario Cancer Registry (OCR). This registry contains information on all incident cancers (other than NMSC) since 1964 in Ontario and has been estimated to be more than 95% complete.\(^16\) The OCR registers the first incident cancer for a cancer site and does not capture disease recurrence. All malignant neoplasms occurring at least 30 days after transplantation were considered posttransplant de novo malignant neoplasms. Patients who had a malignant neoplasm before transplantation (n = 1124), including those whose indication for transplantation was cancer (n = 442), were still at risk of a posttransplant de novo cancer in another organ; therefore, they were not excluded. However, these patients did not contribute person-years at risk for death from posttransplant de novo cancer for the same cancer site as the antecedent cancer.

**Key Points**

**Question** What is the cancer mortality in solid-organ transplant recipients (SOTRs), and are they at increased risk of cancer mortality compared with the general population?

**Findings** In this population-based cohort study of 11,061 SOTRs, cancer mortality was significantly elevated, irrespective of age and transplanted organ, compared with the Ontario population. The increased risk was observed. Cancer site-specific mortality risk for SOTRs was at least as high or higher than that of the general population for all cancer sites.

**Meaning** Cancer was the second leading cause of death in all SOTRs, indicating a substantial cancer burden in this population.

**Outcome Assessment and Classification**

Mortality was determined from death certificates using the Office of the Registrar General of Ontario death database (ORGD) and verified using OCR cause of death. A high level of agreement in the cause of death has been reported between the OCR and a prospective cohort of patients with cancer with intensive clinical follow-up.\(^17\) Causes of death were coded using the *International Classification of Diseases, Ninth Revision (ICD-9)*, and classified into ICD-9 disease chapters; deaths coded ICD-9 140-239 were considered cancer related. To determine whether cancer deaths were caused by a posttransplant de novo malignant neoplasm or the recurrence of a pretransplant malignant neoplasm, the cause of death was matched to cancer diagnosis information from the OCR (eFigure 1 in the Supplement). Because the OCR does not collect incident information for NMSC, we assumed that patients who died of NMSC received a diagnosis after transplantation (ie, these were de novo malignant neoplasms). Malignant neoplasms diagnosed between 7 days before and 30 days after transplantation (n = 234 [21%]) were considered present at transplantation and the mortality associated with them over follow-up was considered recurrent cancer deaths (vs deaths from a de novo cancer). We grouped year of transplantation into 4 equal periods to look at secular trends. Malignant neoplasms were classified as having a related or possible-related infectious etiology as described by Grulich et al.\(^18\)

**Statistical Analyses**

The ratios of observed to expected number of cancer deaths, the cancer standardized mortality ratios (SMRs), were calculated for all SOTRs. Cancer mortality rates in the general population were calculated using information obtained from ORGD and population estimates from Statistics Canada. Cancer mortality rates in the SOTRs were compared with those in the general Ontario population.
population using indirect standardization per year, and stratified into 5-year periods (eg, 1991-1995), age group (eg, 30-34 years), and sex. The ratio of actual (observed) cancer deaths in the study cohort to expected number of deaths in the corresponding provincial population estimated the SMR. An SMR greater than 1 indicates greater than expected mortality whereas an SMR less than 1 indicates lower than expected mortality. The Byar approximation of the exact Poisson distribution was used to calculate the 95% confidence intervals assuming that the observed cancer deaths followed a Poisson distribution. Cancer mortality site information was obtained from the ORGD cause of death field. When cause of death was coded as a malignant neoplasm of unspecified behavior, unknown site, benign, or secondary, an algorithm was applied to attribute the case to a malignant site category when possible (eTable 1 in the Supplement). A sensitivity analysis was performed considering these cases as unknown. For the analyses by transplanted organ, patients who underwent combined organ transplantation were allocated to the organ associated with the need for the highest degree of immunosuppression. Given the small number of pancreas and small bowel transplant recipients, these groups were not analyzed separately and were assigned to another organ group.

Cause of death was grouped by ICD-9 chapter and described using percentages. The cumulative incidence function of cancer deaths was calculated, treating other deaths as a competing risk. Cumulative incidence functions by transplant period were compared using the Gray test and cancer and non–cancer-specific mortality cumulative incidence functions were compared according to Aly et al. Analyses were performed using SAS, version 9.3 (SAS Institute).

Results

We identified 11,061 SOTRs. The median (interquartile range) age of recipients was 49 (37-58) years, and 4004 (36.2%) were women. The distribution of transplanted organ was as follows: 6516 (59%) kidney, 2606 (24%) liver, 929 (8%) heart, and 705 (6%) lung. The median (interquartile range) follow-up time was 6.63 (3.27-11.53) years, representing 85,557 person-years.

In total, 1124 (10%) patients had a history of pretransplant malignant neoplasm. Among these, malignant neoplasm was the underlying reason for transplantation in 442 (39%) patients, 234 (21%) had a malignant neoplasm diagnosed around the time of transplantation, and 448 (40%) had malignant neoplasms in presumed remission. Posttransplant de novo malignant neoplasms occurred in 1267 (11%) patients. Median (interquartile range) time from transplantation to posttransplant de novo cancer diagnosis was 5.16 (2.22-9.43) years.

Patient characteristics at the time of transplantation are summarized in eTable 2 in the Supplement. In this study cohort, there were 3068 (28%) deaths of which 603 (20%) were cancer related. The majority of cancer-related deaths were secondary to posttransplant de novo malignant neoplasms (n = 411 [68%]), while recurrent malignant neoplasms were responsible for 21% (n = 127). Most of the cancer deaths associated with pretransplant malignant neoplasms were caused by malignant neoplasms that were the indication for transplantation (n = 98 [77%]) and recipients who underwent transplantation for cancer accounted for a much greater proportion of those who died of cancer (liver, 89 of 215 [41%]; lung, 9 of 40 [22%]). In 65 cases of cancer-related deaths, the death events could not be attributed to the timing of cancer diagnosis (1%) (eFigure 1 in the Supplement). Most cancer-related deaths occurred in patients with functioning grafts (n = 473 [78%]). The cumulative incidence of cancer and non–cancer-related deaths is presented in Figure 1. Although the risk of non–cancer death exceeded cancer-related mortality (P < .001), the risk of cancer-related death increased steadily over time. Cancer was the second leading cause of death for all SOTRs (20%) after cardiovascular disease (24%) and the most common cause of death in liver transplant recipients (26%) (eTable 3 in the Supplement).

Lung cancers were the most common cause of cancer death (n = 126 [21%]), followed by liver cancers (n = 107 [18%]), most due to cancers that predated transplantation, non-Hodgkin lymphoma (NHL; n = 96 [16%]), and colorectal cancer (n = 43 [7%]). In contrast, NMSC accounted for a small proportion of cancer deaths (n = 20 [3%]). The distribution of cancer deaths by site is presented in Figure 2.

For all transplant recipients, the overall age and sex standardized SMR from cancer was statistically significantly increased compared with the general population (SMR, 2.84 [95% CI, 2.61-3.07]). No differences in SMR by sex were observed (data not shown). The excess risk persisted after excluding deaths from malignant neoplasms that were the indication for transplantation (SMR, 2.38 [95% CI, 2.18-2.60]), and when only mortality from posttransplant de novo malignant neoplasms was considered (SMR, 1.93 [95% CI, 1.75-2.13]). Deaths and SMR by cancer site are shown for all cancer-related deaths in Figure 2, and for posttransplant de novo malignant neoplasms in Figure 3. Site-specific overall and posttransplant de novo malignant neoplasm SMRs were at least equal to or greater than those for the general population for all SOTRs for all cancer sites. Including all cancer deaths, skin cancer had the highest incremental risk of death for SOTRs (SMR, 29.82 [95% CI, 18.23-46.10]), followed by NHL (SMR, 9.76 [95% CI, 7.91-11.93]). Solid-organ transplantation recipients had a much higher risk of death from skin cancer than the general population (SMR, 29.82 [95% CI, 18.23-46.10]) compared with the general population (SMR, 1.93 [95% CI, 1.75-2.13]).
higher risk of death from liver cancer (SMR, 12.72 [95% CI, 10.43-15.37]) although the risk of death from liver cancer was greatly reduced when patients who underwent transplantation for liver cancer were excluded (SMR, 2.28 [95% CI, 1.35-3.61]). The SMRs of malignant neoplasms with presumed infectious etiology were higher (SMR, 6.57 [95% CI, 5.76-7.25]) than for those without a presumed infectious etiology (SMR, 1.81 [95% CI, 1.61-2.02]). No difference was observed in the SMR for any analysis when metastatic, unknown site, or unspecified behavior malignant neoplasms were not reassigned based on our algorithm using the cancer diagnosis codes (data not shown).

The overall SMR for cancer was higher for SOTRs than for the general population across all age groups (eFigure 2a in the Supplement). Notably, the risk of cancer death was highest in the pediatric transplant population (SMR, 84.61 [95% CI, 52.00-128.40]) and lowest in transplant recipients older than 60 years (SMR, 1.88 [95% CI, 1.62-2.18]) when compared with the general population. The same pattern was observed for posttransplant de novo malignant neoplasm–associated cancer deaths. There was an excess cancer mortality risk for SOTRs irrespective of transplanted organ (eFigure 2b in the Supplement), and a similar excess cancer mortality risk for de novo malignant neoplasm. The SMRs for all cancer deaths by cancer site and transplanted organ are presented in eTable 4 in the Supplement. Although all transplant recipients were at increased risk of NHL mortality, cardiothoracic recipients had the highest risk. Several differences existed in the site-specific risk of cancer mortality across transplant recipients.
mortality. Liver transplant recipients were at increased risk of dying from posttransplant de novo liver cancers, while only kidney recipients were at increased risk of mortality from leukemia, melanoma, and colorectal, oral cavity/pharynx, and prostate cancer. Liver, heart, and lung recipients were at increased risk of mortality from esophageal cancer. The cumulative incidence of deaths due to cancer over time did not differ by transplant period (eFigure 3 in the Supplement).

Discussion

Our study represents, to our knowledge, the largest population-based study evaluating cancer mortality from posttransplant de novo and recurrent malignant neoplasms in all SOTRs. This report demonstrated that SOTRs were at increased risk of cancer death compared with the general population, regardless of age, sex, transplanted organ, and transplant period. Moreover, the excess risk of cancer death persisted after excluding cancer mortality from cancers diagnosed before transplantation. Cancer was the second leading cause of death in all SOTRs, indicating a substantial cancer burden in this population. In our study, cancer site–specific mortality risk for SOTRs was at least as high as or higher than that of the general population for all cancer sites.

There are few prior estimates of cancer mortality in SOTRs. A large population-based study that examined cancer mortality in 164,078 US kidney transplant recipients reported no excess risk of cancer mortality compared with the general population; this finding was attributed to the competing risk of noncancer death in this group.4 However, in this study a large number of patients who died had an unknown cause of death (41% of deaths). These were deemed non–cancer related for the analysis, and this fact may have contributed to the failure to find an increased risk of cancer deaths in that population. In contrast, our findings are consistent with European and Australian population-based reports that have shown an increased risk of cancer mortality in kidney3 and liver, heart, and lung transplant recipients.5

Assessment of the overall cancer mortality, including deaths caused by recurrent pretransplant malignant neoplasms and those associated with posttransplant de novo malignant neoplasms, is important to fully quantify the cancer burden and to develop strategies to reduce cancer deaths. Previous studies were unable to ascertain the type of cancer responsible for death and therefore could not determine whether

**Figure 3. Distribution of Cancer Deaths and Standardized Mortality Ratios (SMRs) by Cancer Site for Posttransplant de Novo Cancer Deaths in All Solid-Organ Transplant Recipients**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Observed Deaths, No. (%)</th>
<th>SMR (95% CI)</th>
<th>Decreased Mortality</th>
<th>Increased Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonmelanoma skin</td>
<td>20 (4.9)</td>
<td>29.85 (18.23-46.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>79 (19.2)</td>
<td>8.05 (6.38-10.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>13 (3.2)</td>
<td>3.42 (1.82-5.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone and soft tissues</td>
<td>7 (1.7)</td>
<td>3.06 (1.23-6.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>17 (4.1)</td>
<td>2.46 (1.43-3.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>15 (3.6)</td>
<td>2.29 (1.28-3.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity and pharynx</td>
<td>11 (2.7)</td>
<td>2.07 (1.03-3.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>41 (10.0)</td>
<td>1.78 (1.28-2.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>98 (23.8)</td>
<td>1.58 (1.28-1.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>18 (4.4)</td>
<td>1.56 (0.92-2.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>7 (1.7)</td>
<td>1.46 (0.59-3.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>8 (1.9)</td>
<td>1.14 (0.49-2.24)</td>
<td></td>
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</tr>
<tr>
<td>Prostate</td>
<td>10 (2.4)</td>
<td>1.06 (0.51-1.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecologic</td>
<td>7 (1.7)</td>
<td>1.01 (0.40-2.07)</td>
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<tr>
<td>Liver/biliary</td>
<td>12 (2.9)</td>
<td>1.52 (0.78-2.65)</td>
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</tr>
<tr>
<td>Kidney</td>
<td>5 (1.2)</td>
<td>0.92 (0.30-1.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12 (2.9)</td>
<td>0.63 (0.33-1.11)</td>
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</tr>
<tr>
<td>Breast</td>
<td>6 (1.5)</td>
<td>0.53 (0.19-1.15)</td>
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<tr>
<td>Unknown primary site</td>
<td>25 (7.02)</td>
<td>3.56 (2.30-5.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious5</td>
<td>174 (42.3)</td>
<td>3.74 (3.21-4.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninfectious</td>
<td>237 (57.7)</td>
<td>1.42 (1.24-1.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Any</strong></td>
<td>411 (100)</td>
<td>1.93 (1.75-2.13)</td>
<td></td>
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</table>

Standardized mortality ratios are presented in a log scale, with symbols indicating SMR, and error bars, 95% CI.

Malignant neoplasms were classified as having a related or possible-related infectious etiology as described by Grulich et al18: Hodgkin and non-Hodgkin lymphoma (Epstein-Barr virus); Kaposi sarcoma (human herpesvirus 8); hepatocellular carcinoma (hepatitis B and C virus); gastric cancer (Helicobacter pylori); and malignant neoplasms from the cervix uteri, male and female genitalia, anus, oral cavity and pharynx, esophagus, larynx, eye, and nonmelanoma skin cancer (human papillomavirus).
Cancer Mortality Among Recipients of Solid-Organ Transplantation in Ontario

Research Original Investigation

The factors underlying the increased burden of cancer mortality in SOTRs are complex. The higher mortality likely reflects the underlying increased incidence of cancer after transplantation. However, it is possible that other factors might be associated with the observed increase in cancer mortality. Transplant recipients who develop malignant neoplasms have been reported to experience worse outcomes than patients with cancer in the general population. Differences in cancer treatment have been associated with the worse cancer outcomes in SOTRs. Furthermore, malignant neoplasms after transplantation can have different clinical features that may explain higher mortality. In transplant recipients, NHL is part of the spectrum of posttransplant lymphoproliferative disorders and there are no clinical correlates of this disease in the nontransplant population. Non-Hodgkin lymphoma in the nontransplant population differs with respect to etiology, management, and prognosis. The high incidence of posttransplant lymphoproliferative disorders and the differences in the prognosis of NHL in transplant recipients could explain the elevated SMR for this disease. Last, although some similarity exists between the pattern of site-specific cancer mortality and the incidence patterns previously reported for Canadian transplant recipients; there are several discrepancies. Cancers of the bladder, kidney, and oral cavity and pharynx, for example, had similar mortality risk to that of the general population despite increased incidence rates.

Although posttransplant care guidelines have included the existing routine cancer screening recommendations for the general population, effectiveness and adherence to these are unknown. A tailored approach to cancer screening is likely required for transplant recipients. Given the high mortality of lung cancers, strategies to improve pretransplant and posttransplant lung cancer screening may be necessary. Screening with low-dose computed tomography in high-risk groups such as thoracic organ recipients and patients with smoking history could be considered. Specific cancer screening strategies for liver cancers should be evaluated in hepatic transplant recipients and for melanoma, colorectal, oral cavity, and prostate cancer in kidney recipients. Finally, cancer preventive strategies such as limitation of sunlight exposure, sun protection, smoking cessation, reduction in alcohol consumption, dietary changes, and physical activity should also be considered.

The major strengths of this study are its population-based nature, the large number of SOTRs, the comprehensive availability of the cause of death for all SOTRs, and the ability to link to a provincial cancer registry. Additionally, this is the only study that compares cancer mortality by type of SOTR and that evaluates recurrent vs posttransplant de novo cancer deaths. However, our study has some limitations. Although a high level of agreement in cause of death has been documented between the registries and primary sources, the multiple comorbidities that coexist in transplant recipients could affect the accuracy of the underlying cause of death on death certificates, increasing the chances for misclassification. Moreover, because NMSC incidence is not captured in our cancer registry, these deaths were considered to arise from new malignant neoplasms diagnosed after transplantation. Although this may have led to an overestimation of the risk of de novo NMSC death, published evidence suggests that this is unlikely. Importantly, these limitations are unlikely to have resulted in an overestimate of the total burden of cancer mortality in SOTRs.

Conclusions

Despite the fact that SOTRs have shorter life expectancies and a higher risk of dying of non–cancer-related causes, these patients have an elevated risk of cancer death as compared with the general population. Addressing the cancer burden in SOTRs is critical to improving the survival of these patients. Cancer is a leading cause of death in this population, and its incidence is expected to increase in the next 10 years as the median age of transplant recipients increases and improvements in survival with a functioning transplant lengthen exposure to immunosuppression. Specific strategies for cancer prevention, screening, surveillance, and optimization of treatment may be required to improve cancer outcomes for these patients.
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Study concept and design: Acuna, Hicks, Sutradhar, Kim, Baxter.

Acquisition, analysis, or interpretation of data: Acuna, Fernandes, Daly, Sutradhar, Kim, Baxter.

Drafting of the manuscript: Acuna, Daly, Sutradhar, Baxter.

Critical revision of the manuscript for important intellectual content: Acuna, Fernandes, Hicks, Sutradhar, Kim, Baxter.

Statistical analysis: Acuna, Fernandes, Daly, Sutradhar, Kim, Baxter.

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REFERENCES


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