A REVIEW OF CONDITIONAL SURVIVAL IN UROLOGICAL MALGNANCIES AND THREE LEADING CANCER PRIMARIES.

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ABSTRACT

OBJECTIVES:

To conduct a review of conditional survival (CS) in urologic oncology, in addition to examining CS in other leading cancer primaries. CS provides dynamic information on a patient's probability of survival by accounting for disease free interval (DFI), which invariably improves survival probability relative to immediate estimates at diagnosis or treatment.

METHODS:

A review of the literature was performed using PubMed, Medline, and Cochrane databases focusing on all articles addressing CS. Electronic articles published ahead of print were also considered. Search was limited to the English language and relied on keywords: conditional survival, oncology, urological oncology, and cancer. Studies were selected according to sample size, contemporaneity, and clinical relevance of the results.

RESULTS:

CS estimates are available for six urological cancers: (1) renal cell carcinoma, (2) squamous cell carcinoma of the penis, (3) urothelial cancer of urinary bladder, (4) upper tract urothelial carcinoma, (5) prostate cancer and (6) testicular cancer. Furthermore, CS estimates are available for three leading cancer primaries: (1) breast cancer, (2) colorectal cancer and (3) lung cancer. These estimates have been devised based on population data, as well as institutional databases. External validation and accuracy were reported for two CS models predicting cancer specific mortality in renal cell carcinoma and penile carcinoma.

CONCLUSIONS:

CS improves the precision of predictions, among patients who enjoy a disease-free survival (DFS), by accounting for DFS time. It is a dynamic measure that results in better prognosis in proportion to the length of DFS. Despite its advantage over survival probabilities

without adjustment for DFI, CS is not incorporated in most prognostic models.

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1. INTRODUCTION

Survival statistics, notably, overall survival (OS) and disease free survival (DFS) are important to both physicians and patients. Physicians' interest stems from the need to optimize cancer control outcomes, as well as, provide most accurate survival estimates to patients (1). OS and DFS are usually presented as relative survival rates (RS), and can be found in the International Cancer Registries (1, 2). Unfortunately, RS is a static prediction, that is calculated from the date of diagnosis and does not account for accumulated DFS time(3, 4). In that regard, RS provides pessimistic estimates that are of limited use to the patient, especially if DFS duration is considerable. (2, 5).Specifically, most cancer mortality rates are substantially decreased after 1-2 years of survival, and therefore, after that period, RS rates are rendered inaccurate (1). Such pessimistic and inaccurate RS rates may have a negative impact on patient's well-being. For example, Hart et al. (6), showed that patients fearing recurrence of their prostate cancer after radical prostatectomy (RP) reported lower health-related quality of life. In a similar tone, Bouvier et al. (7) reported that financial institutions refused to give cancer survivors life insurance. Due to the multiple RS limitations described, the use of conditional survival (CS) was proposed to shed a more objective light on life expectancy after cancer diagnosis and treatment.

CS can be calculated with the following formula: CS(t/s)= S (s+ t) / S (s), where s denotes the number of years the patient has survived, and t quantifies projected survival years from starting point of treatment or diagnosis (4). It provides dynamic information on a patient's probability of surviving extra years by quantifying the patient's changing risk over time (5, 8, 9). For example, immediately after a radical cystectomy (RC) for bladder cancer, a patient may have a 69.3% probability of DFS at 5 years, however after a 3 year of disease free interval (DFI) this probability increases to 81.7% (9).

Two type of CS definitions have been described: relative and absolute. Relative CS is mostly used for public health purposes, comparing patient survival rates with the healthy population. Absolute CS applies to individual patients and can be estimated by parametric, nonparametric, and regression models such as Kaplan–Meier and Cox models(4). CS allows for adjustment of surveillance plans, salvage therapies and is a useful counseling aid in all clinical fields of oncology (5). In this article, we review the existing English language literature on CS in oncology, with specific focus on urologic oncology.

2. METHODS

A review of the literature was performed using PubMed, Medline, and Cochrane databases focusing on all articles addressing CS. Electronic articles published ahead of print were also considered. Search was limited to the English language and relied on keywords: conditional survival, oncology, urological oncology, and cancer. Studies were selected according to sample size, contemporaneity, and clinical relevance of the results.

3. RESULTS

3.1 CS in Urological Oncology

CS estimates are available for six urological cancers: (1) renal cell carcinoma, (2) squamous cell carcinoma of the penis, (3)

urothelial cancer of urinary bladder, (4) upper tract urothelial carcinoma, (5) prostate cancer and (6) testicular cancer. (Ref. Table 1)

3.1.1 Renal Cell Carcinoma (RCC)

In the English language literature seven studies evaluated CS in RCC (1, 5, 10-14). In 2009, Karakiewicz et al.(10) devised a survival nomogram which included CS. This nomogram was applied to 3,560 American patients treated with nephrectomy (NT) for stage I to IV RCC. First, they found that 5-year CS of patients increased to 90.6% and 89.6% at 5 and 10 years post NT, compared to 74.2% RS, immediately after NT. Second, Karakiewicz et al. (10) validated and quantified DFS increases that might be expected with DFI. For example, a high risk kidney cancer patient with advanced grade and stage that survived 24 months after NT had a CS gain of 7%. Third, Karakiewicz et al.(10) externally validated their nomogram with a cohort of 3,560 patients from 15 institutions. The accuracy of prediction at 5 and 10 years was found to be 87% and 90.5%, respectively.

In 2012, Harshman et al. (5), evaluated CS in 1673 mRCC patient, from the International mRCC Database Consortium, treated with first-line VEGF-targeted therapies between 2003 and 2010. First, they found that RCC CS was dynamic, depending on the time elapsed from treatment initiation and duration of therapy. They reported an improvement in 2-year survival: CS increased from 44% at 0 months to 68% at 2 years, after initiation of VEGF-targeted therapy. Second, Harshman et al. (5), found that the poor-risk group has the most marked improvement in 2-year CS: it increased from 11% at 0 months to 33% at 18 months. On the other hand, the 2-year CS increase was less apparent in the favorable group, increasing from 74% at 0 months to 90% at 2 years post VEGF-targeted therapy. Finally, Harshman et al.(5) found that the incorporation of CS optimized predictive nomograms, specifically the predictions of the Heng et al. model(15).

In 2013, Bianchi et al.(11), evaluated CS in 42 090 American patients with RCC treated with NT between 1988 and 2008. First, they found that, immediately after surgery, the 5-year cancer specific mortality (CSM) was 83.5%. The 5-year CS 1 year after NT was 87.0% and increased up to 92.3% at 5 years post-NT. Second, similar to the previous reports, Bianchi et al. (11) reported an important increase in 5-year CS in poor-prognosis patients. For example, patients with stage III and stage IV tumors had CS gains of 8.4% and 23.2%, after surviving 2 years since NT. Furthermore, patients with increased tumor size between 71-100mm and 101 mm had a 10.3% and 18.4% CS gain, provided they survived 2 years after NT. On the other hand, they found minimal change in CS, according to age. Bianchi et al. (11) concluded, that once patients with aggressive disease survived two years after NT, they had similar CSM rates to low risk RCC patients, at the onset of follow-up.

3.1.2 Squamous Cell Carcinoma of the Penis (SCCP)

In the English language literature only one study evaluated CS in SCCP (8). In 2011, Thuret et al. (8), developed a nomogram for CSM prediction using CS. They evaluated 670 American patients with SCCP treated with primary tumor excision (PTE) between 1998 and 2006. This nomogram, included 3 variables: tumor category, node category, and

tumor grade. First, the investigators (8) found that 5-year CSM-free survival of patients at the time of PTE was 84.3%. The CS rate increased to 95.0% and 97.8% after 2 and 5 years of DFS since PTE, respectively. This result supports the data that mortality from SCCP is rare beyond 5 years after PTE. Second, they found a marked increase in CS in patients with advanced disease. For example, patients with T2cN0G2 disease had a 5-year CSM-free estimate at 85%, provided they survived 2 years post PTE, compared to 57.0% at the time of PTE. Finally, Thuret et al.(8) externally validated their nomogram with 575 patients. The accuracy was 78.1% at 5 years after PTE.

3.1.3 Bladder Cancer

In the English language literature seven studies evaluated CS in bladder cancer (1, 3, 9, 12, 14, 16, 17). The first article evaluating CS in bladder cancer was published by Sun et al. in 2012 (9). They used cumulative survival estimates to generate conditional survival rates. They evaluated 4991 American patients diagnosed with urothelial carcinoma of the urinary bladder (UCUB), who were treated with RC. First, Sun et al. found a CSM- free survival rate of 63.9% at RC. This rate increased to 71.0%, 77.5%, 81.7%, 85.9% and 86.3% in patients who survived 1, 2, 3, 4 and 5 years, respectively. Second, similar to other cancers, they found improved prognosis 2 years after RC in patients with pT2–4 diseases, with +19%, +36% and +26% CS gains in patients with pT2, pT3 and pT4 UCUB, respectively. Similarly, patients with lymph node metastases had significantly improved CS, as of 2 years after RC. These gains became increasingly more significant with longer DFI. For example, after surviving 5 years, the 5-year CS gains were +32 and +34% in pN1 and pN2–3 subgroups, respectively. On the other hand, low risk patients, had a CS gain of +8%, virtually regardless of the duration of survival since RC. Last but not least, Sun et al.(9) showed that patients with unfavorable baseline characteristics, notably, advanced age, female gender and multiple comorbidities, had most significant survival gains from DFI of at least 2 years after RC. In consequence, they concluded that the closest follow up should be performed during that critical period of the initial two years after RC.

In 2013 Ploussard et al. (3) evaluated 5- year CS in 8141 patients treated with RC and pelvic lymph node dissection (PLND) at 15 international academic centers between 1979 and 2012. First, they found an increase in 5-year overall CS and conditional CSS from 60.7% and 67.7%, after 1-year DFI to 74.3% and 95.9% after 10-year DFI, respectively. Second, they noted that adjuvant chemotherapy was associated with adverse OS within the first 2-years after RC, but was associated with improved outcome once 5-year DFI was reached. Third, similar to Sun et al. (9), Ploussard et al. (3) found that the impact of negative clinical and pathological characteristics decreased over time. For example, the 5- year OS in patients with pT3-4 bladder cancer was 39% at RC, while the 5-year CS after 5-year DFI after RC was as high as 71%. Ploussard et al. (3) concluded that the risk of dying of bladder cancer after RC is not constant and it decreases with time.

In 2015 Kang et al. (16) calculated conditional OS and CSS in 473 patients treated with RC and PLND at Seoul National University Hospital, between 1991 and 2012. First, they found that patients with 5-year DFI

had 5- year CS of 85.2%, compared to 69.9% in patients with only 1-year DFI. Second, they found that the only significant prognostic variable for 5-year CS was age, with OS rate being constantly 18% lower in patients >65 years, regardless of survival times. Conversely, tumor stage, grade, nodal and margin status lost its significance on OS, 2-3 years after RC. Third, similar to the previous reports, Kang et al. (16) found most significant CS gains in patient with unfavorable pathologic characteristics. For example, patients with tumors ≥pT3 had a 5-year CS of 67% at 3-year DFI after RC, compared to only 45% at RC. Furthermore, patients with lymph node positivity had a 30% increase in CS at 3 years post RC.

Additionally, CS in bladder cancer was evaluated in multiple studies that focused on CS analyses in multiple primary tumor sites (1, 12, 14, 17). They found 5-year CS, after 5-year DFI, of 94% in localized and as high as 69-74% in metastatic bladder cancer (1, 14, 17). After surviving 10 years, the 5-year CS did not reach the survival rate of the general population, and remained at 93.5%(12). Furthermore, Ellison et al. (1) found that the 5-year CS was slightly poorer in females. However, Baade et al. (12) found that the difference in survival between genders decreased soon after diagnosis.

3.1.4 Upper Tract Urothelial Carcinoma

In the English language literature only one article focused on CS in upper tract urothelial carcinoma(18). Ploussard et al. (18) evaluated the 5- year CS in 3544 patients treated with radical nephron-urecterectomy (RNU), between 1989 and 2012 at several international centers. First, they found the 5-year bladder cancer DFS, CSS, and OS rates at diagnosis, to be 54.9%, 72.2%, and 62.6%, respectively. The 5- year CS rates increased at 1-, 2-, 3-, and 4-years of DFI to 65.2%, 69.3%, 71.5%, and 73.0%, respectively. Additionally, the 5-year conditional CSS increased from 75.5% to 88.8%, with 5-year DFI. Last but not least, Ploussard et al. (18) found that the positive impact of age and gender increased with DFI duration, while the impact of pathologic parameters decreased with time. For example, younger patients had up to +17% CS gains, while patient >70 years of age had marginal CS gains of +1%. At 5-year DFI after RNU, patients with stages pT3-4 had CS gains of +26%, while patient with pT2 tumors only had +17% CS gains.

3.1.5 Prostate Cancer (PCa)

In the English language literature seven studies evaluated CS in PCa (1, 12, 14, 17, 19-21). In 2015, Briganti et al. (20), quantified CS for BCR in 2,065 patients with high-risk PCa treated with radical prostatectomy (RP) at 7 tertiary referral centers, between 1991 and 2011. First, they found that the 5-year BCR-free survival rate was 55.2%, and increased to 62.8% and 78.6% given BCR-free status at 1 and 5 years. Second, they found that patients with more aggressive disease had highest risk of BCR right after surgery, with decreasing risk over time. For example, patients with Gleason score of 8-10 had an increased risk of BCR for the first three years after RP. Similarly, the presence of metastatic lymph nodes increased the risk of BCR in the first year after RP. Briganti et al. (20) concluded that the diminished effect of aggressive disease characteristics on survival was most probably due to BCR-free survival of high risk patients, who benefited most from active treatment.

Additionally, PCa-specific CS was

evaluated in several studies that focused on CS in analyses of multiple primary tumor sites (1, 12, 14, 17, 21). Provided 5 to 10-year DFI, these studies found a 5-year CS ranging between 87 and 90%, reaching 100% in localized prostate cancer (1, 12, 14, 17, 21). It is noteworthy that, Ito et al. (21) found a slight decrease in 5- year CS in localized prostate cancer, which they hypothesized was due to recurrence or tumor progression during long term follow-up. Furthermore, they found a slightly lower CS in younger patients (50-59 years old) due to more advanced disease at diagnosis in those patients.(21)

In 2012, Abdollah et al.(19), introduced a novel concept, evaluating the conditional rate of urinary continence (UC) and erectile function (EF) recovery. They evaluated 1135 American patients with prostate cancer, treated with nerve-sparing RP, between January 2000 and June 2011. Abdollah et al. (19) showed that immediate post-operative recovery estimates were pessimistic and did not apply to patients, who remained impotent or incontinent. They found that the most significant UC and EF recovery increments were within the first year, decreasing to virtually zero at 36 months. For example, the conditional recovery of UC was 89.5%, 94.7%, and 97.0% at 6-, 24-, and 36-months of follow-up, respectively. Similarly, the conditional recovery of EF was 53.6%, 65.0%, and 67.5% at 6-, 24-, and 36-months of follow-up, respectively.

3.1.6 Testicular Cancer

To the best of our knowledge, in the English language literature, there are no studies that evaluated CS specifically in testicular cancer patients. Only 2 studies, that focused on CS analyses in multiple primary tumor sites, alluded to testicular cancer (1, 13). Janssen-Heijnen et al. (13) found that CS was similar in all age groups. After 1-year DFI, 5-year CS was similar to the general population. Furthermore, they found that patients with metastases reached a similar 5-year CS to patients with low risk disease, provided they survived 3 years. They concluded that after 1 to 2 years, surveillance intensity may be decreased (13). Similarly, Ellison et al. (1) found a 5-year CS of 100% provided 4-year DFI.

3.2 CS in Non-Urological Oncology

In the English language literature, eight studies focused on CS analyses in multiple primary tumor sites (1, 7, 12-14, 17, 22). (Ref. Table 2) Bouvier et al. (7), evaluated the conditional probabilities of death, also known as annual hazard, in 205,562 French patients diagnosed with breast cancer, prostate cancer, colorectal cancer, and lung cancer, between 1989 and 1997. Janssen-Heijnen et al. (13), evaluated 13 cancer sites in European patients diagnosed between 1985 and 2004. Merrill et al. (17), evaluated 11 cancer sites in 1,151,496 American patients, diagnosed between 1990 – 2001. Baade et al. (12), evaluated 189 591 patients from the Queensland Cancer Registry diagnoses with invasive cancer between 1982 and 2007. Ellison et al. (1), evaluated the five-year conditional relative survival ratio (RSR) in a large number of cancers using records from the Canadian Cancer Registry. Yu et al. (14), evaluated 11 cancer sites in 193,182 Australian patients diagnosed between 1972 and 2006. Bryant et al. (22), evaluated Canadian patients (excluding Quebec) with female breast, colorectal, and lung cancer, between 2004 and 2006. Ito et al.(21), evaluated 38,439 Japanese patients with

stomach, colorectal, lung, breast and prostate cancer, diagnosed between 1990 and 2004.

First, these studies found that the initial discrepancy in CS in different age groups, gender and across disease stages decreased or even disappeared over time, specifically, after the patient had survived 3-4 years. This was due to a more pronounced increased in 5-year CS in patients with poor prognostic characteristics (1, 13, 14, 21). However, older patients continued to have poorer CS, regardless of the years they survived. Baade et al. (12) hypothesized, that the age discrepancy in CS was probably due to late recurrences, adverse treatment effects, secondary tumors or increased comorbidities. Second, these studies found that in many low risk pathologies, including cutaneous melanoma, colorectal and testis cancer, patients with 5-year DFI had 5-year CS exceeding 95%, which was a similar OS rate of the general population. However, patients with more aggressive tumors, such as lung or breast cancer, had a 5-year CS of <90% and therefore, required continued surveillance, for at least 10 years after diagnosis. These studies found multiple noteworthy results for specific cancers that will be discussed in the following paragraphs.

3.2.1 Breast Cancer

In the English language literature, the first study to evaluate CS in breast cancer was published by Henson et al. in 1995(2). They evaluated CS in 56,368 American female patients diagnosed with invasive breast cancer from 1983 and 1987. They found that women with stage IV breast cancer had higher CS over time. Conversely, CS in patients with a less aggressive disease decreased over time. For example, OS of stage 1 cancer was 99% at diagnosis, and the CS decreased to 95% after surviving 4 years. Furthermore after 5-year DFI, CS did not achieve the survival rate of the general population (2). It is noteworthy, that even though breast cancer has an excellent initial prognosis, it only has a slight improvement over time, with a 5- year CS that is lower than that of colorectal cancer, provided 5-year DFI (12).

In 2009, Bouvier et al.(7), found that patients in the younger and lower age groups had lower RS. Between the ages 15 to 44 and 65 to 74, the 5-year RS was 85% and 83%, respectively. Between the ages of 45 and 54 the 5-year RS was 87%. Once the patient had survived 5- to 10- years, the discrepancy in age in CS estimates only persisted in the younger group, <44 years old, at 87% compared to 90% in patients over 45 year of age. Others found similar 5-year CS, ranging between 85- 93 %, provided patients have already survived 5 years. (12-14, 17)

3.2.2 Colorectal Cancer

In the English language literature, the first study to evaluate CS in colorectal cancer was reported in 1998 by Merrill et al. They found that regardless of the time survived, stage and race continued to influence CS in American patients diagnosed with colon cancer, between 1983 and 1987. Similarly, in 2010, Merrill et al. (17), found that stage continued to influence CS regardless of years survived, with a 5-year CS of 95%, 91%, and 79%, in localized, regional, and metastatic colon cancer, respectively. Additionally, Zamboni et al.(23) showed a continued discrepancy in age and nodal status, even after 5-year DFI. For example, patients < 50 years increased their 5-year CS from 79% to 95%, while patients >70 years had an unaltered CS, regardless of the years survived. Patients with

positive nodes had a marked 5-year CS improvement from 57% to 86%. Chang et al. (24) found similar results in American patients diagnosed with colon adenocarcinoma between 1988 and 2000.

Other studies have found similar results, with 5-year RS of 63-64% at diagnosis (1, 22) and a 5- year CS between 91 and 97%, provided 5-year DFI (1, 13, 17, 21). Baade et al.(12) and Yu et al. (14) found 5-year CS of 98.8% and 99.2%, respectively, provided 10-year DFI. Similarly, Bouvier et al. (7) found that the conditional probability of death in colorectal cancer decreased to 1%, after 10-year DFI. They found a discrepancy in CS according to age, specifically in older male patients, that was almost zero after surviving 3 years. Renfro et al. found similar results(25). This data emphasizes the importance of early screening and diagnosis of colorectal cancer.

In 2007, Wang et al. calculated CS in 36,321 American patients diagnosed with rectal cancer, between 1988 and 1998. First, they found that even though more aggressive stages had a marked increase in CS compared to lower stages, a difference in CS persisted between stages, regardless of the years survived. For example, provided 5-year DFI, the 5- year CS changed from 73% to 74% for stage I disease, 56% to 66% for stage II, 47% to 65% for stage III, and 6% to 48% for stage IV. Second, patient age continued to have an impact on CS. Patients > 65 years old had a 5-year CS of 59%, provided 5-year DFI, compared to 45% at diagnosis. Patients < 65 years of age had an increase in 5-year CS from 61% and 81%, provided 5-year DFI. Third, Wang et al. found that men had a lower CS than females. Provided 5-year DFI, females had a 5-year CS of 71%, and males had a 5-year CS of 68%. Furthermore, CS gains in black patients were lower than the CS gains recorded in white patients, regardless of diseases stage and DFI. This was especially true in patients with stage IV rectal cancer. For example, black patients with stage IV rectal cancer, that had survived 5 years, had a 5-year CS of 37% compared to 47% in their white counterparts. Last but not least, in 2001, Wang et al. develop a prediction model that estimated the changing prognosis for rectal cancer patients by using CS. This model took into consideration age, race, sex, and stage and had a concordance index of 0.75.

3.2.3 Lung Cancer

Patients with lung cancer have a <10% of 5-year CSM-free survival rate, with an initial 5-year RS of 14% in advanced disease (14, 26). The 5-year CS remains lower than the general population regardless of DFI duration. However, CS doubles once a patient survives one year (13). Depending on disease stage and provided 5-year DFI, studies found a 5-year CS between 56 and 77% (14, 17, 22). With 10-year DFI, the 5-year CS increased up to 94%(12, 14). It is noteworthy that, patients with poor prognosis had the most marked improvement with an initial 5-year RS of 14%, 5-year CS of 33% and 85% provided 1 and 10-year DFI, respectively (14).

Studies have found that CS in lung cancer varied depending on age, gender and histological subtype. First, Merrill et al.(27), who evaluated the conditional probability of death, in 95,283 American patients with lung cancer, diagnosed from 1983 to 1992, found that patients with bronchioloalveolar carcinoma had a lower conditional probability of death, compared to small-cell carcinoma. This discrepancy became virtually nil provided

the patient survived 5 years. Second, Skuladottir and Olsen (26), found that the 5-year CS increased from 33% to 60% in men, and from 36% to 67% in women provided 5-year DFI. Similarly, Bouvier et al. (7) found that the conditional probability of death from lung cancer remained high in the first 4 years and was more significant in men. Last but not least, Skuladottir and Olsen (26) found that younger patients had a drastic increase of 5-year CS, from 33% to 81%, provided 1 and 5-year DFI, respectively. Conversely, patients aged between 60 and 69 years had an increase in 5-year CS from 23 to 52%, provided DFI of 1 and 5 years, respectively. Similarly, Bryant et al. (22) found that the highest gains in CS were recorded for individuals aged 15 to 44 and Yu et al.(14) found that CS remained lower in older patients regardless of the years survived.

4. DISCUSSION

CS provides dynamic information on a patient's probability of surviving extra years by quantifying the patient's changing risk over time after accounting for DFI (5, 8, 9). In this manuscript we reviewed the concept of CS in several urological malignancies and in leading non-urologic cancers.

To our knowledge, in the English language literature, CS was first calculated in breast cancer by Henson et al. in 1994 (28). They found that the CS increases drastically after surviving >1-year post diagnosis. In 1998, Merrill et al. (29) came to a similar conclusion when they calculated CS in colon cancer patients. Similar results were found in urological cancers. For example, in bladder cancer, 2 years after RC, Sun et al. (9) found a +36% CS gain in patients with pT3, compared to +8% in low risk patients. Henson et al. (28) hypothesized that CS selects patients that have survived their cancer and cancer specific treatment, and therefore, on average, should have a better prognosis than newly diagnosed patients. In some pathologies, patients had a 5-year CS of >95%, which was a similar mortality risk to the general population. Some authors went as far as a saying that with a CS >95% the patient was "cured" from their cancer (13, 17).

We observed some noteworthy findings in our review. First, patients with poor prognosis had the most drastic increase in CS. For example, Baade et al. (12) found that the 5-year CS of stomach cancer increased to 58% and 101%, provided that the patient has survived 5 and 10 years, respectively, compared to the 5-year RS of 29% at diagnosis. Merrill et al. (17) found similar results, with greatest CS improvement in patients with poor-prognosis pathologies, such as lung or pancreatic cancer. Similarly, Karakiewicz et al.(10) found that the 5-year CS in patients with RCC increased from 74.2%, at the time of NT, to 90.6% 5 years after NT. Merrill et al. (17) concluded that this phenomenon may be due to a natural selection bias, in which patients with greater risk die, while the lower risk patients survive. Furthermore, Ploussard et al. (3), hypothesized that tumors primarily relapse within the first 2 years, therefore poor prognosis patients that do not have disease recurrence, have better CS after 2 years. On the other hand, pathologies with favorable initial prognosis, such as SCCP, melanoma, and breast cancer showed a less marked increase in CS (8, 12). It is noteworthy, that the only cancer that did not show substantial increase in 5- to 10- years CS was chronic leukemia. Baade et al. (12) found

OS of chronic leukemia to be 58% at diagnosis, while, the 5-year CS 10 years after diagnosis was, substantially lower than stomach cancer, at 82%. Similarly, Ellison et al. (1), noted that chronic leukemia had a marginal increase in CS.

Second, studies found differences in CS with different patient characteristics. For example, on average, younger patients had a better prognosis than their older counterparts. This age discrepancy persisted, but decreased with 5- and 10- year CS (12, 13). Baade et al. (12) hypothesized that older patients had a decreased CS due to late recurrences, poor treatment response, and most importantly, due increase comorbidities. Conversely, it was found that younger breast cancer patients had lower CS, compared to the older patients (7). Bouvier et al. (7) hypothesized that the lower CS in younger patients was due to the nature and aggressiveness of their diseases.

Third, Abdollah et al. (19) introduced an interesting concept by applying CS to functional outcome recovery rates. They found that erectile function and continence were better several months after nerve-sparing RP, plateauing after 6 months. Merrill et al. (27) and Bouvier et al.(7), focused on another interesting concept, the conditional probability of death, also known as the hazard function (HF). The HF is the conditional probability of a patient dying after time s, under the condition that they are alive at s. CS is inversely proportional to the hazard function, increasing with decreasing HF(4).

Finally, even though our report emphasizes the benefits of CS over survival data that do not account for CS, the quantification and application of the CS concept to either group or individual predictions is not without its challenges and limitations. First, CS calculations require large mature cohorts (4) with long term follow-up(2). This can be especially problematic as patients' characteristics, as well as treatment modalities may change over time(4). Second, CS cannot be used for comparing different cancers and their prognoses(17). Last but not least, CS cannot be use to track cancer OS in the general population(17).

In conclusion, the results of CS have been so promising that studies have suggested adding CS to prognostic nomograms (5, 8). CS improves the precision of predictions, among patients who enjoy a DFS, by accounting for DFS time. It is a dynamic measure that results in better prognosis in proportion to the length of DFS. Despite its advantage over survival probabilities without adjustment for DFS, CS is not incorporated in most prognostic models. We hope that this review will stress the importance of using CS to inform patients of their improved prognosis, notably poor risk patients that have survived >1 year. By doing so, clinicians will be able to better treat their patients, and most importantly, patents' quality of life will be drastically improved (12).

Table 1: Urological oncology

Tumor Site	Authors	Sample Size	Database	Treatment	RS %	5- year CS % (years survived)
RCC	Karakiewicz et al. (10)	3,560	15 American institutions	NT	74.2	90.6(5) 89.6 (10)
	Harshman et al.(5)	1673	International mRCC Database Consortium	VEGF-targeted therapies	44	68 (2)*
	Bianchi et al. (11)	42 090	SEER	NT	83.5**	87.0 (1) 92.3 (5)
SCCP	Thuret et al. (8)	670	SEER	PTE	84.3**	95.0 (2) 97.8 (5)
UCUB	Sun et al. (9)	4991	SEER	RC	63.9	71.0(1) 86.3(5)
	Ploussard et al. (3)	8141	15 international academic centers	RC and PLND	-	60.7 (1) 74.3 (10)
	Kang et al. (16)	473	Seoul national university hospital	RC and PLND	-	69.9 (1) 85.2 (5)
UTUC	Ploussard et al. (18)	3544		RNU	62.6	65.2 (1) 73.0 (4)
PCa	Briganti et al. (20)	2,065	7 tertiary referral centers	RP	55.2***	62.8(1)*** 78.6(5)***

CS: conditional survival, CSM: cancer specific mortality, NT: nephrectomy, PCa: prostate cancer, PLND: pelvic lymph node dissection, PTE: primary tumor excision, RC: radical cystectomy, RCC: renal cell carcinoma, RNU: radical nephron-urecterectomy, RP: radical prostatectomy, RS: relative survival, SCCP: squamous cell carcinoma of the penis, UCUB: urothelial carcinoma of the urinary bladder, UTUC: upper tract urothelial carcinoma.
*2-year CS **CSM *** BCR free survival/CS

Table 2- Non Urological Oncology

Authors	Sample Size	Database	Tumor Sites	5-year RS %	5- year CS%
Bouvier et al. (7)	205,562	French Network of Cancer Registries	Prostate	70-83	82-87*
			Breast	83-87	87-91*
			Colorectal	56-63	88-93*
			Lung	13-26	62-81*
Janssen-Heijnen et al. (13)	22.7 million	EUNICE	Kidney	-	87-93
			Testis	-	98-100
			Breast	-	86-90
			Colorectal	-	90-91
			Lung	-	64-87
Merrill et al. (17)	1.15 million	SEER NCI*	Bladder	47.0**	86.8**
			Prostate	100***	100***
			Breast	81.5**	85.3**
			Rectum	59.1**	82.4**
			Colon	68.9**	90.7**
			Lung	19.5**	66.2**
Baade et al. (12)	189 591	Queensland Cancer Registry	Kidney	65.6	87.7
			Bladder	75.5	91.4
			Prostate	85.6	87.3
			Breast	88.0	91.8
			Colorectal	65.9	93.2
			Lung	14.0	70.9
Ellison et al. (1)	-	Canadian Cancer Registry	Kidney	67	94
			Bladder	73	94
			Prostate	96	99
			Testis	95	100
			Breast	88	93
			Rectum	64	93
			Colon	63	97
			Lung	16	75
Yu et al. (14)	193,182	NSW Central Cancer Registry	Kidney	64.0	89.6
			Bladder	62.5	89.8
			Prostate	90.2	90.0
			Colorectal	65.0	93.2
			Breast	88.6	91.6
			Lung	13.9	75.5
Bryant et al. (22)	-	Canadian Cancer Registry (excluding Quebec)	Colorectal	88	96
			Breast	63	92
			Lung	16	75
Ito et al.(21)	38,439	Osaka Cancer Registry Database*	Prostate	83	84
			Colorectal	57	90
			Breast	79	85
			Lung	21	74

EUNICE: European Database- European network for Indicators on Cancer
NSW: New South Wales
*10-year CS
**results shown for regional disease
*** results shown for local disease

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