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Long-Term Survival in Patients with Cancers

A SEER-based analysis

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Abstract

Objectives: Long-term survival is an important endpoint in management of different malignancies which is rarely assessed due to unfeasibility of follow-up for long duration of time. In this study, we explored real-world data on cancer's long-term survival using historical records from the Surveillance, Epidemiology, and End Results (SEER) Program. Besides reporting the 5-year relative survival, we analyzed the 10- and 20- year survival rates for different types of cancers. Additionally, survival trends as a function of time, age, and tumor type were reviewed and reported. ***Methods:*** We used SEER*Stat (version 8.3.6.1) for data acquisition from the SEER 9 Regs (Nov 2019 Submission) database. Data of patients diagnosed with cancer between 1975 and 2014 were retrieved and included in the analysis. ***Results:*** For patients diagnosed with any malignant disease (n = 4,412,024), there was a significant increase in median overall survival over time ($p<0.001$). The 20-, 10-, and 5-year survival rates were higher in solid tumors compared to hematological malignancies (50.8% vs. 38%, 57% vs. 47.4%, and 62.2% vs. 57.4%, respectively). The highest 20-year relative survival rates were observed in thyroid cancer (95.2%), germ cell and trophoblastic neoplasms (90.3%), melanoma (86.8%), Wilms' tumor (86.2%), and prostate cancer (83.5%). ***Conclusions:*** Long-term follow-up data were suggestive of high 20-year relative survival

rates for most tumor types. Relative survival showed an improving trend over time especially in solid tumors.

Keywords: Survival; Neoplasms; SEER Program; Prognosis; United States.

Advances in Knowledge

- There was a significant increase in long-term survival rates in cancer patients over the period between 1975 and 2014.
- The highest 20-year relative survival rate is seen in thyroid cancer, germ cell and trophoblastic neoplasms, melanoma, Wilms' tumor, and prostate cancer.
- Twenty-year relative survival rate is higher in solid cancers compared to hematological malignancies.

Application to Patient Care

- Improved cancer diagnostics and therapeutic options have led to a substantial increase in survival rates over time. This necessitates the development of long-term follow-up programs to accommodate the growing number of cancer survivors.
- Twenty-year survival rates for some malignancies are high. Patients diagnosed with those types of tumors should be aware of their probability of survival and counseled about cancer survivorship.

Introduction

In the United States (US), nearly 609,360 persons are projected to die from cancer in the year 2022. In fact, cancer is currently considered the second most common cause of death in both men and women in the US.[1] This domination over other causes of death is a daunting fact for cancer patients and their families that remains consistent among different races and variable age groups.[2]

Although many researchers have studied cancer-related mortality, cancer survivorship usually remains an underrepresented topic in literature despite growing interest in the concept in the past decade. In 2019, more than 16.9 million Americans have survived cancer—a number that is projected to reach more than 22.1 million by 2030.[3] With recent advances in cancer diagnostics and therapeutics, survival is expected to become even much better with a further increase in the number of cancer survivors among the overall population.[4,5]

Cancer survival rates can vary according to tumor type and patients' clinicodemographics.[4,5] Exploring survival rates can not only provide insights into the natural history of different cancers but also enlighten us about the changes that happened across time because of the introduction of novel treatment options or incorporation of new preventive strategies including screening programs. Most studies reporting on cancer survival, including clinical trials, have addressed either 5-year or 10-year survival rates.[6–9] However, looking into survival rates from a more holistic approach that goes beyond 10 years is imperative; though this is usually impractical to address in short-term studies or even in the context of prospective clinical trials.

In this study, we aimed to investigate long-term survival, including 20-year survival rates, of different cancers in the US. We also tried to explore possible differences in survival rates across tumor types, their association with different sociodemographic parameters, and their trends as a function of time.

Methods

Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program.[10] SEER is a program that was initiated in the early 1970s by the US National Cancer Institute to collect data from nationwide cancer registries. Its current databases cover 47.9% of the US population and are presumably generalizable to patients with cancer all over the US. The SEER 9 database (Nov 2019 Submission), which covers 9.4% of the population and includes historic data that go back to 1973, was used as the data source in this study. The study was exempted from institutional review board approval being a SEER-based study according to National Bureau of Economic Research`s guidance.[11]

The case-listing function in SEER*Stat 8.3.6.1 was used to export data on cancer cases diagnosed between 1975 and 2014. We included patients with known ages who had cancers with malignant behavior at the time of initial data entry. The relative survival was calculated in SEER*Stat using the Ederer II method. The probability of relative survival compares survival in the patients included in the analysis with the expected survival of the general population obtained from the US 1970–2017 Expected Survival Life Tables.[12] For relative survival, cases with a missing cause of death and/or survival time were excluded from the analysis.

According to the third edition of the International Classification of Diseases for Oncology, we classified tumors into either solid tumors (8000/3-9581/3) or hematological malignancies (9590/3+). Age at diagnosis was categorized into five main categories (0–14, 15–24, 25–54, 55–64, and 65+ years). For comparing trends over time, we stratified years of diagnosis into four groups with a 10-year interval for each group.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0. (Armonk, NY: IBM Corp). Frequencies and percentages were used to describe categorical variables. Survival analysis was performed using the Kaplan–Meier analysis method, where the log-rank test was used to test for statistical difference. Cox regression analysis was performed to adjust for potentially confounding factors. The *p*-value of 0.05 was used to determine statistical significance.

Results

In this analysis, we included 4,412,024 cases diagnosed with cancer between 1975 and 2014. Elderly population (65 years and over) was the largest age group in our study (55.6%; n = 2,452,512). The majority of the study cohort were male (51.3%; n=2,262,378) and white (84%; n=3,705,309). The most commonly encountered diagnosis was breast cancer (14.9%; n = 657,211); with solid tumors constituting 91.1% (n = 4,019,427) of the included cohort (Table 1).

The median overall survival for all patients included in the study was 66 months (95% confidence interval (CI): 65.8–66.2 months) and showed a significant increase over time (35 months, 51 months, 77 months, and 101 months for cases diagnosed between 1975 and 1984, 1985 and 1994, 1995 and 2004, and 2005 and 2014, respectively; $p<0.001$) (Figure 1). The highest 20-year relative survival was observed in thyroid cancer (95.2%), germ cell and trophoblastic neoplasms (90.3%), melanoma (86.8%), Wilms' tumor (86.2%), and prostate cancer (83.5%) (Table 3).

Survival was compared across different prognostic factors including age, gender, stage, grade, and cancer type. Results revealed that the 15-24 age group had better median overall survival compared to 25-54, 55-64 and 65+ age groups (363.3 months vs 261 months, 112 months, and 37 months ; $p<0.001$) (Figure 1). Female patients had longer overall survival compared to male patients (83 months vs 54 months, $p<0.001$) (Figure 1). Patients of black races had lower

survival rates compared to (American Indian/AK natives, Asian/pacific islanders) and white races (115.2 months vs 152.2 months, and 134.9 months, p<0.001). In Cox regression analysis, improvement in survival across time remained significant (hazard ratio (HR)= 0.899) and the significance was also maintained across different age groups (HR=1.865), genders (HR: 1.008), races (HR: 0.939), and tumor types (HR: 0.781) (Table 2).

Despite consistent increase in survival rates in both tumor types, the 20-, 10-, and 5-year survival rates were higher in solid tumors compared to hematological malignancies (50.8% vs. 38%, 57% vs. 47.4%, and 62.2% vs. 57.4%, respectively). Table 4 shows survival rates for commonly diagnosed cancers.[1]

Discussion

The progress made in the oncology field has substantially improved cancer outcomes [13] but little is known about how this was translated into a long-term survival benefit in patients with cancer. To the best of our knowledge, this is the widest-scale analysis of long-term survival for cancer patients that explored follow up data for up to 20 years after diagnosis using a tumor agnostic approach. Data presented in this study are crucial to inform treating physicians about the probability of long-term survival in different malignancies. This information is commonly addressed during doctor–patient conversations, particularly in patients with advanced disease. Current evidence suggests that the accuracy of oncologists' expectations for survival in end-stage cancer patients was as low as 25%. This inaccuracy can not only lead to a lack of credibility in physicians' disclosed information but also mislead treatment-related decisions, such as the need to refer patients for hospice care or the necessity of continuation of active treatment.[14–16]

We have demonstrated, based on data from US cancer registries, that several malignancies have a considerable long-term survival. The highest 20-year relative survival was observed in thyroid cancer (95.2%), followed by germ cell and trophoblastic neoplasms, melanoma, and Wilms' tumor (90.3%, 86.8%, and 86.2%, respectively). A potential explanation for high survival rates in these tumors is the early disease-related manifestations, the availability of easy-access diagnostic approaches, and the advances in treatment options with curative intent in those tumor types. Similar data were reported in the United Kingdom (UK) by Quaresma et al., who have reported the highest 10-year survival in patients with testicular cancer (98.2%).[19]

Although some data support the notion that the highest rates of cancer survival are reported in the US and Canada,[18] trends in our survival analysis were consistent with findings from other studies in other parts of the world. Most publications addressing shorter survival intervals have reported improved survival over time; which is usually attributed to the introduction of new treatment options for various tumors.[18–20] This has been consistent with data reported in our study, which showed a steady increase in 5-, 10-, and 20-year survival across almost all tumor types. Interestingly, the survival probability showed an incremental decrease after 5 years as compared to anticipated linear increase in the probability of death. For example, breast cancer survival probability fell from 86.4% at the 5-year follow-up to only 70.1% at 20 years. In colorectal cancer, the 20-year survival rate of 50.5% actually compares to that of 61.4% at 5 years. This highlights the fact that most death events would occur early in the course of disease. Therefore, informing patients about the long-term prognosis of their illness should not rely only on short-term survival data, which can sometimes be misleading. Our findings are concordant with data from a similar study that was done twenty years ago and reported on long-term survival of patients diagnosed between 1974-1991. In the study by Wingo et al, an incremental decrease in survival rates happened after 5 years in patients with colorectal cancer with 15-years survival rate reported as 50% compared to 57% survival rate at 5 years.[17]

Our findings suggest that solid malignancies have a higher 20-year relative survival than hematological malignancies. This difference in survival was consistent among all age groups and was more prominent in older patients versus patients less than 14 years old who had better survival with hematological malignancies. Improvements in the survival rate in hematological malignancies seem more prominent (73.6% increment increase) than solid malignancies (51.2% increment increase). These data conform to the data reported in previous studies from different geographic areas.[7,21,22] The survival difference between different age groups was also reported in a population-based study in the UK where the net survival in the elderly population was lower than that in younger patients over a 40-year period (1971–2011).[19] Thus, observing such a discrepancy is not surprising as both solid and hematological malignancies are a heterogeneous group of different diseases with different natural histories and treatment options. Elderly patients commonly show late manifestations and have multiple comorbidities that can affect both treatment decisions and liability to treatment-induced toxicity.

Improvements in survival, however, do not come without a cost. Long-term cancer survivors are more likely to experience treatment-induced long-term side effects, including organ failure

and secondary malignancies. Long-term nonmedical effects, including financial toxicity and lifestyle changes, can also add a burden to long-term survivors. Thus, addressing cancer survivorship issues, particularly in patients with potentially high survival rates, and establishing follow-up guidelines that not only go beyond the normal follow-up periods but also address medical and non-medical needs of cancer survivors are imperative. An effort to address the cancer survivorship issue was made by the European Society for Medical Oncology (ESMO) which provided expert consensus guidelines for management of cancer survivorship. The guidelines identified core components that need to be addressed in cancer survivors including physical and psychological effects, social and financial impact, active surveillance for recurring cancers and second primaries, and promotion of well-being including improvement of cancer prevention approaches and overall health. [23]

This study addressed a huge number of patients with a long follow-up duration. Notwithstanding the resulting comprehensiveness of analysis, our study has several limitations. First, the SEER database does not provide detailed data on treatment options that patients received. The included cohort was diagnosed over a long period of time which might have resulted in heterogenous availability of treatment options and subsequent differences in clinical outcomes. Second, the 20-year survival data could only be calculated for the SEER 9 database, which includes cancer registries present since the inception of the SEER Program. Major updates in SEER were performed, which currently include 22 cancer registries covering 47.9% of the total cancer population in the US. However, the use of long-term data from newly incorporated cancer registries will not be feasible until a couple of years later when the follow-up duration can allow for long-term survival analysis. Third, methods to evaluate survival rates can vary and lead to differences in outcome interpretation [24]. For example, there has been a reported slightly higher relative survival rates with Ederer II method compared to Hakulinen or Ederer I method when follow up duration exceeds ten years. In some cases, as in malignancies that are diagnosed over a wide range of ages (e.g. thyroid), long term relative survival for all ages combined may vary depending on the method used to estimate expected survival; since Ederer I and Hakulinen methods will provide similar and higher relative survival compared to that calculated by Ederer II [25]. Finally, in general and as with data originating from cancer registries, SEER extracted data must be interpreted with caution given the challenges of unrecorded variables, underreported and incomplete adjuvant treatment data, disparity in coding and reporting, and migration of patients between SEER registry regions .[26]

Conclusions

Long-term follow-up data suggests that 20-year relative survival rates are high for many tumor types. The relative survival rates have significantly improved over time. Long-term follow up programs for cancer survivors should be incorporated into clinical management of patients with cancer.

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Authors' Contribution

MAG conceptualised the study. RAS, EIZ and MAG designed the methodology. RAS, AAN, EIZ and MAG drafted the original manuscript. AAN reviewed and edited the manuscript and supervised the work. All authors approved the final version of the manuscript.

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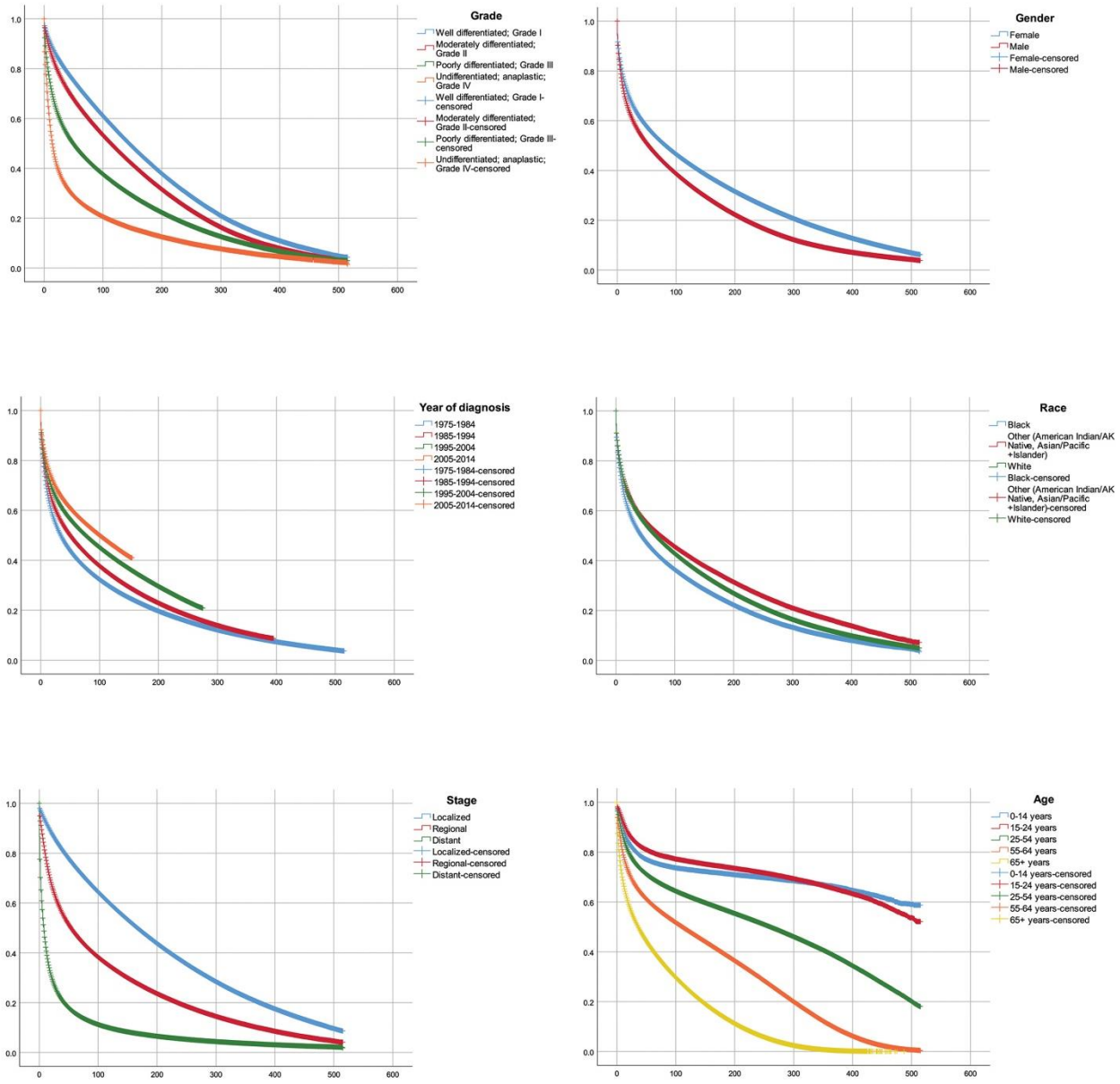

Figure 1: Kaplan–Meier curve for cases diagnosed with cancer between 1975 and 2014 stratified by age group, race, gender, stage, grade, and year of initial diagnosis.

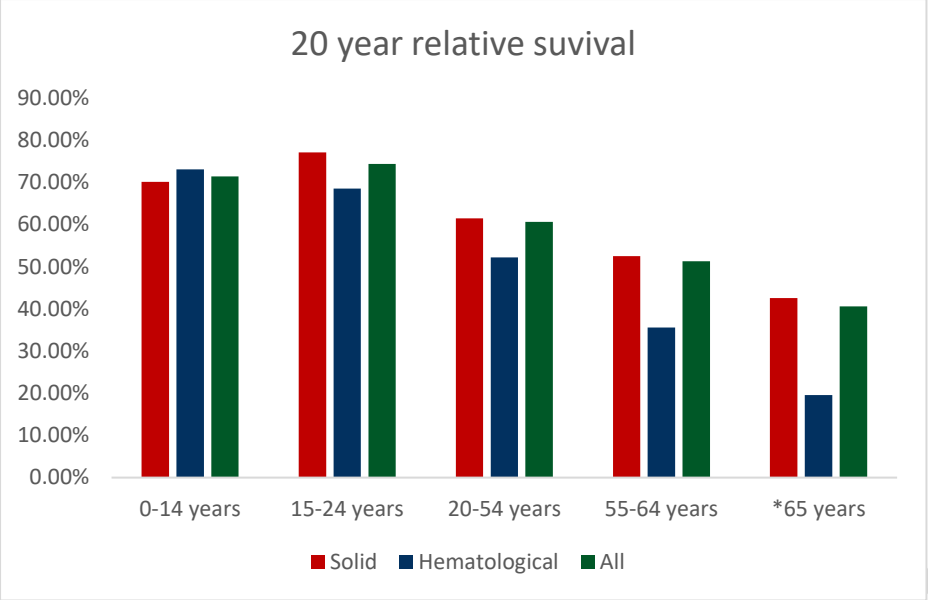

Figure 2: Twenty-year survival for different age groups stratified according to tumor type. The highest survival rates are observed in the 15-24 age group. Age groups are plotted on the x axis and survival probability is plotted on the y axis.

Table 1: patients' characteristics in the included cohort.

		N	%
Age group	0–14 years	31,594	0.7%
	15–24 years	41,614	0.9%
	25–54 years	917,720	20.8%
	55–64 years	968,584	22%
	65+ years	2,452,512	55.6%
Gender	Male	2,262,378	51.3%
	Female	2,149,646	48.7%
Race	White	3,705,309	84%
	Black	407,066	9.2%
	Other (American Indian/AK native, Asian/pacific islander)	281,266	6.4%
	Unknown	18,383	0.4%
Year of diagnosis	1975–1984	758,808	17.2%
	1985–1994	1,025,529	23.2%
	1995–2004	1,220,374	27.7%
	2005–2014	1,407,313	31.9%
Tumor type	Solid	4,019,427	91.1%
	Hematology	392,597	8.9%

Diagnosis	Breast	657,211	14.9%
	Prostate	610,247	13.8%
	Lung and Bronchus	592,921	13.4%
	Urinary Bladder	196,378	4.5%
	Melanoma of the Skin	168,236	3.8%
	Corpus Uteri	136,199	3.1%
	NHL - Nodal	120,148	2.7%
	Kidney and Renal Pelvis	114,658	2.6%
	Pancreas	112,114	2.5%
	Other tumors	1,703,912	39%

Table 2: Cox regression analysis for different prognostic factors affecting survival time. P-value < 0.001

	Regression Coefficient	HR	95.0% CI for HR	
			Lower	Upper
Age	0.623	1.865	1.862	1.867
Year of diagnosis	-0.106	0.899	0.898	0.900
Stage	0.163	1.177	1.176	1.178
Grade	0.071	1.073	1.073	1.074
Cancer Type (solid and Hematological)	-0.242	0.785	0.781	0.788
Sex	0.008	1.008	1.006	1.011
Race	-0.063	0.939	0.938	0.940

Table 3: Survival data of cancers having highest 20-year relative survival.

	5 year survival					10 year survival					20 year survival				
	1975-1984	1985-1994	1995-2004	2005-2014	All Years	1975-1984	1985-1994	1995-2004	2005-2014	All Years	1975-1984	1985-1994	1995-2004	2005-2014	All Years
Thyroid carcinoma	92.90%	94.60%	96.60%	98.50%	96.80%	91.40%	93.50%	95.90%	98.50%	96.10%	90.10%	92.40%	95.10%	N/A	95.10%
Germ Cell and Trophoblastic Neoplasms	85.10%	92.50%	94.40%	95.50%	92.60%	83.80%	91.50%	94.20%	95.20%	92.00%	80.40%	90.30%	93.30%	N/A	90.30%
Melanoma	82.00%	87.50%	91.00%	93.10%	89.90%	77.10%	84.40%	89.10%	92.10%	87.40%	75.00%	83.40%	88.90%	N/A	86.70%
Wilms tumor	79.30%	91.10%	90.70%	94.10%	89.00%	77.70%	90.50%	89.10%	93.00%	87.80%	76.60%	89.00%	86.10%	N/A	86.20%

N/A: 20 years survival rates cannot be calculated for this patient population due to short follow up to date.

Table 4: Survival data for commonly diagnosed tumors. Cancers listed are those shown to have highest incidence rates according to Siegel et al 2022.

	5 year survival					10 year survival					20 year survival				
	1975-1984	1985-1994	1995-2004	2005-2014	All Years	1975-1984	1985-1994	1995-2004	2005-2014	All Years	1975-1984	1985-1994	1995-2004	2005-2014	All Years
Breast	75.50%	84.00%	89.00%	91.10%	86.10%	63.60%	76.10%	83.50%	86.30%	78.80%	53.20%	67.50%	75.70%	N/A	69.80%
Prostate	70.50%	89.10%	98.60%	99.10%	93.40%	55.70%	81.90%	97.90%	99.10%	89.70%	39.60%	72.40%	94.40%	N/A	81.70%
Lung and Bronchus	12.70%	13.40%	15.30%	19.60%	15.40%	8.70%	9.00%	10.20%	13.10%	10.40%	4.80%	4.80%	5.50%	N/A	5.60%
Colon and Rectum	52.10%	60.00%	64.00%	66.40%	60.80%	46.50%	53.90%	58.40%	60.10%	54.90%	42.60%	49.50%	52.60%	N/A	50.00%
Corpus and Uterus, NOS	83.50%	82.80%	83.60%	83.20%	83.30%	81.60%	80.40%	80.70%	80.30%	80.80%	79.50%	76.80%	76.40%	N/A	77.70%
Urinary Bladder	74.60%	78.80%	79.80%	78.70%	78.20%	66.50%	71.50%	73.10%	72.30%	71.00%	55.20%	60.10%	61.50%	N/A	59.70%
Melanoma of the Skin	82.90%	88.60%	92.00%	94.00%	90.90%	78.40%	86.00%	90.50%	93.40%	88.90%	76.60%	85.20%	90.40%	N/A	88.40%
Kidney and Renal Pelvis	51.50%	58.40%	65.50%	75.10%	65.80%	44.50%	50.80%	57.70%	68.80%	58.40%	36.80%	40.90%	47.00%	N/A	47.60%
Non-Hodgkin Lymphoma	49.00%	51.30%	63.20%	73.40%	61.70%	37.20%	41.10%	55.70%	66.50%	52.60%	26.80%	31.70%	46.60%	N/A	41.80%
Oral Cavity and Pharynx	52.50%	55.00%	60.50%	67.40%	59.30%	42.30%	44.40%	51.30%	59.30%	49.40%	29.80%	32.40%	38.40%	N/A	36.10%
Leukemia	36.20%	44.20%	52.30%	64.50%	50.90%	25.40%	33.90%	44.70%	57.60%	41.60%	17.90%	26.70%	37.00%	N/A	32.90%
Pancreas	2.70%	3.80%	4.90%	9.10%	5.60%	1.80%	2.60%	3.60%	6.50%	3.90%	1.30%	1.80%	2.10%	N/A	2.60%
Thyroid	92.70%	94.40%	96.50%	98.40%	96.60%	91.30%	93.30%	95.80%	98.40%	96.00%	89.90%	92.10%	94.90%	N/A	95.00%

N/A: 20 years survival rates cannot be calculated for this patient population due to short follow up to date.