research article

Trends in population-based cancer survival in Slovenia

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Radiol Oncol 2021; 55(1): 42-49.

Received 2 January 2021
Accepted 10 January 2021

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Disclosure: No potential conflicts of interest were disclosed.

Background. The aim of our study was to describe the survival of Slovenian cancer patients diagnosed in the last twenty years. An insight is given into the improvement made in different cancer types, population groups and prognostic factors.

Materials and methods. The principal data source was the population-based Slovenian Cancer Registry. The survival analysis included patients diagnosed with cancer in twenty years period from 1997 to 2016, which has been divided into four consecutive five-year periods. In addition, the analysis was stratified by cancer type, gender, age and stage. The survival was estimated using net survival calculated by the Pohar-Perme method and the complete approach has been applied.

Results. The survival of Slovenian cancer patients has been increasing over time. During the 20 years observed, five-year net survival increased by 11 percentage points. Significantly higher growth was observed in men. Age and stage at diagnosis are still crucial for the survival of cancer patients. Five-year net survival is lowest in those over 75 years of age at diagnosis but has also improved by seven percentage points over the past 20 years. The five-year net survival of patients in the localized stage increased by ten percentage points over the 20 years under observation. Survival of patients in the distant stage has not been improving. In both sexes, survival for melanoma, colorectal and lung cancers have increased significantly over the last 20 years. Progress has also been made in the two most common gender specific cancers: breast cancer in women and prostate cancer in men. Still, the significant progress in prostate cancer is probably mostly due to lead-time bias as during the study period, Slovenia used indiscriminate PSA testing, which probably artificially prolonged survival.

Conclusions. The survival of Slovenian cancer patients has been increasing over time, which gives us a basis and an incentive for future improvements. To monitor the effectiveness of managing the cancer epidemic, the cancer burden needs to be monitored also in the future, using quality data and scientifically justified methodological approaches. In this process a well organised population-based cancer registries should play a key role.

Key words: cancer burden; cancer survival; time trend; Slovenian Cancer Registry

Introduction

Global health indicators show that cancer is an epidemic of modern times. Epidemiological indicators from Slovenian Cancer Registry confirm similar situation also in Slovenia. Among all causes of death, it ranks 1st in men and 2nd in women. In recent years, 15,000 Slovenes per year have developed cancer, and slightly over 6,000 have died of cancer. There are more than 120,000 people living in Slovenia who had ever been diagnosed with cancer. Since cancer is more common among the elderly (only a third of patients are younger than 65 years at the time of diagnosis), and the Slovenian

population is ageing, it is expected that the burden of this disease will increase, even if the level of risk factors remains the same as today.[1,2]

Continuous and systematic collection, storage and analysis of data on all cancer patients in a defined population is the basis for controlling this major public health problem – a key role is played by population-based cancer registries. One of their main purpose is to collect accurate and complete cancer data that can be used to plan and evaluate the National Cancer Control Programmes, specifically in the fields of primary and secondary prevention, diagnostics, treatment and rehabilitation and palliative care, to plan the capacities and resources needed to manage cancer (staff, medical equipment, hospital and rehabilitation facilities).[3] Incidence, mortality and survival are the main cancer burden indicators that are reported by the population-based cancer registries. Cancer mortality is the primary indicator of the cancer burden worldwide, since it is available for the largest number of countries. Mortality depends on the number of new patients (incidence) on one hand and on their survival on the other. Survival itself does not depend on the incidence, as it considers only those who have already fallen ill, so it indirectly indicates the success of diagnosis and treatment (in patients with earlier diagnosed disease and prompt treatment according to guidelines, a better survival is expected) and is considered as the most powerful indicator. The population survival of cancer patients, as shown by cancer registries is, therefore, a composite indicator. It reflects the characteristics of patients as well as the organization, accessibility, quality, and efficiency of the healthcare system. Clinical studies usually present the results of survival of groups of patients with a specific disease and for specific well-defined treatment, where strict entry criteria for the study group are defined, such as stage, performance status 0 or 1, normal organ function, age under 70 years etc. Population data on survival significantly differs from that. Population survival is affected, for example, by the disease stage at diagnosis, which depends on the time length from the first signs to the visit of general practitioner and further to the time of diagnosis. This time may be reduced through informing the population about when to visit a physician in case of health problems and the ability of general practitioners to consider the possibility of a serious disease, through increasing the availability of diagnostic tests, and minimising waiting times. The availability of screening programmes with proved benefit further increases the chances of cure or at least better survival, as they detect precancerous lesions or early-stage of the disease. Once diagnosed, the success of treatment depends on the type of cancer, the patient's characteristics (age, comorbidities, general physical performance, etc.) and also on the availability of multidisciplinary treatment and the qualifications of the medical team. All of these diverse factors that determine population survival must be considered by the researcher or clinician who interprets the results of population survival studies, and even more so when comparing survival between countries.[4]

In this study we are presenting the survival of Slovenian cancer patients diagnosed in the last twenty years. An insight is given into the improvement that was made in different cancer types, different population groups (gender and age) and stage at diagnosis. The survival improvements support reported ongoing progress achieved by Slovenian oncology and Slovenian healthcare system. The results of survival analysis are further discussed in the comprehensive report, which contains also insights from clinical experts who are involved in specific treatment of cancer patients in Slovenia.[5]

Materials and methods

The principal data source for the analysis is the population-based Slovenian Cancer Registry (SCR). Thus, the data refer to all cancer patients, residents of Republic of Slovenia at the time of diagnosis, irrespective of where they have been diagnosed, treated or where they have died. The SCR's quality and completeness indices prove that cancer registration in Slovenia adequately covers the entire population.[6] To assure completeness and to obtain additional information on registered cancer cases, SCR is linked with several governmental and health databases. Synchronisation of data between different sources is based on unique personal identification number, which is assigned to every resident in Slovenia and recorded in every state registry including SCR. Using unique personal identification number guaranties data integrity, data quality and prevents duplication. SCR is linked with the Central Register of Population through secure on-line connection (24/7 availability) and daily updates information on vital status and address for each person registered by SCR. The electronic linkage to the national Mortality Database and to the breast, colorectal and cervical screening registries is performed at least once per year.[6,7]

The data on gender, date of diagnosis, age at diagnosis, code of primary site according to the International classification of Diseases (10th edition), stage at diagnosis (general categorization into localized, regional or distant stage) and vital status with the date of end of follow-up (date of death, date of lost to follow-up or date of the end of study) were extracted from the SCR's database for all cancer cases. The survival analysis included patients who were diagnosed with cancer in the years from 1997 to 2016. The entire observed period has been divided into four consecutive five-year periods. The patients older than 95 years of age were excluded from survival analysis. Separate analyses were made for children (0–14 years), adolescents (15–19 years) and adults (20–94 years).

All analyses were performed on data registered in the SCR database on 1st September 2019 and 234,827 cases of cancer were extracted from the database. Among them, there were 37,917 non-melanoma skin cancer patients. Because this is a frequent but almost completely curable disease, we excluded these patients from the analysis. Further, we excluded 1,711 cases of cancer being registered by death certificate only, since the date of diagnosis is unknown, 4,470 cases in which the date of registration was the same as the date of death (mostly they are diagnosed at autopsy), and 668 cases in which the person was 95 years of age or older. The vital status of patients was last checked on 31st August 2019. At the end of the observation period, the person can be alive, dead or lost from the vital statistics records. Between 1997 and 2001, 26 persons with no follow-up data in the Central Register of Population were registered in the SCR (0.06% of 45,390 new cancer cases during this period) and only 3 persons with no follow-up data between 2002 and 2016 (0.002% of 189,437).

In the group of patients, the survival is interpreted as the proportion of patients who are still alive after a certain time from the diagnosis. Survival time is defined as the time between the date of cancer diagnosis and the date of the end of follow-up. The survival was estimated using net survival calculated by the Pohar-Perme method. Net survival is the survival that would be observed if the only cause of death was the disease we are studying, i.e. causal specific survival. For example, a net survival of 30% over five years tells us that in a hypothetical case where patients would die only from cancer and no other causes, 70% of those patients would die within five years from diagnosis.[8,9] Because all the included patients were not followed-up for five years we have applied the complete approach in the survival calculation.[10] For the calculation, we used the *relsurv* library for the R software environment.[11]

Results and discussion

There were 191,154 patients aged 20 to 94 years diagnosed between 1997 and 2016 with any cancer (non-melanoma skin cancer excluded). Throughout the observed period, slightly more men than women were diagnosed, of which most were aged from 50 to 74 years. In solid tumours, the disease was mostly detected in the localized stage. The five most frequent cancers in Slovenia – non-melanoma skin, prostate, colorectal, breast and lung cancer – account for 60% of all new cancer cases.[1]

Survival of cancer gradually increased in relation to the year of diagnosis. Over the 20-year period, five-year net survival increased by slightly less than 11 percentage points (Figure 1). The rise is in concordance to observed in our last three reports on survival of Slovenian cancer patients diagnosed with cancer between 1963–1990, 1983–1997 and 1995–2005.[12,13,14] According to the CONCORD-3 study which compared the five-year net survivals of adult patients with 15 different cancers between 2010 and 2014 in 26 European countries, in most cases the survivals of Slovenian cancer patients are below the European average.[14]

As presented in Table 1, in the first observed period, between 1997 and 2001, the net five-year survival for all cancers combined was much better for women than for men, with a difference of 16 percentage points. In the 20-year period significantly higher growth was observed in men, where five-year net survival increased by 17 percentage points (from 38% to 56%). In women, five-year net survival increased by six percentage points (from 54% to 60%). At a first glance, it seems that men have started to take better care of their health and that the 'macho' male population (refusing to see a doctor) is disappearing. Undoubtedly, breast and prostate cancer, which represent as many as a fifth of all cancer patients in men and women, contribute the most to reducing the gap between the genders. A large proportion of the increase in survival in men can be attributed to the survival of patients with prostate cancer, where it rose by as much as 21 percentage points (Table 1). However, this significant progress in prostate cancer survival is probably mostly artificial (lead time bias), since we used indiscriminate PSA testing in Slovenia quite uncritically during the study period, with which we also detected those prostate cancers that devel-

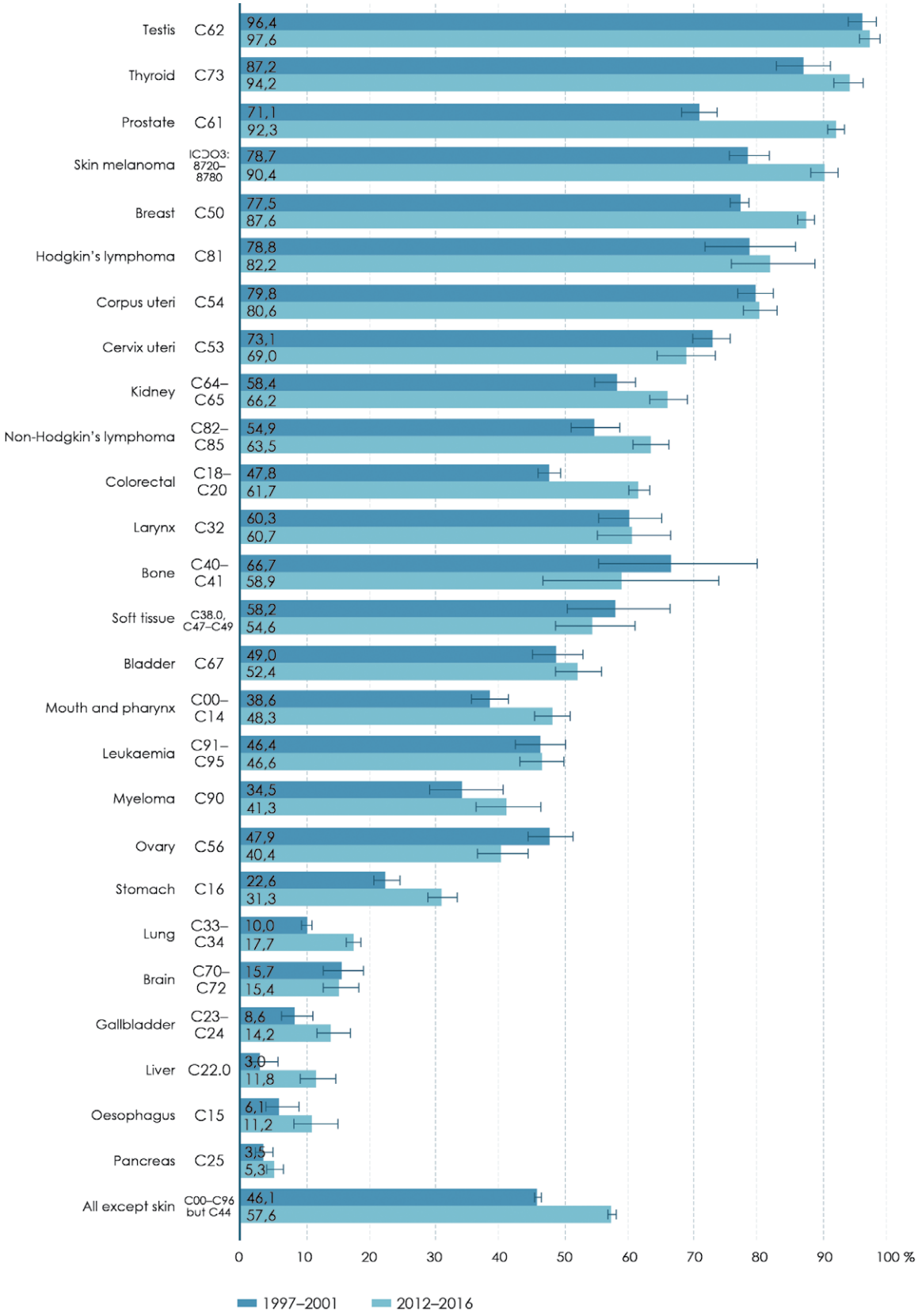

FIGURE 1. Five-year net survival (with a 95% confidence interval) of adult patients (20–94 years) with selected cancers, Slovenia 1997–2001 and 2012–2016.

TABLE 1. Five-year net survival (with a 95% confidence interval) of adult patients (20–94 years) with selected cancers by sex, Slovenia 1997–2001 and 2012–2016

Cancer type	Male				Female			
	1997–2001		2012–2016		1997–2001		2012–2016	
	Five-year net survival	95% confidence interval	Five-year net survival	95% confidence interval	Five-year net survival	95% confidence interval	Five-year net survival	95% confidence interval
C00-C14 Mouth and pharynx	34.4	31.6-37.3	43.6	40.6-46.8	61.1	53.8-69.4	65.2	58.5-72.8
C32 Larynx	59.4	54.4-64.9	62.1	56.3-68.4	67.9	55.2-83.5	51.5	38.6-68.5
C15 Oesophagus	5.1	3.2-8.1	10.5	7.5-14.9	8.2	3.7-18.3	14.2	8.0-25.1
C16 Stomach	20.7	18.4-23.4	31.6	28.8-34.7	25.4	22.4-28.9	30.7	27.3-34.7
C18-C20 Colon and rectum	47.1	44.9-49.5	63.1	61.1-65.2	48.7	46.3-51.2	59.7	57.4-62.1
C22 Liver and intrahepatic bile ducts	2.9	1.3-6.4	12.3	9.5-15.9	3.4	1.0-11.6	9.1	4.8-17.1
C23-C24 Gallbladder and billiary tract	11.9	8.0-17.5	14.7	11.2-19.3	6.5	4.3-9.9	13.7	10.6-17.8
C25 Pancreas	4.3	2.7-4.8	4.7	3.4-6.6	2.8	1.7-4.8	6.0	4.5-8.0
C33-C34 Trachea, bronchus and lung	9.6	8.6-10.7	15.5	14.3-16.8	11.4	9.5-13.6	22.1	20.2-24.1
C38.0, C47-C49 Connective and soft tissue	61.3	51.1-73.7	58.0	48.9-68.7	55.0	45.1-67.0	52.0	44.8-60.3
C40-C41 Bone	66.7	52.3-85.1	65.7	48.9-88.3	66.0	50.7-86.1	51.8	36.5-73.3
C43 Malignant melanoma of skin	75.4	70.9-80.3	90.0	87.0-93.2	81.8	77.9-85.8	90.8	88.0-93.7
C50 Breast	-	-	-	-	77.5	76.0-79.0	87.6	86.3-88.9
C53 Cervix uteri	-	-	-	-	73.1	70.2-76	69.0	64.7-73.7
C54 Corpus uteri	-	-	-	-	79.8	77.1-82.6	80.6	78.0-83.3
C56 Ovary	-	-	-	-	47.9	44.5-51.6	40.4	36.7-44.5
C61 Prostate	71.1	68.4-73.8	92.3	91.0-93.7	-	-	-	-
C62 Testis	96.4	94.2-98.7	97.6	95.9-99.3	-	-	-	-
C64-C65 Kidney with renal pelvis	56.5	52.1-61.3	64.6	61.1-68.3	61.4	56-67.4	69.3	64.8-74.1
C67 Bladder	48.5	44.1-53.2	55.3	51.3-59.6	50.5	42.9-59.4	44.4	38.4-51.3
C70-C72 Central and autonomic nervous system	13.2	9.8-17.9	15.8	12.4-20.1	18.7	14.2-24.7	15.0	11.4-19.7
C73 Thyroid gland	88.1	79.5-97.7	90.6	85.1-96.4	86.6	82.1-91.4	95.3	92.7-97.9
C81 Hodgkin's lymphoma	78.3	69.3-88.5	78.3	69.2-88.5	79.0	69.5-89.7	85.7	77.3-95.1
C82-C85 non-Hodgkin's lymphoma	55.1	49.8-60.9	65.7	61.9-69.8	54.7	49.8-60.1	61.3	57.6-65.2
C90 Multiple myeloma and malignant plasma cell neoplasms	36.8	28.9-46.9	38.9	32.6-46.4	32.8	26.4-40.7	44.0	37.5-51.5
C91-C95 Leukaemias	49.8	44.7-55.4	46.0	41.8-50.6	41.6	36.2-47.9	47.2	41.9-53.0
C00-C96 (but C44) All sites, but skin	38.4	37.6-39.2	55.8	55.0-56.5	54.3	53.4-55.1	59.9	59.1-60.6

op slowly and would not cause health problems for men during their lifetime. This artificially prolongs survival, as the disease is detected earlier, but the course of the disease is not changed.[15] However, the most common cancer in women, breast cancer, has not seen such a large improvement in survival (Table 1). The breast cancer screening programme was introduced across the whole country only in 2018, so it could not make a significant contribution to the results of our current analysis.[16]

In both sexes, survival for other three common cancers have increased significantly over the last 20 years: colorectal cancer (by 14 percentage points, from 48% to 62%), cutaneous melanoma (by 11 percentage points, from 79% to 90%), and lung cancer (by 8 percentage points, from 10% to 18%) (Figure 1). These results reflect earlier diagnostics and advances in systemic treatment. Despite treatment progress, the survival of lung cancer patients remains low. There are some other cancers where almost no progress over time was observed and in which survival remains low including pancreatic, oesophageal, gallbladder and bile duct, liver and brain cancers.

Age and stage at diagnosis are prognostic factors for disease development and treatment outcome and also for the survival of cancer patients. The survival of persons aged 20 to 49 was better in the last two periods compared to other age groups and improved by 15 percentage points in period 2012 to 2016 compared to the period 1997 to 2001 (Figure 2). Five-year net survival is lowest in those over 75 years of age but also in this age group has improved by seven percentage points over the last 20 years. The number of older patients with cancer is increasing in Slovenia, for example, the number of patients aged over 75 has more than doubled in the analysed period.[17] It is precisely these patients who most frequently have comorbidities that can severely limit attainability of specific oncological treatment, which explains why the proportion of patients without specific oncological treatment remained roughly the same through time despite the increasingly complex treatments available - around 20% according to the last SCR's report on cancer patient's survival.[5] We can conclude that doctors equally often decide to treat elderly patients, although more complex treatments are often accompanied by many more side effects. Consequently, as seen from our analysis in the last three time periods, the five-year net survival of the oldest group of patients still remained almost the same, while in the younger groups it increases steadily and significantly. Apparently, the age and concomitant diseases are a wall that we cannot scale with today's treatments.

The importance of the stage at diagnosis cannot be overemphasised. The five-year net survival of patients diagnosed with solid tumours in localized stage increased by 10 percentage points over the 20 years of observation and reached 85% in the last period. Five-year net survival of patients diagnosed with cancer in regional stage approaches 55%, whereas in patients diagnosed with cancer in distant stage it is only slightly below 25% and does not improve statistically significantly through time (Figure 3). Despite a number of new insights into prognostic and predictive factors and with the advancement of molecular biology which enabled more effective treatments, the classical stage of TNM remains the basic predictor of disease progression and survival (together with the age of cancer patient). Reporting the stage in cancer registries is historically simplified into three groups: localized, regional, and distant disease. Results show, that nowadays the disease is more frequently diagnosed in the localized stage and less often in the regional stage; the percentage of patients with distant disease remains the same. This is partly due to more accurate and accessible diagnostic methods that allow detecting more and smaller distant lesions despite on a whole the diagnostic is done earlier.

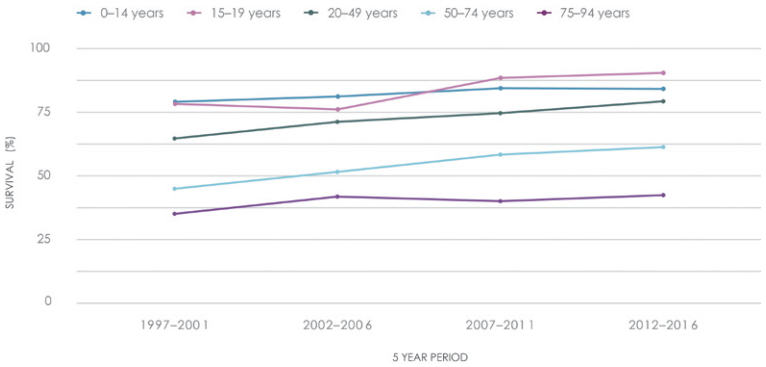

FIGURE 2. Five-year net survival of patients with cancer (all sites but non-melanoma skin cancer) by age group, Slovenia 1997–2016.

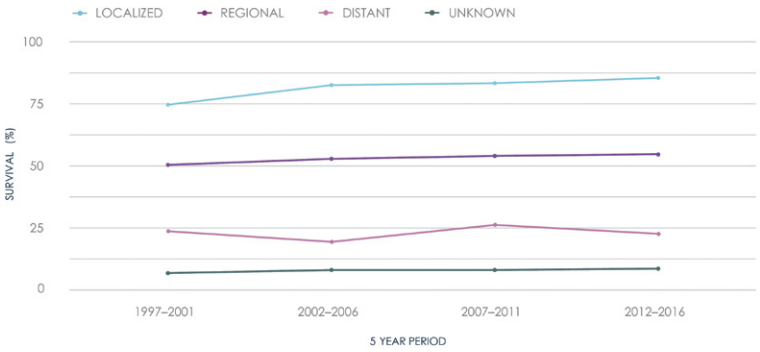

FIGURE 3. Five-year net survival of patients with cancer (all solid tumours but non-melanoma skin cancer) by stage at diagnosis, Slovenia 1997–2016.

From our analysis, we can conclude that the improvement in survival can be explained by the disease being diagnosed at an earlier stage and is not just the consequence of the stage-shift described above. This is certainly the case for the last period for colorectal and breast cancers. For all patients who respond to the screening invitation, the five-year risk of death is four to five times lower than for those who do not respond to the invitation, due to the disease being diagnosed at a lower stage.[18] Of course, survival is not a measure of the success of a screening programme (it's biased due to time advantage), but treatment of the disease at an earlier stage undoubtedly affects recovery and consequently cause specific mortality. Successful screening programmes and high population responsiveness are therefore improving survival.

Although rarely, cancer is diagnosed in children as well. In the present survival analysis, we included

TABLE 2. Five-year net survival of children (0–14 years) and adolescences (15–19 years) with cancer by period of diagnosis, sex, age group and stage at diagnosis for solid tumours, Slovenia 1997–2016

Period of diagnosis	Gender		Age at diagnosis				Stage (C00-C80)			All
	Male	Female	0–4 year	5–9 year	10–14 year	15–19 year	Localized	Regional	Distant	
1997 – 2001	205	146	93	48	78	132	116	59	20	351
2002 – 2006	180	149	96	49	51	133	114	52	21	329
2007 – 2011	170	161	89	53	69	120	126	33	18	331
2012 – 2016	200	168	104	74	56	134	144	53	27	368

1,379 children and adolescents (aged 0 to 19 years) diagnosed in Slovenia in the target period 1997 to 2016. The net survival has been gradually increasing with respect to the year of diagnosis. For example, the five-year net survival for all childhood cancers combined increased by almost 8 percentage points and exceeded 85% in the last period 2012–2016 compared to the first period 1997–2001 and being less than 30% fifty years ago.[12,19] There is a significant difference in the survival among patients with different cancer sites: patients with malignant brain tumours survived five years in 70%, those diagnosed with leukaemia in 88%, but all of those diagnosed with lymphomas survived five years in 98%. The 20-year improvement was the highest in lymphomas – for 12 percentage points. Clearly, the malignant diseases in children are heterogeneous group and a retrospective analysis of factors contributing to the observed improvement in survival is difficult. In Slovenia, all children suspected of having cancer undergo a diagnostic workup and treatment in a single national paediatric centre, which positively affects their survival along with developments in diagnostics and treatment.[19,20]

Similarly, as in adults, boys achieve slightly lower survivals than girls, but the gap between the sexes has been narrowing over time (Table 2). Five-year net survival was similar in children and in adolescents in all observed periods (Figure 2, Table 2). In the first two observed periods, between 1997 and 2006, it was slightly better in the 0 to 14 years age group, and in the last two periods, between 2007 and 2016, it was reversed being better in the 15–19 age group. In the last observed period, from 2012 to 2016, it reached 85 and 91% for children and adolescents, respectively. The five-year net survival of children and adolescents with solid tumours with localized and regional stage disease exceeds 85% in the last ten years. In children and adolescents with distant disease at diagnosis, the five-year net survival approaches 70% (Table 2).

Conclusions

Population-based cancer survival is a composite indicator reflecting the characteristics of patients as well as the organisation, accessibility, quality, and efficiency of the healthcare system. This analysis is the starting point of our fourth comprehensive report on the survival of Slovenian cancer patients[5] and shows the progress of Slovenian oncology and healthcare, as well as Slovenian general attitude towards cancer over the last twenty-year period. As we determined, the survival of Slovenian cancer patients has been increasing over time, which gives us a basis and an incentive for future improvements. In addition, the lag in survival of Slovenian cancer patients in comparison with the patients from other European health systems identified in some cancers in the CONCORD-3 study[14] and in the last EUROCARE study[21]provides us with a legitimate basis for considering improvements in the future.

The National Cancer Control Programme delivers a comprehensive set of activities in the fields of primary and secondary prevention, diagnostics, treatment and rehabilitation, as well as palliative care. Therefore, in order to reduce the cancer burden and improve the quality of life and economic sustainability, all evidence-based primary and secondary prevention programmes must be established and used, and evidence-based treatment implemented in scientifically acceptable time frames. The development of medical science, oncology and molecular biology in the last 20 years has brought many revolutionary insights into the field of oncology, which undoubtedly have had an impact and will have an even more significant impact on the survival of cancer patients in the future. To monitor the effectiveness of managing the cancer epidemic of today, also in the future the burden of cancer will need to be monitored based on quality data and scientifically justified methodological approaches both provided by established cancer

registries. Further on, cooperation between oncological epidemiologists and clinical specialists is crucial for a comprehensive review and preparation of proposals for improvement.

Acknowledgements

The authors thank the staff of the Slovenian Cancer Registry whose endless efforts to collect accurate and complete data have made this report possible.

We express a sincere thankfulness to professor Viljem Kovač, professor Primož Strojan and doctor Maja Primic Žakelj for their careful review and commenting on the presented research and report.

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