Life expectancy after cancer

Dr Botta: Good evening, everybody. I am Laura Botta, I'm a biostatistician at the National Cancer Institute. I'm a researcher and I'm also a PhD student at the University of Bourgogne, in France. I'm going to give you a brief overview of the methods and the epidemiological indicators that are used to reply to frequently-asked questions raised by the healthcare community. Yeah, all right, okay. Yeah. Several measures are used to quantify the magnitude of disease occurrence in a population. And each one is valid for a slightly different proposal. For example, we have a prevalence and incidence. Prevalence is different from incidence because it collects all the cases included in a specific time, whereas, incidence includes only the new cases. Therefore, we have for prevalence, the new cases and the pre-existing cases. These measures are useful for examining the need of healthcare and the public health services. In Italy, for example, we have a number of people that living after a cancer diagnosis is increasing by 3% yearly, as you can see from the graph in this specific slide. This is prevalence because it's number of people living, no matter at which time since diagnosis we are. So, this is increased. And this information is mainly powered by the increasing in incidents that it's also occurred because of the ageing of the population, and all the advances in treatment, and all the early-detection of the cancers. Of course, thanks for all these indicators, and the question that the healthcare community raised to the epidemiological researcher are those such as how many years of life I have lost having the diagnosis of cancer? How many years will I have to wait to consider myself cured? How many patients are already cured from the disease? And how many patients will be cured for the disease? Okay, so... just... okay. To express the effect of cancer, I will give you an overview of survival. That is an important indicator that evaluates the effectiveness of the health system. We're speaking about epidemiology, and therefore, we use population-based cancer registry data. Population-based is a registry that is institutional-mandated to collect all the incidences, that means new cases, that occur in a specific population. And also, these cases will be followed-up for updating the life status. With this information, we can calculate survival. In this graph, you can see the observed survival, that's the curve in red, that represents the survival for any causes that occurs in a specific cancer patient population. Then, we have the expected survival, it's the green line dotted. That is the survival experienced by a comparable group of the general population. And usually, the variables that we are using in order to be comparable are sex, age, years and the specific of the residence of the patients. Then, we have the relative survival. That is the ratio between these two quantities, and expresses the excess of mortality that the cancer patients have in comparing to a general population with the same characteristics. Another indicator that can be used for the estimation of long-term effect is the life expectancy. And we have the patient life expectancies expresses as the mean estimate number of remaining life-years for a cancer patient at a specific age, sex, calendar year, and time of diagnosis. And we can calculate the difference between the life expectancy of the cancer patients with those of the general population. And this difference is called year-of-life lost. And it's an important indicator to estimate the burden of the cancer in the long run in a specific population. Given this tool, sorry. Yeah. Given this tool we're obtaining, we can reply to the first question, how many years of life I had lost having the cancer? So, let's look at this graph. We have in the black line, the

population life expectancy for male and female for the general population. Then, in the blue line, we have a specific patients' cohort by age of diagnosis. And you can see in the arrow, the red arrow represented year-of-life lost. We have a similar pattern for life expectancy, no matter if it was about male and female. And so, we have a first phase, where there is the largest drop at the beginning when the patient is diagnosed, and this drop is even larger if you're a younger patient. This is because, of course, in this, the life expectancy of the population is higher, because, actually, the whole contribution will be about the cancer. I mean, the competitive cause of cancer in the general population for younger patients is really not that important. Then, we have a second phase where we have an increase in the few years after diagnosis because the patients surviving the high-risk-of-death are concentrated in the first year and therefore, their life expectancy is going to go up, and try to reach those of the population. And then, we have a third phase, that is that fill, the life expectancy starts to drop again and try to reach those of the general population, even if in the long run, as you can see from these figures that represent the life expectancy in the Italian population, still, lagging behind those of the population. You can see that the red arrow still is persistent even after 25 years after diagnosis if a patient then goes up to 45. Always remember too, you can ask questions and comments in the Chat. So, after life expectancy, we can also use cure indicators in order to estimate the long-term survival. Cure indicators start from a definition of cure that was proposed by Easson in 1960s. And it's a group of disease-free survivors whose progressive death rates from all-cause is similar to that of a normal population of the same age and sex, constitution. So, in the '90s, some researchers like Lambert, you have the reference in the below part of my slide, invented this mixture cure model that divided in two the patients. Part of patients who will die of the disease. You can see their survival in the red line, in the graph in this slide, that goes and try to approach 0. And then, another part of the patients who are cured and the relative survival of these patients is 100%, is a straight line, horizontal line that you can see above the graph, in blue. This is that there is a part of the population who will experience the same survival as a comparable population. Because of that, the relative survival of this specific population it's about 1. In red, sorry, in green, you have the relative survival of the overall population of cancer divided into the cured and uncured patients. And of course, when the relative survival reaches a plateau, that means that the excess-risk-of-death of the cancer patients is nearly 0. You can see and you can have the estimation of the cure proportion that in this specific graph is about 55%. And then, you can also see in the x-axis, the time, sorry, the time to... yeah... the time-to-cure. And this is the formula that applies to the mixture cure model. So, with this tool, we can also reply to the second question that was raised from the healthcare community, such as how many years will I have to wait to consider myself cured? And as you can see, we define this as the time span after cancer diagnosis necessary to eliminate the excess mortality due to cancer. In this, of course, the best solution would be that the conditional relative survival that is expressed here yearly, it's the blue line. The ideal option would be that this conditional relative survival is 100%. In this case and in the estimation of the time-to-cure is reached when this conditional relative survival goes up to 95%, including the possibility that it's very, very unlikely that the patient is going to die for the cancers. You can estimate this indicator for all the cancers occurred in a population for female, male, and also stratified by age. All these results that I reported here are coming from Italian data, and their reference can be found at the bottom of my slides. There are a lot of methodologies, different methodologies that use model- based of conditional relative survival for the estimation of this quantity. But anyway, it's an important quantity and epidemiology cannot reply to this question. Moreover, another question is, how many patients are already cured for the disease? The already-cured patients are those who survived longer than the time-to-cure estimated as the previous slide. So, in these cases, you can see the prevalence. Do you remember, prevalence are all cancer cases alive at a specific time point. That means new cases, older, pre-existing cases. So, this is, for example, all the cancer patients that is alive after nine years, because you remember nine-year was the time-to-cure. So, all the prevalent cases that are diagnosed since nine-year are the already-cured survival. Another indicator is, another question was, how many patients will be cured from the disease? So, coming back to the mixture cure model that divided the population in two, the cured and uncured patients, we can obtain the fraction, the cure fraction, the proportion of cure. So, it's the amount of patients who are expected to reach the same death of

the general population who will not die as a result of their cancer. So, this is the assumption underneath this model is that the cancer patients at some point reach the same level of survival of a comparable general population. This is as we have seen before, they reach the plateau of the relative survival, as you can see here. And, for example, in Italy, if you're a male, and you've been diagnosed at age of 60 up to 74, your cure fraction is 43%. And this can be calculated for the most common cancers. But of course, the assumption underneath the previous slide was that the survival of the cancer patients reached the same level of the survival of the general population. But as you can remember, in the first slide, I showed you also the year of life lost. And if you remember, the red arrow still remaining even after many, many years since diagnosis. So, it looks like that an excess risk-of-death of also for cured cancer patients still exists if comparing from the general population. So, it's well-known actually from literature that cured patients are no longer at risk of dying from cancer, but anyway, are fragile, are more fragile than general population, and at risk of, for example, develop disease-related to the treatment received or develop pathologies related to the risk factors common to cancer. Such as, smoking is a risk factor for lung cancer, but it's also a risk factor for a lot of cardiovascular disease. And also, cancer patients are keener to develop a second tumour, a lot of literature is speaking about this. So, we try to include in the mixture cure model a correction factor that can be expressed as the relative-risk-of-death of other causes of cured cancer patients. And with this correction factor, we can estimate rather than the proportion of cured intended as when the cancer patients reach the same level of the general population, a cured proportion that, as you can see from the graph, from the figure on the left part of the screen, and reach not really the general population, but reach a comparable population. Because anyway, this is important estimation because it's not really fair if you compare the cancer patients to the general population, because it's known that in the long run, anyway, they have still some excess risk. Not related maybe to the cancer, but it's not the cancer, it's not the relapse or the recurrence. So, we also calculated the difference between the proportion of cured using this specific model. And this relative-risk-of-death actually was found in data. So, we included it in the model, and we used the observed data to estimate these relative-risks in the model, and the relative-risk-of-death actually was bigger than 1. That means that the cancer patients have this relative-risk. So far, we used USA data, cancer data, that are public-available using the SEER software and asking for permission to the NCI. But we're going to apply also to European data and to Italian data, this specific model. Our goal was to include this relative-risk-of-death for cured cancer patients because, and as you may know, in 2016, the Right-To-Be-Forgotten was included in the French law. It's a right that allows cancer patients, at some point of their lifetime, not to be obliged to declare their previous cancer and disease while speaking with insurance for loan, or also for others financial transaction. Therefore, what we see in this paper, that also, for example, cardiovascular disease is affecting the possibility to have a home loan. So, what we thought it was that we know that cancer patients have an increased risk of cardiovascular disease compared to the general population. So, when we want to estimate the indicators that are used with the Right-To-Be-Forgotten, to define at which point specific cancer patients can omit the fact that had a previous cancer in their life, it's important to take in consideration, not counting twice the specificity of cancer patients. So, with this new model, we try to disentangle the effect, all the comorbidities related to the treatment also to the risk factors that brings the patients to have the cancer, and take off from the cancer itself. So, that's more or less an easy explanation can be that we do not include the risk-of-death for cancer to these patients, but we move to other causes such as cardiovascular disease or other specific information. And this kind of estimation, it's keener on reflecting the question, I propose a definition cure proposed by Haupt in 2007, that it's "Cure refers only to the original disease, regardless of any potential for, or presence of, disabilities or side effects of treatment." So, if you want to conclude and to take some home take-home message, we presented estimates. In particular, those for cure-fraction and time-to-cure where average figures refer to the group of patients. So, it means it's not individual, it's a group of patients. It's an on-average figure. The ability of this indicator as a high potential impact on planning, clinical practise, and patients' perspective. The results presented provide quantitative information and number of patients though not on their general health status. I'm so sorry, but population-based cancer registries cannot collect comorbidities, socio-economical status as other factors that can influence this quantity. And also, that

research is keep on moving to find the best epidemiological/statistical approach in order to reply to all these important questions. Thank you very much for your attention, and I will give you the floor to Monica.

Dr Terenziani: Good afternoon, and nothing to disclose. I'm Monica Terenziani. I am a Paediatric Oncologist. I'm going to speak of some clinical problems after the presentation of Laura. I'm a clinician. And for children and adolescent, and young adults, focus on the cure of cancer cannot be the only endpoint today. Although, many cancer patients have a comparable life expectancy to the adult population, some of them have disabilities and chronic psychological disorders. And Paediatric Oncologist was the first to recognise the problems of survivors and as healthcare providers, we must educate and follow-up this population. In this slide, you can observe the improvement of survivors during the year, and currently, about 80% of children and adolescents will survive more than five-year. This group will become long-term cancer survivor. This definition is widely accepted in the world of paediatric oncology. However, there is no such a precise definition in the world of adult oncology practise. However, we need to remember that cancer still remains the most common cause of disease-related mortality. There is a consistent number of survivors of childhood cancer in Europe, for some of these follow-up and medical care are and will be lifelong. For others, there is a little long-term risk. Based on self-reported outcomes and cancer registry, we know that 60 to 75% of survivors have at least one late effect. 20-30% of them have severe late effects. Elevated risk of morbidity and mortality among survivors increases in a significant way after the fourth decade of life. And very important, the risk increases with ageing without reaching a plateau. Remember, you can ask questions and send comments. However, based on medical assessment, we will find a substantial number of unrevealed problems typically observing adult population. And this is an example of St. Jude Lifetime cohort, it's a cohort of survival childhood cancer who completed a two three-day clinical evaluation. And you can observe that almost all, 90-80% of the cohort had one or more chronic health conditions, and 67 of them had a serious or disabling health condition. Luckily, childhood cancers are only 1-2% of all cancers. In adults, the percentage of patients defined as cured reach about 27% of the entire population of cancer patients, and an increase in life expectancy creates new challenges for the Oncologist too. And today, investigation may be not just pre-clinical and clinical, but also is research and assistance, and survivorship care. We need to also recognise that about 2/3 of patients with cancer are over the age of 65. So, comorbidity condition could be already present at the time of diagnosis and can be exacerbated by cancer treatment. So, according to the age of the patient, cancer could be just one of severe disabling diseases. And the better or worse quality of life and life expectancy could depend also on the wise management focused on the person and not on the disease. And in this case, the role of GP, General Practitioner is fundamental. Now, we know that there is a cost of cure. The treatment has been defined in the past like a battle. And survivors were those who were winning the war, so they were lucky to survive. But now, we know that for survivors, life is defined as disturbing, and cure doesn't always mean being well. As a professional, we are responsible for the transition between treatment and long-term follow-up. And we're also responsible for a correct use of economic resources. There are many models of care and a debate within the oncological community about the best model for survivorship is under-way. A coordination between professionals is essential to guide patients through their journey of different phases of cancer, from diagnosis to the treatment, and now, also survivorship. And this model has to consider the different patients' categories, the age, the type of disease, the comorbidity, the distance from the hospital, the services available, the insurance, and the national systems. In this slide, you can observe the blue line, it's the line of the general population. And the red line is the line of cancer survivors. They experience an excess lifetime morbidity and advanced onset of morbidity. And with the future research we would like to try to reduce this gap between these two lines. These data suggests that a premature ageing could be a consequence of the therapies that are used to cure cancer. This is another example of what I said. PanCareSurFup is the largest study with the longest follow-up or late mortality among European five-year cancer survivors. Here, you can observe death for the first neoplasm increased from 5 to 10 years after diagnosis and then slowed. In contrast, mortality from second neoplasm, cardiovascular disease, infection disease, was low during the first decade but increased thereafter. You can ask and send comments. Cancer

treatment-associated morbidities are related to many factors. Some of them are related to providers, some of cancer, and we need to consider new treatments. Some are related to patient and familial and genetic predisposing factors are very important. Some however are related to different health system policies. In this study, a comparison of late mortality among childhood cancer survivors in US and UK evaluate also different national health systems. It's a retrospective study. And all-cause of cumulative 10-year mortality from diagnosis were lower in US cohort compared to the Britain cohort. However, 40 years from diagnosis, the US cohort had a higher risk of mortality from late toxicity. These data suggests that US survivors may have a more intensive treatment to achieve higher cure-rate, but the cost of this approach could be higher risk of late toxicity. However, this example highlights also that US survivors could lack access to consistent follow-up care and survivorship care. And the lack of insurance could be one of these predictive factors and problems. A better risk stratification is a crucial point in oncology practise. It's a way to select patients according to different risk categories to define a different treatment strategy. And nowadays, it's also a way to define a personalised survivorship care plan. We can try to intensify therapy for all with the risk of increased morbidity for all. We can try to reduce the therapy in all with the risk of decreased survival rate. But a better way, it would stratify patients according to prognostic factors. We need to also consider that the current knowledge is based on old treatment modalities that are modified during the years with the reduction of emission of cumulative doses of chemotherapy and radiotherapy for some type of diseases. These modifications have reduced the treatment burden and the occurrence of late complications. On the opposite, these old treatment modalities are modified during the years with the treatment intensification in selected high-risk group. These modifications had increased the treatment burden with a better cure-rate, but we have and will expect higher risk of late toxicity. To note, the recent advent of immunotherapy and targeted therapy for the treatment of some form of cancer would not change the scenario. Their mode of action differs from conventional treatment, but a detrimental effect on future health cannot be excluded. And some of these treatments could be used together or after the conventional chemotherapy. Finally, we have some traditional treatments and new technology development. For example, patients treated until '90s received as a standard of care 2D-planned radiotherapy. Since 2000, CT scan-based 3D-planned radiotherapy and multi-beam technique have been implemented. Compared to 2D radiotherapy, the dose delivered to the healthy tissue surrounding the tumour is lower, and this is very important for late effects. However, we know that a larger area of healthy tissue receives low doses of radiotherapy. And data on these low doses including long-term follow-up are still unknown. This is a paper reporting a reduction in late mortality among five-year cancer survivors in selected group. And the author underlined that with respect for some categories and for Hodgkin lymphoma above all, they suggest that the factor other than reduced treatment exposure may have caused the reduction in late mortality. And potential contribution of this decreased late mortality could be an accuracy in screening method and survivorship care. So, we need to screen and survey high-risk patients, because we now know that many studies show that the screening could identify a substantial proportion of survivors with previously unrecognised treatment-related complications. Some of these related complications may benefit from some kind of treatment or preventive remedial intervention. Based on different latency of toxicity, we can enact different surveillance and remedial intervention. And here, two different examples. Cisplatin hearing-loss toxicity develops soon after treatment, and it's very important in young children. We need to monitor hearing during treatment. We can act, modify and try to avoid cisplatin, if it's possible, but also, we can act so remedial intervention to optimise language development and academic achievement. On the opposite, the risk of secondary cancer, breast and colon cancer after radiotherapy at a median time to diagnosis of 20 or 10 years, depending on many factors. So, we need to recommend early surveillance, but this early surveillance could stop many years after the end of the treatment. For this reason, we needed to have a consensus-based clinical guideline. An International Guideline Harmonisation Group could try to do this. And please remember you can ask questions. Consensus based on scientific studies and expert opinion has been validated with the same methodology by answering the following questions: Who needs surveillance? At what age I need to start surveillance? What surveillance will be used? And what should be done if abnormalities are identified? They try to validate an international guideline recommendation with

a specific colour-code similar to traffic light. Strong recommendation, green, go ahead. You can have surveillance. There is no scientific evidence. Stop, you don't need surveillance. This is one of the recommendation guidelines for cardiomyopathy. First of all, they develop risk stratification patients, high-risk, risk, moderate-risk, low-risk. And finally, in the end, I would like to leave you with a clinical case as a take-home message. But first, I ask you to pay attention to this study. It's a cumulative burden of cardiovascular morbidity in paediatric adolescents and young adults of Hodgkin lymphoma. As you can see in this slide, survivors aged 50-years will experience a consistent number of chronic cardiovascular condition compared to community control. But among this, the number of severe cardiovascular condition was impressive. And finally, we have a female born in 1978. She had, at the age of two, had a renal tumour with bilateral lung metastasis. She was treated with nephrectomy and three-drugs chemotherapy including Doxorubicin, that is a cardiotoxic drug, whole lung radiotherapy, and left flank radiotherapy. Luckily, the girl was cured, and then, she started follow-up at late effect clinic. At the age of 22-years-old, she had a pregnancy and delivered a healthy baby. When she was 42-years-old, after 40 years from her paediatric cancer, she had a breast biopsy for the presence for microcalcification, and the pathology report was negative for cancer, luckily. But she had also a reduction of 80% of left ventricular ejection fraction compared to the echocardiography of the previous year. And finally, she had a diagnosis of secondary thyroid carcinoma. According to the clinical and pathological feature of thyroid carcinoma, the Medical Oncologist suggested a post-operative radio-metabolic treatment. But however, we need to balance between the risk of relapse of thyroid carcinoma and the risk of adding another toxic treatment. And what should have worried us most for this woman? According to this slide, according to the age of the patient, according to the previous cardiotoxic treatment, according to the radiotherapy to the lung and to the heart, according to the reduction in her ejection fraction, we were worrying on her cardiac function. So, we omitted any further treatment, she started the follow-up, and now, she's alive without a relapse of thyroid carcinoma, but she's on treatment for cardiomyopathy. So, we need to maintain success to increase the survival rate. We need to try to reduce the treatment burden to avoid too toxic treatments for our patient, but we need to also focus on survivorship care. Thank you. So, we have... Do you have questions? Please, don't be shy if you have questions. No comments? I have a question for Laura. Can I, Laura?

Dr Botta: Yes, please, sure.

Dr Terenziani: As a clinician, I'm very interested in your work, but because I have many problems to understand your numbers, and it's very important for me to try to understand well and better. And I try to understand how we can connect our worlds, the world of the clinician and the world of the epidemiologist for a better understand and better work together.

Dr Botta: Sure, okay... In general, Okay, I tried to explain you briefly all indicators. And then, at the end, I put emphasis on what I'm studying right now for my PhD. That was this correction that actually comes from the needs of understand at which extent the patients need no more, let's say, be taken in charge of the Oncologist rather than the General Practitioner, and so, the follow-up for other important disease. What we would like to try to understand, so what amount the care of this patient can be shifted from a different follow-up rather than follow-up for the disease itself. So, we want to try to understand. And of course, tell you, of course, as I stressed in my last slide, it's an average. I'm sorry, we work at a population level, therefore, individualization of the cure, it's very difficult, because we see from another point of view. It's just that you look at the patients, and I look at the numbers. Therefore, what we try to achieve is something more related to the healthcare. But I think it's really important for you too, because, for example, for a specific cancer, I can tell you that from now on, your patients will not die for the cancer, specifically, the cancer. Could die for, as you say, from the patients on your cohort, cardiovascular disease, disease related to the treatment, but it's not anymore, a problem of the cancer. Then, first can be taken in consideration for the follow-up from the general practitioner, and the hospital, and the cardiovascular disease unit rather than an oncology unit. And this is also important in my point of view for the psychology of the patients, because to know, I mean, if you have

a cancer when you were a child or also adolescent, and then find out a new relapse of your cancer is a different, totally different feeling compared to having a health problem in terms of cardiovascular disease, maybe, can be treated easier. I won't say easier, but anyway, in a less aggressive way, and can be monitored rather than treated with intensive care. So, I think in this way we can communicate, even if we're speaking about averaging on the world population. And of course, it's population based, it's not clinical. And I'm really happy to discuss with you if you think it's working, because we're also trying to applying this model to childhood cancer that, as you may know, have some specificity about this, because there are a few, and you always compare with the population that it's not dying for a lot of, fortunately, the difference between the general population and cancer patients. Of course, they reach the same, they really increase on that starting about age of 45. So, from 15 up to 45, it is the cancer that you see from the survival, unfortunately. So, it's a very big issues for modelling. I'm sorry, I'm speaking about numbers now. But so, do you think that this model can reply a little bit to your questions?

Dr Terenziani: Yes.

Dr Botta: Okay.

Dr Terenziani: Yes, it was very clear for me.

Dr Botta: It was clear? Okay.

Dr Terenziani: Yes. I hope also for the audience.

Dr Botta: And we also try to disentangle these excess risks of that for cured patients, we would like to use the information on treatment in order to understand a little bit more to what extent this extra-risk is due to the treatment or to what extent is due to other factors.

Dr Terenziani: Yes, and I think it's very important to recognise now that the genetic and cancer predisposing syndrome are very important topics in young children with cancer, in adolescents, and young adults too. Because our knowledges are improving in this topic, and nowadays, we know. When I started to study paediatric oncology, the cancer predisposing syndrome were less than 10%. Now, we are up to 18%. So, our knowledges are increasing. There is something new to predispose to cancer, and maybe, something that predispose to late toxicity, and something different, and not only toxicity of our treatment, because we know this is an important factor. But there are many connections between all these factors, and we need to study to understand better, thank you.

Dr Botta: Yes, and moreover statistic is very important because, as you know, it's survival long-term, so, you need to model. Of course, it's based on assumption.

Dr Terenziani: Yes.

Dr Botta: But it's what we have, so we can always make an assumption and some prediction, and then, with the observed data in the future, understand if we predict correctly or not. But anyway, we can do something.

Dr Terenziani: And another important thing to consider that the people in UK said that the cancer is sticky. So, when you have cancer, you always have cancer. And in clinical practise, when after many, many, many, many, many years, when there is a problem, the first thing that people think was "It was my first cancer." And sometime, we need to convince the other colleagues to say, "No", there is, "maybe it's something different, which is not the first cancer."

Dr Botta: Yeah, that was a question raised from the people that convinced us to do this model in the Right-To-Be-Forgotten community, that it's an important lobby. It's in France, Luxembourg, and Belgium, but in Italy, for example, it's not a law, it's not any law.

Dr Terenziani: Yes.

Dr Botta: So, we really need to fight to get the better prediction for this estimation, for sure, and also to understand that you can have something different. Even if it was caused by cancer, it's not cancer anymore.

Dr Terenziani: Yes, okay.

Dr Botta: And it's important also at a psychological level.

Dr Terenziani: Yes, I agree with you.

Dr Botta: Thank you very much.

Dr Terenziani: So, if you have no questions, I think we can finish this.

Dr Botta: Yes, it's seven o'clock.

Dr Terenziani: Yes.

Dr Botta: And have a nice evening, everybody.

Dr Terenziani: Thank you, bye, Laura. Bye, everybody.

Dr Botta: Bye, Monica. Thank you, everybody.