

The importance of secondary cancer screening programs in Hodgkin lymphoma survivors

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Since the late 1960s, when combination chemotherapy and radiation therapy were introduced for the treatment of classical Hodgkin lymphoma (HL), survival has dramatically increased. Cure has come at a price, however, because the treatment of HL has been shown to significantly increase the risk of subsequent malignant neoplasms and other late effects.¹ Although very high relative risks have been observed for secondary leukemias, especially in patients treated with alkylating agents, second solid cancers (e.g., lung cancer), which are primarily related to procarbazine or mustine alkylating chemotherapy and/or radiotherapy, contribute most to the absolute excess risk of second cancers in long-term survivors of this disease.² Survival rates of patients otherwise cured of their HL are still significantly lower than that of the general population adjusted for age and sex.³

Undoubtedly, the establishment of screening programs in this patient population would favor the early detection of these secondary neoplasms, would allow the establishment of therapeutic strategies in early stages and, finally, not only improve the long-term survival of patients cured of their underlying disease but also have a significant impact on their quality of life as well as on the economic burden that the development of a secondary neoplasm has on society. In the ever-smoking general population, two large prospective randomized clinical trials established the role of low-dose computed tomography (LDCT) scan screening as an adequate strategy for early detection of otherwise asymptomatic lung cancer; the National Lung Cancer Screening Trial (NLST) **that** randomized a chest radiograph *versus* a LDCT scan of the thorax as a screening strategy for the ever-smoking population, was able to demonstrate a 20% reduction in lung cancer mortality in the LDCT scan arm.⁴ In the NELSON (Netherlands-Leuven Longkanker Screenings Onderzoek) randomized prospective clinical trial that included ever-smokers aged 50 to 75 years, the LDCT screening was associated with a reduction in lung cancer

mortality of 24% in men and 33% in women.⁵

Broadbent *et al.*⁶ have made a step forward in this specific field; patients with the underlying diagnosis of HL are generally excluded from screening strategies for lung neoplasms applied to the general population. However, they constitute an at-risk population. Long-term survivors were approached with specific invitation letters by post and, the non-responding group received a reminder through a telephone call. This prospective pilot study indicates that the currently validated LDCT protocols already validated for the ever-smoking general population are able to detect asymptomatic and early-stage lung neoplasms in the population of long-surviving patients with HL. Additionally, coronary artery calcifications were detected in 36.5% of the cases, clinically significant in 2.9%. This is undoubtedly a very relevant investigation, which highlights the development of more structured screening techniques in this pathology, which is one of the success stories of today's oncohematology.

We do have other examples in the literature that highlight the impact of screening strategies not only because of the early detection of lung cancer but because of a concomitant and parallel increase in quality-adjusted life year (QALY); Wattson *et al.* developed a Markov decision-analytic and cost-effectiveness model to estimate the merits of annual LDCT screening among HL survivors.⁷ In this specific analysis, annual LDCT screening was cost effective for all smokers. A male smoker treated with mantle radiotherapy at age 25 achieved maximum QALY by initiating screening 12 years post-HL, with a life expectancy benefit of 2.1 months and an incremental cost of \$34,841/QALY. Among non-smokers, annual screening produced a QALY benefit in some cases, but the incremental cost was not below the willingness-to-pay (WTP) threshold for any patient subsets. With this prospective pilot study, we have opened the door; there is no doubt that secondary cancer screening programs are essential for several reasons: early detec-

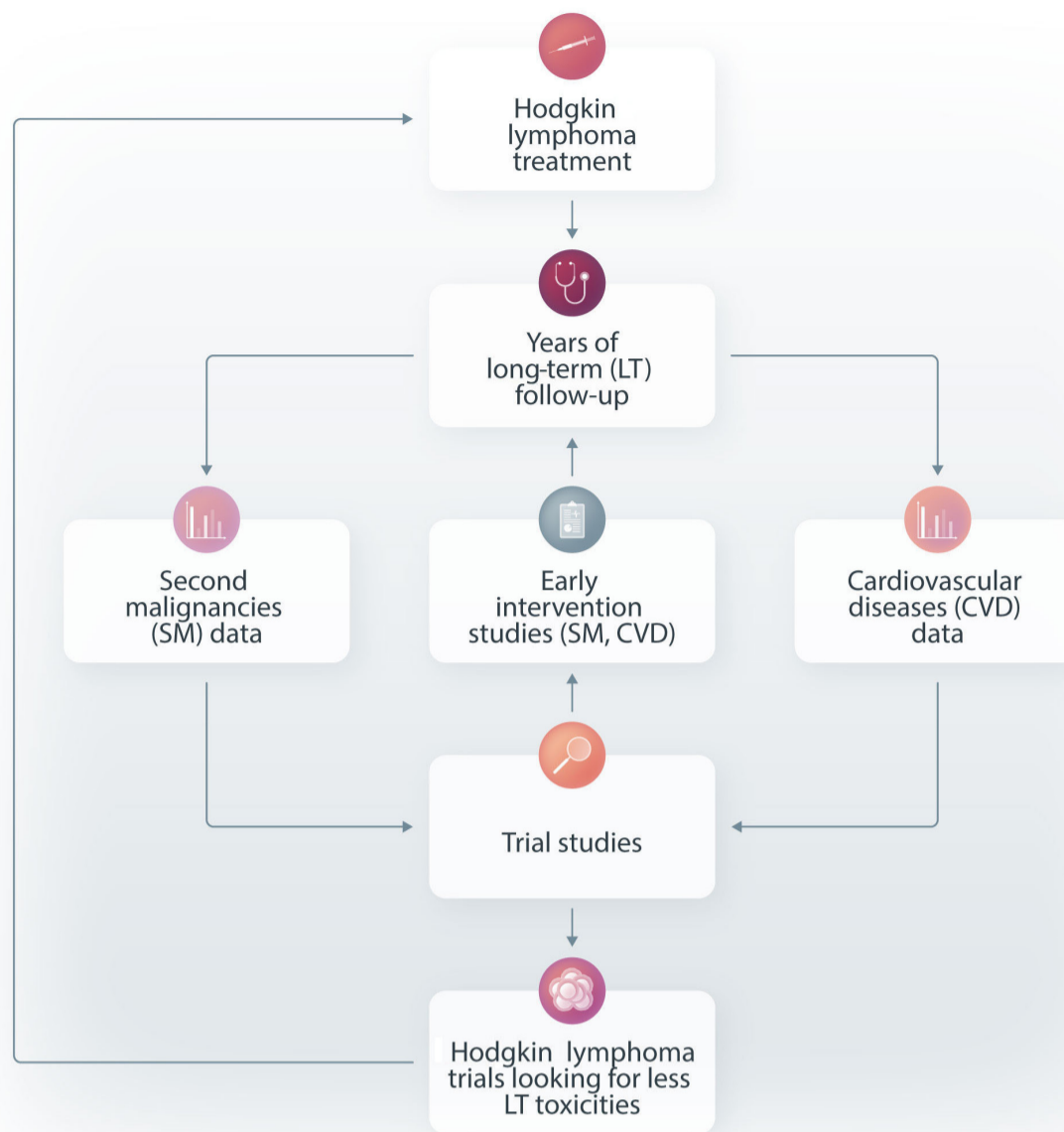


Figure 1. The long journey of understanding and intervening in the prevention of neoplasms and cardiovascular diseases secondary to the treatment of Hodgkin lymphoma.

tion, tailored surveillance, improved survival, quality of life and reduced health care costs. But, on the other side, for secondary cancer screening programs to be effective, they must encompass several key components: risk assessment evaluating the survivor's treatment history, genetic predispositions, and other risk factors; evidence-based guidelines that would provide valuable frameworks; multidisciplinary approach including clinical hemato-oncologists, radiologists, primary care physicians, and other specialists, is essential for comprehensive care; regular follow-up and patient education and support: educating survivors about their risks and the importance of screening empowers them to participate actively in their healthcare. Support services, including counseling and survivorship programs, can also provide emotional and psychological assistance.

And last, but not least, there are some well-known barriers that can eventually hinder the effectiveness of second cancers in general and lung cancer in particular screening programs; lack of awareness - both survivors and healthcare providers may lack awareness of the potential increased risk of lung cancer and the importance of regular screening; in fact, early introduction of the concept of potential lung cancer screening strategies in long-surviving lung cancer patients by the

responsible onco-hematologist and primary care physician may have increased the uptake in terms of responsive patients in the Broadbent pilot study;⁶ it is vitally important to work on improving the process. Access to care - geographic, financial, and logistical barriers can limit access to necessary screening services, particularly for those in underserved areas. Insurance coverage - inconsistent insurance coverage for screening tests can be a significant barrier. Advocacy for comprehensive insurance policies that cover necessary screenings is essential and, in those countries in which the health care system is public, all the economic considerations that repeated testing in a potential group of patients that might not need them can eventually have and, psychological barriers - fear of cancer recurrence and the emotional toll of undergoing regular screenings can deter survivors from participating in screening programs. Final considerations go to the false-positive and -negative rates, sensitivity and specificity of the process. In this pilot study, 88.2% of the LDCT results were negative, 9.8% indeterminate and only 2.0%, positive. Two 3-month surveillance scans were positive and of four positive scans, two patients were diagnosed with small-cell lung cancer and one, underwent curative surgery.⁶ These numbers are a clear example of the need to properly

balance the potential pitfalls of these screening strategies, including the deleterious effects of unnecessary irradiation doses in the vast majority of patients, with the undoubted benefits of this approach. Additional thoughts should be given to the fact that first line treatment strategies in these patients have been optimized with the objective to increase effectiveness but to decrease early, mid- and long-term toxicities; screening programs should take into consideration this new reality.

In summary, the prospective pilot study presented by Broadbent⁶ and colleagues demonstrates the feasibility and medical importance of lung cancer screening strategies in patients with HL who are long survivors but, on the other hand, opens up a number of questions that will force us to improve them in the future (Figure 1).

Disclosures

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Contributions

MAS and ASB discussed the preliminary concept and wrote the first draft of the manuscript; all authors discussed and prepared the final draft of the manuscript and agreed on the final content.

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