



Mammography and MRI for screening women who underwent chest radiation therapy (lymphoma survivors): recommendations for surveillance from the Italian College of Breast Radiologists by SIRM

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Abstract Women who underwent chest radiation therapy (CRT) during pediatric/young-adult age (typically, lymphoma survivors) have an increased breast cancer risk, in particular for high doses. The cumulative incidence from 40 to 45 years of age is 13–20 %, similar to that of BRCA mutation carriers for whom contrast-enhanced magnetic resonance imaging (MRI) is recommended. However, in women who underwent CRT, MRI sensitivity is lower (63–80 %) and that of mammography higher (67–70 %) than those observed in women with hereditary predisposition,

due to a higher incidence of ductal carcinoma in situ with microcalcifications and low neoangiogenesis. A sensitivity close to 95 % can be obtained only using mammography as an adjunct to MRI. Considering the available evidence, women who underwent CRT before 30 receiving a cumulative dose ≥ 10 Gy should be invited after 25 (or, at least, 8 years after CRT) to attend the following program: 1. interview about individual risk profile and potential of breast imaging; 2. annual MRI using the same protocol recommended for women with hereditary predisposition; 3.

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annual bilateral two-view full-field digital mammography or digital breast tomosynthesis (DBT) with synthetic 2D reconstructions. Mammography and MRI can be performed at once or alternately every 6 months. In the case of MRI or contrast material contraindications, ultrasound will be performed instead of MRI. Reporting using BI-RADS is recommended. At the age for entering population screening, the individual risk profile will be discussed with the woman about opting for only mammography/DBT screening or for continuing the intensive protocol.

Riassunto Le donne sottoposte a radioterapia toracica (RTT) in età pediatrica o giovane-adulta, tipicamente per linfoma di Hodgkin, hanno un rischio aumentato di sviluppare tumore mammario (TM), in particolare quelle trattate con RTT ad alte dosi. L'incidenza cumulativa di TM tra 40 e 45 anni è del 13–20 %, simile a quella delle donne BRCA mutate, per le quali è ormai consolidata l'indicazione alla risonanza magnetica (RM) con mezzo di contrasto (MdC) annuale. Tuttavia, rispetto agli studi di screening delle donne ad elevato rischio eredo-familiare, nelle donne sottoposte a RTT si è osservata una sensibilità relativamente maggiore della mammografia e relativamente minore della RM con MdC, correlate alla maggiore incidenza di carcinoma duttale in situ con microcalcificazioni e minore neoangiogenesi. Sulla base dell'evidenza disponibile, le donne sottoposte a RTT prima dei 30 anni di età con dose cumulativa ≥ 10 Gy dovrebbero essere invitate a partire dai 25 anni o almeno da 8 anni dopo la RTT a partecipare a un programma di sorveglianza che preveda: 1. colloquio informativo finalizzato all'informazione della donna sul proprio livello di rischio correlato alla RTT e ad eventuali altri fattori e sul potenziale delle tecniche di imaging; 2. RM con MdC bilaterale annuale con il medesimo protocollo raccomandato per lo screening delle donne ad elevato rischio eredo-familiare; 3. mammografia digitale bilaterale annuale o tomosintesi con ricostruzioni 2D (proiezioni cranio-caudale e medio-laterale obliqua). Mammografia e RM possono essere eseguite contestualmente o alternate a cadenza semestrale. Reperti ed indagini mammografiche e RM saranno classificati secondo la scala categoriale BI-RADS. Nel caso di controindicazioni alla RM o alla somministrazione di MdC paramagnetico, sarà eseguita ecografia mammaria bilaterale anche in presenza di mammografia negativa, contestualmente alla mammografia o con alternanza semestrale. Al raggiungimento dell'età per l'invito ai programmi di screening organizzato, il profilo di rischio della donna sarà rivalutato e discusso al fine di decidere se optare per l'adesione al protocollo di screening basato su mammografia (eventualmente tomosintesi) annuale o biennale o per la prosecuzione dello screening intensivo con mammografia e RM annuali. Si raccomanda che il presente

protocollo di sorveglianza sia effettuato presso centri di radiologia senologica che rispettino i requisiti quali/quantitativi definiti da linee-guida internazionali e che tutti i dati relativi all'applicazione del protocollo, ivi compresi i cancri d'intervallo, siano raccolti mediante database informatizzato al fine di consentire analisi di performance diagnostica e di efficacia su scala multicentrica.

Keywords Breast cancer · Screening · Lymphoma survivors · MRI

Background and rationale

Women who underwent chest radiation therapy (CRT) during pediatric/young-adult age (typically those treated for Hodgkin lymphoma) have an increased breast cancer (BC) risk, in particular those who received mantle CRT with high doses. However, an increased risk is also associated with RT with moderate doses for non-Hodgkin lymphoma, Wilms tumor, leukemia, bone tumors, neuroblastoma or soft tissue sarcoma [1]. The cumulative BC incidence from 40 to 45 years of age in women who underwent CRT is 13–20 %, higher than the incidence observed in the young female general population and similar to that of BRCA mutation carriers [1, 2]. The age at which CRT was performed and the radiation dose impact on the risk and is higher for high doses delivered between 10 and 16 years of age. BC is diagnosed on average about 15 years after CRT at about 40 years [3], compared with a mean age of about 61 years in the general female non-exposed population [1]. Breast cancers in women who underwent CRT are similar to those encountered in the general female population with regard to histopathologic subtype, receptor status, lymphatic invasion and nodal involvement, which play in favor of a potential role of early diagnosis. Conversely, BCs in women who underwent CRT exhibit a more extreme preferential localization at the upper external quadrants than that observed in women with hereditary predisposition (67 vs. 48 %, respectively). Moreover, in these women the possibilities of treatment of BC mostly exclude radiation therapy and chemotherapy with doxorubicin [4].

For women who underwent CRT, international guidelines [2, 5, 6] recommend annual mammography and contrast-enhanced magnetic resonance imaging (MRI), starting from 25 years of age or, for those women who had CRT before 30 years, 8 years after the end of treatment. The rationale behind is the similar BC incidence at a young age for women who had CRT and for women with hereditary predisposition to BC, associated with the relatively lower sensitivity of mammography, also related to the need to start at a young age, and the higher sensitivity of MRI [7].

The availability and application of guidelines/recommendations for the surveillance of women who underwent CRT is relevant for good clinical practice. In fact, BC risk of these women and, as a consequence, the importance of breast surveillance is frequently underestimated. In the USA, a study published in 2009 [8] reported that of 551 women with previous CRT, 47 % of those 25–39 years of age never had a mammogram and only 37 % had biannual screening mammography; the same percentages were 8 and 53 % between 40 and 50 years of age. Importantly, the screening rate was higher in the presence of a specific medical recommendation. The last point highlights the need for clear statements from medical bodies.

Before the introduction of MRI, the breast surveillance of women with previous CRT included annual physical examination and mammography [9]. This protocol allowed for detecting 60 % of BC in the pre-invasive phase or at T1 stage [10–14]. Two prospective [15, 16] and two retrospective studies [17, 18] compared mammography and MRI. The sensitivity ranged from 67 to 70 % for mammography, from 63 to 80 % for MRI, with a 92 % sensitivity reached only in one retrospective study, with a very small sample size for MRI [18]. Importantly, in women who underwent CRT, MRI sensitivity is relatively lower (63–80 %) and that of mammography relatively higher (67–70 %) than those observed in women with hereditary predisposition, due to a higher incidence of ductal carcinoma in situ with microcalcifications [19] and low neoangiogenesis. A sensitivity close to 95 % can be obtained only using mammography as an adjunct to MRI.

An expert panel [20] recently compared the recommendations proposed by the following working groups: North American Children's Oncology Group (COG), Dutch Childhood Oncology Group (DCOG), Scottish Intercollegiate Guidelines Network (SIGN), and UK Children's Cancer and Leukaemia Group (UKCCLG). As a result of this comparison, a series of "harmonized recommendations" were provided: physicians, health-care providers, and women who had CRT should be informed of the treatment-related BC risk (strong recommendation); surveillance is recommended for doses ≥ 20 Gy (strong recommendation); surveillance is recommended for doses between 10 and 19 Gy, taking into account the clinical context and further risk factors (moderate recommendation); surveillance may be reasonable for doses between 1 and 9 Gy, taking into account the clinical context and further risk factors (weak recommendation); surveillance implies annual check from 25 years of age or, at least, 8 years after CRT up to 50 years of age using mammography, MRI or both of them (strong recommendation); physical examination

may be recommended in countries where only clinical surveillance is available (weak recommendation).

Recommendations for breast surveillance of women who underwent CRT

Considering the available evidence for women who underwent CRT before 30 years, a cumulative dose ≥ 10 Gy should be irecommended after 25 years (or, at least, 8 years after CRT) and to attend the following program:

1. dedicated interview about individual risk profile and potential of different breast imaging modalities in this specific setting according to this document or other recommendations [5, 6, 21–23];
2. annual contrast-enhanced MRI using the same protocol recommended for women with hereditary predisposition [2, 23];
3. annual bilateral two-view full-field digital mammography or digital breast tomosynthesis (DBT) with synthetic 2D reconstructions.

Mammography and MRI can be performed at once (preferably during only one visit) or alternately every 6 months, considering the local conditions. Reporting using BI-RADS [24] for individual findings and overall is recommended. In the case of BI-RADS diagnostic category 1 or 2 after MRI plus mammography, the woman will be sent to the next screening event, taking into consideration the lack of evidence in favor of ultrasound if both MRI and mammography are negative. In the case of BI-RADS ≥ 3 , the radiologist will evaluate which workup is needed, including additional mammographic views, DBT (if not already performed), ultrasound, imaging-guided core or vacuum-assisted needle biopsy.

On reaching the age for entering a population screening program, the individual risk profile will be discussed with the woman to opt for the only mammography/DBT screening or for continuing the intensive protocol including MRI.

We strongly recommend this surveillance protocol to be conducted at breast imaging centers with respect to the quantitative and qualitative requirements defined by international guidelines [2, 25] and that all data and results provided by the application of this protocol, including interval cancers, are stored on electronic databases. This will allow for future analyses of diagnostic performance and clinical efficacy on a multicenter scale.

Compliance with ethical standards

Conflict of interest The authors declare no funding and no conflict of interest for this article.

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

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