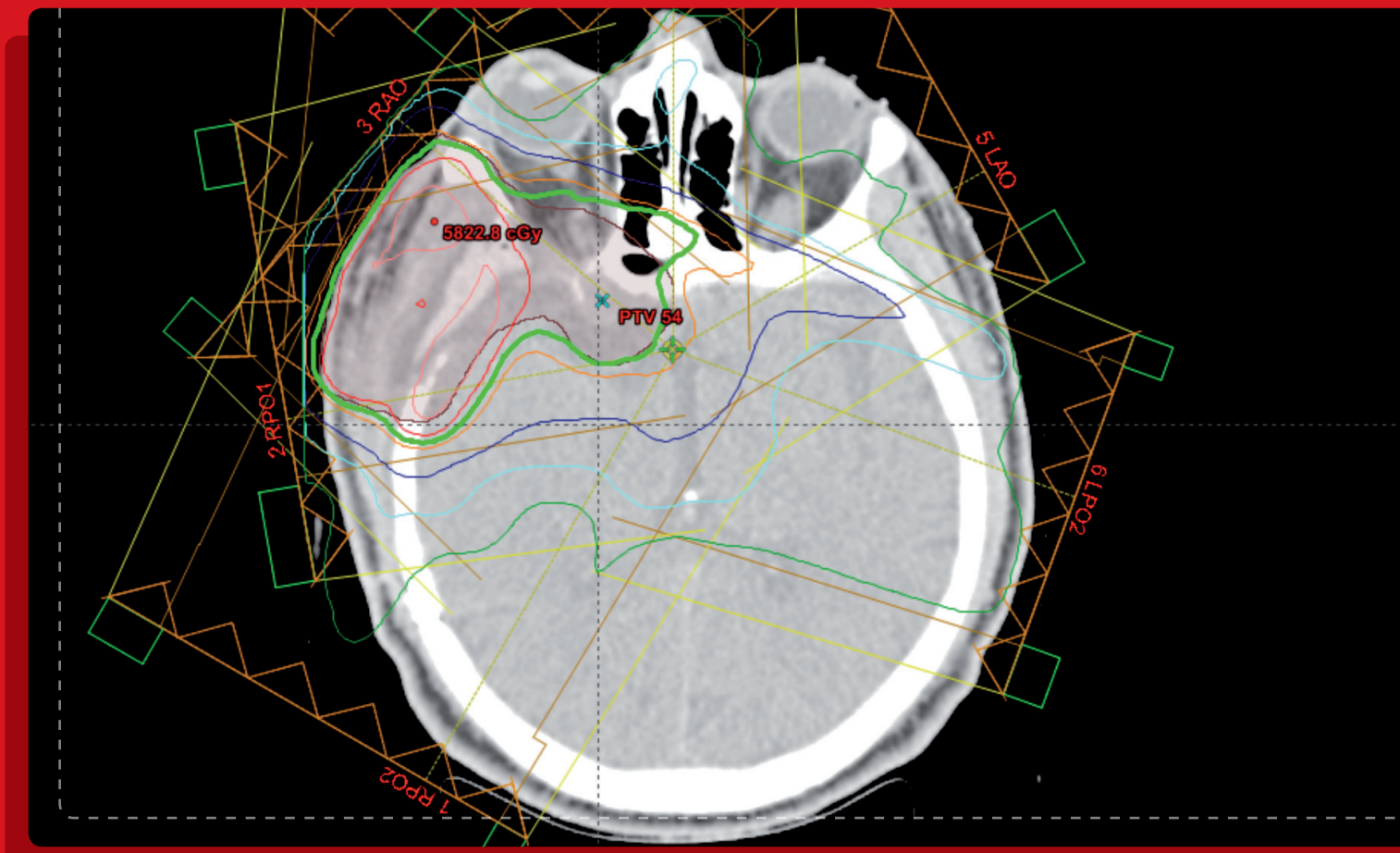

POSITION PAPER

BREAST CANCER AND LATE EFFECTS FOLLOWING RADIATION THERAPY AND CHEMOTHERAPY FOR HODGKIN LYMPHOMA

FACULTY OF RADIATION ONCOLOGY

THE ROYAL AUSTRALIAN AND NEW ZEALAND COLLEGE OF RADIOLOGISTS®

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THE FACULTY OF RADIATION ONCOLOGY, RANZCR, is the peak bi-national body advancing patient care and the specialty of Radiation Oncology through setting of quality standards, producing excellent Radiation Oncology specialists, and driving research, innovation and collaboration in the treatment of cancer.

VISION

To have an innovative, world class Radiation Oncology Specialty for Australia and New Zealand focused on patient needs and quality.

OUR VALUES

In undertaking our activities and in managing the way we interact with our Fellows, trainees, members, staff, stakeholders, the community and all others with whom we liaise, the Faculty of Radiation Oncology, RANZCR, will demonstrate the following values:

- Quality of Care - performing to and upholding high standards
- Integrity, honesty and propriety - upholding professional and ethical values
- Patient orientation - understanding and reflecting the views of Fellows and members and working with them to achieve the best outcomes
- Fiscal responsibility and efficiency - using the resources of the College prudently.

OUR PROMISE TO THE PATIENTS

We will advocate for the best possible care for individual patients in multidisciplinary meetings and for all patients with government.

OUR PROMISE TO TRAINEES

We ensure the highest standard of training in radiation oncology by combining a world-class curriculum with passionate and supportive supervisors. The voice of trainees is valued in Radiation Oncology.

OUR PROMISE TO OUR FELLOWS

We are a member based organisation that utilises its resources effectively and strategically to fulfil our vision, purpose and core objectives. We strive for best practice and facilitate life-long learning of our members.

OUR PROMISE TO OUR PARTNERS & STAKEHOLDERS

We are a transparent and collaborative organisation that strives to promote partnerships and participation of all relevant stakeholders to ensure that patients across Australia and New Zealand receive a high-quality, timely and appropriate level of care.

This paper summarises current knowledge on two of the most important late effects in patients who have had supra-diaphragmatic radiation therapy for Hodgkin Lymphoma and describes clinical care and national strategies for both routine and lost to follow-up patients.

RADIATION INDUCED BREAST CANCER

As cancer survival rates improved around the Western world over the last 30 years the problem of second primary malignancies (SPM) has become a concern. Where 20 year survival rates are above 90%, even a 1-2% risk of any late effect (benign or malignant) is very significant, in relation to all the dimensions of survivorship (Ganz 2009) (Bellizzi et al. 2009). This issue is important in the treatment and follow-up of a variety of malignancies (including Hodgkin Lymphoma), particularly in the paediatric and young adult groups (AAP/COG 2009) (Inskip et al. 2009) (Diller et al. 2009) (Zeltzer et al. 2009) (Bellizzi et al. 2009) (Robison et al. 2009) (Shuryak et al. 2009) (M. M. O'Brien et al. 2010). The risk of a second primary malignancy may be related to initial surgery, chemotherapy, radiation therapy, pre-existing genetic, environmental or lifestyle factors (Tubiana 2009).

These malignancies may present:

- In a random fashion unrelated to any follow-up;
- At regular general practice or oncology protocol based follow-up;
- Or be discovered as part of a targeted, long-term, risk adapted follow-up and screening strategy (a late effects clinic or program).

Around 40,000 patients per year are treated with radiation therapy in Australia and the great majority of these patients treated radically are regularly followed up by surgeons, radiation oncologists or medical oncologists as per local protocols or cancer network multi disciplinary meeting (MDM) guidelines. It should be noted that there is no good evidence to support the long term follow-up of most cancer patients by oncologists. Sometimes patients at risk for SPM's and late effects are lost to follow-up. This may occur with patient default, hospital or departmental closures, loss of long term treatment details, medical failure to inform, or follow-up appropriately.

Similar considerations apply for many other surviving oncology patients (particularly non Hodgkin Lymphoma) to ensure the best quality follow-up but these will not be specifically covered.

One of the challenges faced in long term follow up is the increasing globalisation, increasing world interconnectivity and socio-economic pressures which cause people to perennially move job to job, location to location – while not a direct medical reason, results in great challenges for any good follow up program to keep an eye on its survivors, especially when patients cross geo-political boundaries. This applies to cancer as well as all the chronic diseases – diabetes etc ("World Economic and Social Survey 2013").

Current treatment regimens for early stage Hodgkin Lymphoma achieve 10 year disease free survival rates in excess of 90%. There has been data available since the late 1970s in relation to the risk of second primary malignancies and other organ specific late effects in patients who have received chemotherapy and/or radiation therapy as part of their treatment for Hodgkin Lymphoma. These malignancies include haematological and solid tumours (upper GI cancers, lung cancers, primary brain tumours, endocrine malignancies, skin cancers, breast cancers and second non-Hodgkin Lymphoma). Second malignancies thought to be related to splenectomy are also described (Longo 2009) (D M Greenfield et al. 2006) (Gocheva & Koleva 2010) (Tara O Henderson et al. 2010) (Constine et al. 2008). Other non-malignant late effects, including blood dyscrasias, soft tissue, neurological, bony, pulmonary, endocrine and vascular late radiation effects may also occur. Most of these effects are rare but post "mantle" radiation therapy series

do report a high incidence of pulmonary and cardiac late effects (D M Greenfield et al. 2006) (Alm El-Din et al. 2008) (Raj et al. 2005) (Elerding et al. 1981) (Gagliardi et al. 2010) (Khoo et al. 1998).

By the 1980's data was becoming available suggesting an increased risk of breast cancer, particularly in patients having wide field supra-diaphragmatic ("mantle") radiation therapy to high doses for Hodgkin Lymphoma (Anderson & Lokich 1990) (Carey et al. 1984) (F. P. Li et al. 1981) (Prior & Pope 1988) (Swerdlow et al. 1993).

Subsequent to these early observations, a large number of retrospective single or multiple institution studies reported increased rates of breast cancer (Gocheva & Koleva 2010) (Hill et al. 2005) (Horwich & Swerdlow 2004) (N P Mendenhall et al. 1989) (Wahner-Roedler et al. 2003) (Chen et al. 2004) (Hoskin et al. 2005) (Kilickap et al. 2012) (Alm El-Din et al. 2009) (Crump M, 2012). A significant number of reviews on this subject have also been published in recent years (Alm El-Din et al. 2008) (Carmichael et al. 2003) (Raj et al. 2005). For example, the long term results for a UK trial of 603 patients treated with mantle, inverted Y fields or involved field to 35 Gy - 40 Gy, with 25 year follow-up, the incidence of second malignancies was 21% after Involved Field (IF) and 20% after Extended Field (EF) with a slight excess of lung cancer in the EF group.

Possibly the best quality radiation therapy technical data relating to breast cancer risk comes from a retrospective Dutch analysis covering a treatment period between 1965 to 1995. They analysed 1,122 patients having predominantly supra-diaphragmatic radiation therapy to various doses and volumes prior to age 51 (De Bruin et al. 2009). 120 breast cancers developed in this group representing a cumulative 30 year risk of 19% for the whole group. They demonstrated that patients treated before age 21 years had a 26% (95% CI, 19% to 33%) 30 year risk of developing breast cancer. Mantle fields (covering the axilla, mediastinal, and neck nodes) were associated with a 2.7-fold increased risk (95% CI, 1.1 to 6.9) compared with similar doses (36 to 44 Gy) to smaller fields. Higher risks were found for women younger than 40 years at first treatment, but not for women treated between ages 41 and 50. Women with greater than 20 years of intact ovarian function after radiation therapy at young ages (less than 31 years) experienced significantly higher risks of breast cancer induction than those with fewer than 10 years of intact ovarian function (De Bruin et al. 2009). It is likely that chemotherapy or pelvic radiation therapy in this disease may "protect" against breast cancer via premature menopause.

In a review of the French experience de Vathaire and Chapitre (de Vathaire F, Chapitre VI. 2008),they showed the risk of radiation-induced breast cancer was very important if patients were younger than 20 years at irradiation and was less before age 40. They concluded that diagnostic chest irradiation or radiation therapy for benign or malignant diseases increases the risk of breast cancer for cumulative doses as low as 130 mGy.

Other large analyses include the Cochrane Review by Travis et al. and a German meta- analysis (Franklin et al. 2005) (Franklin et al. 2006) (Travis et al. 2003). Franklin's group published a meta-analysis of various Hodgkin Lymphoma randomised trials with chemotherapy and radiation therapy. They demonstrated that combined modality treatment had lower second malignancy rates (SMR) than with radiation therapy as initial treatment. SMR were marginally higher with combined modality than with chemotherapy as initial treatment. Involved Field versus Extended Field radiation therapy had no significant difference in SMR, although more breast cancers occurred with extended field (Franklin et al. 2006). In a separate publication they show that combined treatment seems to be optimal for most early stage (I-II) patients. For advanced stages (III-IV) chemotherapy alone seems to cause less SMR. Radiation therapy alone gives a higher overall SMR risk than combination therapy due to increased need for salvage therapy. They comment that much of the available data in this disease is limited by outdated treatments and missing long-term data, and that 'one must be cautious in applying these results to current therapies' (Franklin et al. 2005).

A more recent meta analysis confirms these findings. The pooled relative risk (RR) of a breast cancer was 8.23 (95% CI, 5.43-12.47) with a median absolute excess rate of 22.9 per 10,000 person-years. The RR was found to be inversely related to age at diagnosis of Hodgkin Lymphoma. Analysis of the effect of treatment modalities showed that the RR rates were 4.70, 5.65 and 1.19 for radiation therapy (RT) only, combined RT and chemotherapy (CT), and CT only, respectively (Ibrahim E.M, et al. 2012).

Travis et al. reported a matched case-control study of breast cancer in 3,817 females diagnosed at age 30 years or younger, between 1965 and 1994. Breast cancer occurred in 105 patients with HD who were matched to 266 without breast cancer. All analyses had wide confidence intervals. A radiation dose of 4 Gy to the breast was associated with a 3.2-fold increased risk, compared with the risk in patients who received lower doses and no alkylating agents. Risk increased to 8-fold with a dose of more than 40 Gy. Radiation risk did not vary appreciably by age at exposure or reproductive history. Increased risks persisted for 25 or more years following radiation therapy. Treatment with alkylating agents alone resulted in a reduced risk of breast cancer, and combined modality a 1.4-fold increased risk. The risk of breast cancer decreased with increasing number of alkylating agent cycles and among women who received 5 Gy to ovaries (Travis et al. 2003). Radiation dose and the radiation field significantly influence risk, with most cases of breast cancer occurring after mantle radiation therapy, which includes the neck, supraclavicular fossae, axillae and mediastinum and an increased risk with high-dose regimens (Horwich & Swerdlow 2004).

By the mid 1990s the use of wide field, high dose radiation therapy for Hodgkin Lymphoma had been replaced by small field lower dose combined modality protocols. This approach has reduced the relative risk for young women from the order of 20 - 35 times down to the order 3 - 5 times increased lifetime risk (Horwich & Swerdlow).

In a recent report, a change from a 35 Gy mantle field to involved field radiation therapy (IFRT) at the same total dose reduced the estimated 20-year excess RR of BC by 63% (David C Hodgson et al. 2007)

NEWER TECHNIQUES

Theoretical modelling (Koh et al.) using organ at risk (OAR) dose-volume histograms demonstrates that moving from 35 Gy mantle to 35 Gy IFRT reduces the predicted risk for female breast and lung cancer by approximately 65%. Further dose reduction to 20 Gy IFRT reduces risk by another 40%. Others (Chera et al. 2009) report a similar theoretical analysis using conventional radiation therapy (CRT), intensity-modulated RT (IMRT), and three-dimensional proton RT (3D-PRT). The 3D-PRT plan delivered the lowest mean dose to the breast, lung, and total body. The mean dose to the breast was significantly less for 3D-PRT than for either IMRT or CRT. The mean dose and absolute volume receiving 4-30 CGE/Gy for the heart, thyroid, and salivary glands were similar for the three modalities. These data suggest that the trend towards smaller fields (IFRT vs Mantle) and lower dose (20G vs 35G) will result in a reduction in the incidence of SPM (both breast and other sites) and other late effects (non-malignant).

Further reductions in field size are also currently being investigated in this setting. Involved-Node radiation therapy (INRT) for Hodgkin Lymphoma, produced a 20-50% decrease in OAR doses, particularly for the breast and heart when compared to IFRT (Weber et al. 2009) (Filippi et al. 2014) (Dabaia et al. 2012) (Hoskin et al. 2013).

Dose reductions from 30 Gy to 20 Gy are also likely to become routine in the future when mature results are available from the German Group Trials (HD10 and HD11). Selected early stage patients may be spared radiation therapy when the results of newer trials are mature (George P Canellos et al. 2010).

BIOLOGY OF RADIATION INDUCED BREAST CANCERS

Breast cancers developing after radiation therapy for HD are said generally to be biologically and pathologically similar to sporadic breast cancer (Cutuli et al. 2001). This group undertook a retrospective analysis of 133 breast cancers and reported that 108 were invasive ductal carcinomas, 15 were ductal carcinoma in situ (DCIS) and four were lobular carcinoma with six other subtypes. Radiation included breast cancers were more likely to be bilateral (9–29% synchronous and metachronous) and/or medial than de novo cancers (Ralleigh & Given-Wilson 2004). There is some evidence that on gene profiling these tumours have a more aggressive genotype, with basal expression, a chromosomal instability profile and a higher expression of Ki-67 (Broeks et al. 2010). Viet Rubin report in a Surveillance, Epidemiology, and End Results (SEER) analysis that second breast cancers after Hodgkin Lymphoma were less frequently hormone receptor positive, were located more frequently in external quadrants, and were less frequently treated using radiation therapy. These patients had a higher risk for developing a second BC and had a higher BC mortality risk (Veit-Rubin et al. 2012).

BREAST SCREENING

Randomised controlled trials have demonstrated the mortality benefits of mammography for general population screening for women aged 49 to 70 years of age (H. D. Nelson et al. 2009). Unfortunately, there is little good data on the effectiveness of mammography for either population or high-risk screening of women under age 40 years. Mammography generally demonstrates reduced sensitivity in young women, partly due to increased breast density (Evans et al. 2007). The evidence suggests that radiation induced breast cancers are usually visible on mammography in 87–100% of cases (Aisenberg et al. 1997). Although mammographic screening may therefore be of benefit to Hodgkin Lymphoma patients, it involves the use of further ionizing radiation with a consequent risk of cancer induction. There may be a reluctance sometimes to use further X-rays to detect a possible radiation-induced cancer. If we assume a 15% risk of a radiation-induced breast cancer (and ignoring false negatives) for a 30-year-old woman having yearly mammograms until age 50 years the calculated benefit still exceeds the risk of cancer induction by a factor of 100 (Ralleigh & Given-Wilson 2004).

Bilateral breast ultrasound can be used in parallel with mammographic screening in women with dense breasts. The quality of breast ultrasound has significantly improved in the last 20 years with a reduction in the false-positive biopsy rate from 7.5% to 2.4%, with an added cancer detection rate of approximately 0.3% in population screening (Kolb et al. 2002). The current European Consensus guidelines do not recommend breast ultrasound as a primary screening technique because of the high false-negative and positive rates (Teh & A. R. Wilson 1998). The problems of high operator dependence, difficulty covering the whole breast and low sensitivity for microcalcifications and thus DCIS, have also curtailed use of ultrasound for screening. However the ultrasound is widely available at a relatively low cost, does not use ionizing radiation and is a routine part of all malignant or premalignant investigative breast workup at the present time.

Contrast enhanced MRI has a high sensitivity, but variable specificity for the early detection of breast cancer in young women at high risk from other causes (eg. BRCA1 BRCA2). A large review by Warner et al. found eleven relevant, prospective, nonrandomised screening studies. They noted limitations of the studies, in relation to differences in patient population, centre experience, equipment and criteria for positive screening results. They felt that screening with both MRI and mammography might rule out cancerous lesions better than mammography alone in women who are known or likely to have an inherited predisposition to breast cancer (Warner et al. 2008). MRI is also significantly more expensive than mammography or ultrasound, less available and is not tolerated by some patients.

Available data on the role of breast screening in the Hodgkin cohort is sparse. Most series report no more than 120 patients screened but give a sense of the scope of the problem consistent with the larger epidemiologic studies (Diller et al. 2002) (Kwong et al. 2008) (Lee et al. 2008) (Sung et al. 2011).

The most recent results of the Ng et al. from Dana Farber prospectively examined 148 female survivors of Hodgkin Lymphoma who originally received chest RT at age 35 or younger at least 8 years before enrolling into the study. Annual MRI and mammograms were performed concurrently over a 3-year period. They report good compliance and a sensitivity of 63%, for MRI and 68% for mammography. Sensitivity increased to 95% using both imaging modalities. Almost all of the imaging-detected malignancies were preinvasive or sub-centimeter, and none had lymph node involvement (Ng et al. 2013).

Both the US and European peak bodies recommend screening MRI for women with an approximately 20-25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin Lymphoma (Sardanelli et al. 2010) (Saslow et al. 2007). The various International Breast Screening recommendations are summarised in Appendix 1.

Screening initiation and interval data is generally extrapolated from other experience. The UK recommendations are given in Appendix 2 and 3. For those treated under the age of 17 years, screening from the age of 25 years is appropriate; for those treated between 17 and 35 years, screening should begin 8 years after the completion of treatment for Hodgkin Lymphoma. Breast cancer screening for high risk survivors has been shown to be deficient in the USA recently (Oeffinger et al. 2009).

The increased risk of breast cancer with additional low doses of radiation at screening for young patients with dense breasts, have led some authors to recommend that screening mammographic views be limited to one single view (oblique) per breast. Digital mammography should be also considered because of accuracy and lower doses required (Colin et al. 2012).

AUSTRALIAN EXPERIENCE

The Australasian radiation oncology community took an active and visible role in managing late effects in Hodgkin Lymphoma patients from the early 1990's. An extensive network involving several larger academic and smaller centres formed Australasian Radiation Oncology Lymphoma Group (AROLG) in 1994. This group published a number of important audits and patterns of practice studies in this disease. Other Australian workers undertook significant clinical and dosimetric studies in the 1990's which were directly relevant to late effects in Hodgkin Lymphoma (Byram 1996) (P. C. O'Brien et al. 1995) (Barton et al. 2000) (Wirth et al. 2008). Advice was given to several peak groups and to the Department of Health and Aging (DoHA) at that time. Specifically, a strong recommendation was made at that time to include Hodgkin Lymphoma patients in the MRI breast rebate for high risk screening (Langlands 1995).

By the 1990s it was routine for all major academic departments of radiation oncology, medical oncology and haematology to inform their patients of breast cancer risk and institute earlier and more intensive follow-up including mammographic screening for patients in this group. Not all smaller facilities or private practitioners would necessarily have followed this approach. The importance of this subject remains extremely high amongst the radiation oncology community with a 2009 national survey of follow- up practice confirming the need for more uniform protocols (unpublished personal communication Dr Koh, Liverpool NSW, see Appendix 4).

HOW CAN THE FACULTY HELP?

The Faculty of Radiation Oncology, RANZCR, regards all the detrimental effects from the administration of therapeutic radiation (acute, late, teratogenic, carcinogenic and somatic) as part of our core responsibility in terms of integrated cancer care, teaching, research and day-to-day clinical activities.

The place of high quality, evidence-based, contemporary informed consent is paramount for all our patients but especially this group of patients. As indicated in the RANZCR, Faculty of Radiation Oncology Guidelines for Informed Consent 2010, all patients and their carers need a comprehensive oral and written discussion regarding the risks and benefits of the treatment they undertake.

The Faculty has a strong record in relation to lobbying for a doubly redundant record keeping protocol that exceeds the current Australian Medical Record standard of seven years for reasons that are self evident in this document. As indicated in the Faculty Guidelines for Medical and Dosimetry Record Storage, each local oncology provider has a statutory duty to provide adequate clinical and dosimetric records to provide to enable high quality follow-up for any future medical, surgical, cancer recall or treatment required by that patient. Experience across Australasia over the last 25 years indicates that very few oncology units will have adequate paper or electronic data to provide significant details on dose, field size or chemotherapy details beyond 10 years. Commercial demands for offsite storage, disparate and unlinked information systems and obsolete operating systems all contribute to this problem.

Institutions also have a statutory responsibility to provide adequate, physical resources to allow for appropriate numbers and length of follow-up, governed by the evidence based on follow-up protocols. Where there is good evidence for significantly increased risks of second primary malignancies or any other relevant late effect (eg. paediatric cancers, known genetic risks, adult <35 yrs, experimental or trial protocols), specific protocol driven follow up policies should be used and specialist multi-disciplinary late effects clinics should be mandated and supported in larger centres.

CASE RECALL IN HODGKIN LYMPHOMA

The importance of informing and providing care for patients who have late effects or may be at risk for late effects from Hodgkin Lymphoma treatment cannot be understated (http://csn.cancer.org/node/156517 a typical patients Blog for shared Hodgkin Lymphoma experiences). Equally, the difficulty and implications of case tracing need to be carefully considered.

The National Health Service undertook a retrospective case tracing exercise in the United Kingdom in 2003. This exercise mandated recall of all women who were diagnosed at or below the age of 35 from 1962 onwards, in order to identify those women who might be at higher risk of a radiation induced breast cancer. This undertaking represented a very large effort across many Acute Health Trusts (Faulkner & Law 2005) (Ralleigh & Given-Wilson 2004). Screening began in women who were 8 years post supra-diaphragmatic radiation therapy and at least 25-years-old, whichever occurred later.

Five mammography and two magnetic resonance imaging (MRI) centres with sufficient capacity were identified within the cancer networks. It was agreed on a national basis that women would be screened by the network serving their current residence, even if treated for Hodgkin Lymphoma in a different network. Several years later this project has not yet reported nationally. Howell and others (S. J. Howell et al. 2009) have reported the results from the largest UK cancer network representing a population base of 3.2 million. They found a risk increase of 2.9 (standardised incidence ratio) detecting 14 cancers in 415 who attended (58% of cases attended for risk

assessment). Another cancer network reported an uptake rate of 64% (77 of 120) (Greenfield et al. 2006). Other recall studies conducted in North America have published recall rates of 32% (115 of 360) (L. Lee et al. 2008), 28% (47 of 167) (Kwong et al. 2008) and 54% (90 of 167) (Diller et al. 2002).

This data shows the difficulties inherent in this type of exercise, and demonstrate the need for the prospective identification and counselling of such women at completion of treatment. Small psychological and late effects sub-studies (D M Greenfield et al. 2006) (Absolom et al. 2007) have been published. Case recall anxiety in the setting of patients previously treated and considered cured is reported.

However in the small study by Absolom et al. it was not seen to be a problem. Other factors related to screening and case recall are associated with adverse outcomes. These include positive screening results, dissatisfaction with information, and extended time between invitation letter and screening (J Brett et al. 2005) (Eila K Watson et al. 2005).

In the Australian context, we do not know exactly how many women there are in the high risk category who are having inadequate follow up. If we assume an annual incidence of 1 in 25,000 for Hodgkin Lymphoma, then between 1970 and 2000 we would expect a total of around 7,000 diagnoses in women under the age of 35.

Perhaps 25-40% will have received supra-diaphragmatic radiation therapy and perhaps 10-20% will have received higher doses involving measurable breast dose. Thus the target population may be in the vicinity of 1,000 at most, assuming all are having inadequate follow-up. The AROLG survey of 10 departments in Australia in the 1990's found 383 women irradiated between 1969 and 1988 and an overall survival of 48% (M Barton personal communication.) Many of these patients treated before 1990 will be part of a routine breast screening program.

Any targeted Local, State or National effort to answer this question requires reasonable estimates of two values:

1. The Denominator (ie. mediastinal/axillary RT +/- chemotherapy at age <35 received between, for example 1970 and 2000)
2. The Numerator (patients not currently on follow-up, their health status and accurate demography)

A few radiation therapy centres (particularly the larger centres) will have excellent long term records and near 100% follow-up and screening of patients at risk. Some will have excellent quality paper records, but are not following high proportions of this category of patient. Others will have excellent long term follow up programs but poor paper records. A very small number will have excellent electronic records. Not all will have accurate International Statistical Classification Coding (ICD) and most will annotate treatment site and protocol with free text rather than an encoded field. Free text searching radiation therapy data bases will be difficult. By hand searching of radiation therapy treatment fields will be difficult if not impossible in some departments that have moved, lost records or have been forced to dispose of records.

A good recall program would require large amounts of "by hand" searching from remote, poor quality storage sites to find the denominator for some centres. Other centres will have inadequate paper and/or digital retrieval systems and be able to provide little data for either the numerator or denominator. Some will have their follow-up data managed on a separate hospital mainframe with very limited data accessibility.

Many of these patients will be followed up in the private sector and hence the numerator will be irretrievable. Most patients will have changed address multiple times, changed states and surnames and require extremely skilled tracing.

For the above reasons it is extremely unlikely that the information systems of most Australian oncology units will provide a workable recall system for patients in this group who have been lost to follow-up for whatever reason (cf. the UK experience).

Similarly, none of the Australian State-based cancer registries will have the ability to identify radiation therapy dose and field size.

All case tracing activities must be weighed against the inevitable cost, distress, anxiety, and potential ill-effects of mammography/MRI and biopsy of high-risk women who have false positive mammograms. If a case tracing exercise were undertaken, then these potentially unintended consequences need to be transparently identified and managed in advance.

SUMMARY

- Prior radiation therapy to the chest in any patient under the age of 40 involving doses as low as 2Gy can be associated with a significant risk of breast cancer.
- Radiation induced breast cancers may have more aggressive biology and may be multiple.
- Young age and higher doses increase the risk.
- These risks have significant latency and are cumulative with other breast cancer risk factors.
- Evidence based, risk adapted screening is mandatory for these patients.
- Oncology patients who are at risk of any significant long term effects from radiation therapy, chemotherapy or surgery should have access to appropriate long term specialist follow-up based on local multi disciplinary care guidelines.
- Female survivors of Hodgkin Lymphoma and their primary and tertiary care providers who are unaware of specific late effects and/or have been lost to follow-up for whatever reason deserve to be informed or re-informed and have access to appropriate oncology follow-up and specifically to counselling, screening and specialist breast advice if required.
- A large scale targeted recall of high risk female survivors of Hodgkin Lymphoma is probably un-workable in the Australian setting given the limitations of oncology information systems (Cancer Registries) and poor hospital record storage.
- Improving survivorship awareness and care for all oncology patients is a priority in cancer care and requires a co-ordinated education and information strategy in the context of a defined over-arching cancer plan and integrated cancer network.

RADIATION INDUCED CARDIOVASCULAR DISEASE

Hodgkin Lymphoma survivors are at increased risk of developing late cardiovascular complications from radiation therapy, chemotherapy and post treatment insulin resistance syndromes and the so-called metabolic syndrome. Traditional risk factors such as hypertension, obesity, hypercholesteroleamia, family history,depression and diabetes increase the risk of heart disease additionally in Hodgkin Lymphoma patients (Jemal et al. 2008) (Heidenreich et al. 2007) (Moslehi 2013).

The course of these cardiovascular disorders is often asymptomatic, even in the presence of severe disease. Coronary artery disease is pathologically indistinguishable from native atheroma but tends to be more focal and occur at a younger age and in a dose dependent fashion. Traditional presentations with chest pain are said to be much less common in this group (King et al. 1996).

Symptoms are often misinterpreted because of young age and lack of other cardiovascular risk factors. A typical series showed that the risk of a fatal myocardial infarct in these patients is 2.2–7.6-fold greater than in the general population. Aleman reported a cumulative incidence for myocardial infarction of 12.9% by 30 years after mediastinal irradiation (Aleman et al. 2007) (Myrehaug et al. 2008).

These patients have also been reported to have a higher mortality at cardiac surgery (Wu et al. 2013)

In the largest reported study of 294 patients the prevalence of asymptomatic severe coronary stenosis for which intervention was required was 3.1% (Heidenreich et al. 2007).

In Hodgkin Lymphoma patients, both valvular abnormalities (both insufficiency and stenosis)are also reported with older high dose techniques. The incidence of left-sided valvular reflux is reported to range from 16% to 40% (vs. 2% in controls) (Kreuser et al. 1993) (Gottdiener et al. 1983).

There is some data from breast cancer and Hodgkin experience that newer techniques delivering doses of less than 30 Gy to smaller coronary volumes may produce considerably less risk (Darby et al. 2013) (Gagliardi et al. 2010) (Pezner 2013).

SCREENING FOR CARDIOVASCULAR DISEASE

Coronary artery screening has been advocated by many experts in the field. Anderson et al. have suggested CT angiography and calcium scoring (Andersen et al. 2010).

The National Comprehensive Cancer Network (NCCN) Clinical Guidelines recommend annual screening and ‘aggressive management of cardiovascular risk factors’ and a baseline ‘stress test/echocardiogram’ at 10 years.

The most recent international guidelines suggest a risk adapted approach with stress ultrasonogaphy at 5 and 10 years forming the baseline testing regime (Lancellotti et al. 2013).

Chen et al. report a decision-analytic model to evaluate lipid screening in a hypothetical cohort of 30-year-olds who survived 5 years after mediastinal RT. Lipid screening every 3 years was the most cost-effective strategy in this population. High quality evidence on who to screen, how and when is lacking due to long lead times, heterogeneity of patients and case tracing difficulty. Most expert groups suggest treating previous mediastinal RT as an additional risk factor in otherwise standard practice cardiovascular care (Chen et al. 2009) (Crump 2012).

Elena M. van Leeuwen-Segarceanu et al. have extensively reviewed the literature in this setting. Their suggested guidelines are shown in Appendix 5 along with the international consensus guidelines (van Leeuwen-Segarceanu, 2011).

SCREENING FOR CAROTID DISEASE

Atherosclerosis of the carotid arteries is also a well-known late treatment effect of RT particularly in head and neck cancer. It was first described by Silverberg et al. 1970 in 9 patients who had doses of 44-68Gy and presented with a transient ischemic attack (TIA) or stroke 1-30 years post RT.

There has been less attention of carotid disease in Hodgkin Lymphoma. In one study 42 asymptomatic patients were screened by modern Duplex ultrasonography and identified 24% of patients with intima-media abnormalities that did not cause significant stenosis (King et al. 1999).

Hull et al. in JAMA 2003 report on a retrospective study of 415 patients treated 1962-1998 at the University of Florida. Radiation therapy fields covered the heart, subclavian or carotid arteries and at a median follow-up 11.2 years. The incidence of atherosclerotic disease (carotid/subclavian stenosis >40%, TIA or stroke) was 7.4%.

They report a mean latency of 17 years before symptoms and suggest a Doppler screening approach for high risk patients and active management of all other vascular risk factors.

Aleman et al. have reported stroke risks as highly dependent on age at first treatment. Standardised Incidence Ratios of 4 for those treated before the age of 20 years and 2.1 for those treated between 41and 50 years. Females experienced slightly higher risks than males, especially those treated before age 21 (De Bruin et al. 2009).

Newer techniques with lower doses and lower volumes of carotid artery irradiated probably have much risks of intimal thickening or significant stenosis however long term data is lacking (Maraldo et al. 2013) (Morris et al. 2009).

Van Leeuwen-Segarceanu et al. provide an excellent summary of current evidence and suggest screening for carotid stenosis only in very high risk patients or those who have symptoms of vascular damage at other sites.

SUMMARY

- Prior Radiation therapy to coronary and/or carotid vessels involving doses above 25 Gy can be associated with a significant risk of vascular disease.
- These risks have significant latency and are cumulative with other cardiovascular risk factors.
- The evidence does support a risk adapted approach to routine coronary screening using appropriate international guidelines but does not yet support routine carotid screening.
- Oncology patients who are at risk of any significant long term effects from radiation therapy, chemotherapy or surgery should have access to appropriate long term specialist follow-up based on local multi disciplinary care guidelines.
- Survivors of Hodgkin Lymphoma and their primary, secondary and tertiary care providers who are unaware of specific cardiovascular late effects and/or have been lost to follow-up for whatever reason deserve to be informed or re-informed of their risk level (if any) and have access to appropriate cardiovascular follow-up and specifically to counselling, screening and specialist cardiovascular advice if required.
- Improving survivorship awareness and care for all oncology patients is a priority in cancer care and requires a co-ordinated education and information strategy in the context of a defined over-arching cancer plan and integrated cancer network.

FACULTY OF RADIATION ONCOLOGY RECOMMENDATIONS

It is the view of the Faculty of Radiation Oncology, RANZCR, that the best "whole of health" approach for patients at risk of breast cancer and cardiovascular late effects following radiation therapy and chemotherapy for Hodgkin Lymphoma should include, but be not limited to the following strategies:

1 State and/or Federal health organisations to work with key stakeholders to improve patient and primary, secondary and tertiary care health worker knowledge of previous radiation therapy as a risk factor for **Breast Cancer** through existing or new paper and electronic channels, education networks and all appropriate Cancer Networks. This might include but not be limited to:

- Breast Screen Australia
- National Breast and Ovarian Cancer Centre (NBOCC)
- Breast Cancer Network Australia (BCNA)
- Cancer Councils
- NSW Cancer Institute
- Lymphoma Support and Research Association Inc
- Leukeamia Foundation
- The Royal Australasian College of Physicians (RACP)
- Medical Oncology Group of Australia (MOGA)
- Faculty of Radiation Oncology (FRO)
- The Australasian Leukaemia and Lymphoma Group (ALLG)
- The Haematology Society of Australia & New Zealand (HSANZ)
- The Royal College of Pathologists of Australasia (RCPA)
- The Royal Australian College of General Practitioners (RACGP)
- The Australian Nursing Federation (ANF)
- Cancer Voices
- The Royal Australasian College of Surgeons (Breast Interest Group)
- Australia and New Zealand Children's Haematology and Oncology Group (ANZCHOG)
- NSW Oncology Group (NSWOG)

2 A Pilot Project involving the targeted recall of high risk female survivors of Hodgkin Lymphoma might be considered across a small region or state in order to assess costs, logistics and recall success. This pilot project might also consider informing recommendations 3-6 below.

3 Oncology units with adequate data systems develop "reasonably achievable" local recall and follow-up policies for their own radiation therapy, haematology, medical oncology, imaging, breast care and primary care settings. This should be overseen by a multi-disciplinary meeting and an appropriate local clinical governance framework. These might be along the lines of the UK Royal Marsden Protocol (refer to Appendix 2), AAP/COG Guidelines or other guidelines (refer to Appendix 1).

4 Shared care integrated protocols be encouraged in the above context.

5 Superspecialised oncology units continue to develop dedicated late follow-up clinics to serve the clinical needs of a variety of long term survivors of multi modality treatment.

6 The adoption of a consensus Australian screening guideline/protocol for patients that who have been treated for Hodgkin Disease.

7 The adoption by cancer centres of personal hand-held patient records that includes information on prior treatment and future health screening required for patients with Hodgkin Disease.

8 State and/or Federal health organisations to work with key stakeholders to improve patient, primary, secondary and tertiary care health worker knowledge of previous radiation therapy as a risk factor for **Cardiovascular Disease** through existing or new paper and electronic channels, education networks and all appropriate primary, secondary and tertiary Care networks. This might include but not be limited to:

- The Heart Foundation
- National Stroke Foundation
- Diabetes Australia
- Cancer Councils
- NSW Cancer Institute
- Lymphoma Support and Research Association Inc
- Leukeamia Foundation
- The Royal Australasian College of Physicians (RACP)
- Medical Oncology Group of Australia (MOGA)
- Faculty of Radiation Oncology (FRO)
- The Australasian Leukaemia and Lymphoma Group (ALLG)
- The Haematology Society of Australia & New Zealand (HSANZ)
- The Royal College of Pathologists of Australasia (RCPA)
- The Royal Australian College of General Practitioners (RACGP)
- The Australian Nursing Federation (ANF)
- Cancer Voices
- The Royal Australasian College of Surgeons (CARDIOTHORACIC)
- Australia and New Zealand Children's Haematology and Oncology Group (ANZCHOG)
- NSW Oncology Group (NSWOG)

It is the view of the Faculty of Radiation Oncology, RANZCR, that all patients at any risk of breast cancer and cardiovascular late effects following radiation therapy for Hodgkin Lymphoma should have regular clinical review commencing at 3-5 years post treatment by a radiation oncologist in order to manage and assess their risk profile. The radiation oncologist will preferably work in or with a defined late effects multi - disciplinary team.

APPENDIX 1: RECOMMENDATIONS FOR BREAST SCREENING FROM PEAK ORGANIZATIONS

Organization	Total Crude Radiation Dose (Gy)	Annual Screening Protocol
Children's Oncology Group, 2010 (Henderson et al. 2010)	-	Mammography and MR imaging at ≥ 25 years or 8 years after RT
UK National Breast Cancer Screening Program, 2009 (Howell et al. 2009)	≥ 17 Gy	MR imaging at 25–29 years, mammography and/or MR imaging at 30–50 years, three yearly mammographic examinations at ≥ 50 years
EUSOMA Group, 2010 European Society of Breast Cancer Specialists (Sardanelli et al. 2010)	-	NA MR imaging ≥ 8 years after RT
American Cancer Society, 2007 (Saslow et al. 2007)	10-30 Gy	Mammography and MR imaging at ≥25 years or 8 years after RT

APPENDIX 2: ROYAL MARSDEN SCREENING PROTOCOL

Female patients with Hodgkin's disease having had supradiaphragmatic radiation therapy

The following guidelines are based on the recommendations within the Department of Health (DOH) document 'Increased Risk of Breast Cancer after Radiotherapy for Hodgkin's Disease-Patient Notification Exercise' 31 October 2003.

Evidence demonstrates that women who received supradiaphragmatic radiation therapy for Hodgkin's disease at a young age are at a greatly increased risk of developing breast cancer. Based on this evidence the DOH decided to carry out a patient notification exercise to identify and inform those women who since 1962 had Hodgkin's disease and received radiation therapy below the age of 35 and to a field that would included at least part of the breast.

The Royal Marsden Hospital NHS Trust has identified those patients treated within this institution who fulfil the above criteria and have contacted the women involved. They have been offered a consultation either within their standard follow-up clinic or within a specifically set up clinic. Patients seen in the follow-up clinic who fulfil the criteria should have the subject discussed to ensure they have been notified and that the correct information has been given and screening procedures established.

The DOH recommends the following advice; information and screening should be offered to all the women concerned. The DOH suggests the following should be discussed with a patient at the consultation when this issue is raised.

- The treatment that the patient had for Hodgkin's disease (i.e. confirm supradiaphragmatic radiation therapy)
- The risk information now associated with this treatment for women. This is as follows:
  - Women treated for HD in childhood have a cumulative risk of around 15-33% (around 1 in 3 to 1 in 7) by 25 years of follow up of developing breast cancer. The risk is greater with longer follow up;
  - Women treated in young adulthood are also at high risk; cumulative risk of 15-25% (around 1 in 4 to 1 in7) by 25 years of follow up for women treated at ages 20-29, although not as great a relative risk as that for women treated in childhood;
  - The estimated risk for the general population of developing breast cancer by age 50 is about 1 in 54 and the lifetime risk is about 1 in 9;
  - The risk by age 50 of women diagnosed in childhood or young adulthood is of a similar order to that by age 50 of women at high genetic risk of breast cancer;
  - The risk for HD patients will depend on factors such as: age of the patient at treatment, the amount of radiation given, the length of time since treatment and the present age of the woman;
  - There is a substantial induction period after treatment before breast cancer risk rises;
  - The length of this period is not known exactly but risk is probably slight before about 10 years after treatment for women treated in young adulthood and 5 or more years in those treated in childhood;
  - Breast cancer in these HD patients is more often bilateral than breast cancers in the general population.

- The patient's family history of cancer and other individual breast cancer risk factors (both populationand personal such as use of HRT, lifestyle etc) should be documented.
- Breast awareness – written information should be provided on this for the patient to take away if they wish for example the NHS Breast Screening Programme's leaflet 'Be Breast Aware'. (these are available from the Lymphoma CNS; in general outpatients and alternatives are available from the Lymphoma Association).
- Risk management options (such as chemo-prevention and risk reducing surgery) that are available – if the patients wish to discuss these options in more detail it is suggested that a further consultation with an appropriate member of the breast cancer team is arranged. If women are seriously considering bilateral risk reducing mastectomies, they should be referred to a specialist oncoplastic breast surgeon for a consultation and receive appropriate pre-operative counselling.

It is also important for women to recognise that this notification and screening is not about an error in radiation therapy. On the contrary the success of the treatment has meant that patients are living much longer and it is because of this that we are able to assess possible late effects of this specific form of treatment and take appropriate action to respond to this.

Following this consultation it is recommended that a personal letter is sent by the consultant leading the appointment to each woman, summarising:

- The risk information given depending on their individual circumstances; comparing this to the estimated risk for the general population of developing breast cancer;
- Relevant risk management options discussed – this is in line with standard practice following cancer genetic risk assessment consultation - and any actions agreed. Women should also be advised in the letter who is their point of contact if more information is required;
- Surveillance that should be offered;

  Surveillance should start:

  - At age of 25 for those treated under the age of 17;
  - 8 years post treatment for those treated between 17-35 years (inclusive).
- Surveillance is not recommended for women treated for HD over the age of 35.The surveillance recommended varies according to the age of the woman now (not the age at treatment).

The recommended programme is as follows:

- Patients should be informed about the positive and negative aspects of the different surveillance techniques to ensure they give informed consent to take part in this surveillance programme. Where appropriate the patient should have the choice of which technique is used, i.e. a patient may not tolerate MRI in which case they should be offered ultrasound.
- It is possible that some women will be concerned about the radiation risk from mammography.
- Using National Radiological Protection Board (NRPB) risk factors, annual mammography to detect breast cancer in this group of women is considered to be justified in radiation protection terms. For a 30 year old woman with average size breasts having annual mammography until the age of 50, the benefit exceeds the risk by a factor of 11 or so. Annual mammography to age 70 would also be justified, though the benefit/risk ratio is lower.

APPENDIX 3:
ROYAL COLLEGE OF RADIOLOGISTS UK RECOMMENDATIONS

<table>
<tr><th>AGE</th><th colspan="2">RECOMMENDED SURVEILLANCE</th></tr>
<tr><td>< 25 years</td><td colspan="2">No imaging</td></tr>
<tr><td>25 – 29 years</td><td colspan="2">Annual MRI but if contraindicated Annual Ultrasound
(Mammography is not recommended for this age group)</td></tr>
<tr><td>30 - 50 years</td><td colspan="2">Baseline 2 view mammogram. Women should then be divided into two groups.</td></tr>
<tr><td rowspan="3"></td><td>Predominantly Fatty Breast Tissue (1)</td><td>Dense Breast Tissue (2)</td></tr>
<tr><td>Annual 2 view Mammography</td><td>Annual 2 view Mammography plus MRI unless:</td></tr>
<tr><td></td><td>i. there are contraindications
ii. patient cannot tolerate MRI
iii. patient chooses not to have MRI In any of the above cases patients should be offered Annual Mammography plus Ultrasound

If breast tissue becomes predominantly fatty prior to the age of 50 the patient should move into group (1) i.e. annual mammography only</td></tr>
<tr><td>> 50 years</td><td colspan="2">Three yearly mammography within the NHS Breast Cancer Screening Programme (NHSBCS)</td></tr>
</table>

APPENDIX 4: AUSTRALIAN FOLLOW-UP SURVEY OUTLINE AND PRELIMINARY RESULTS

Investigators: E-S.Koh[1], A. Wirth[2], J. Seymour[2], M.B. Barton[1], G.S. Gabriel[1].
[1]CCORE, Liverpool Hospital, NSW; [2]Peter MacCallum Cancer Centre, Vic.

Long-Term Follow-Up of Hodgkin Lymphoma Survivors:
An Australian and New Zealand Patterns of Care study (ALLG HD9)

The primary aim of this study was to describe the current patterns of care of 'long-term' Hodgkin Lymphoma (HL) survivors (defined as more than 5 years post diagnosis) across Australia and New Zealand. Secondary study aims were to identify issues relating to provision and delivery of care in long-term HL survivors, and to describe current surveillance strategies for secondary malignancies and other late effects.

From May to December 2009, an electronic survey was distributed to all health professionals across public and private sectors managing Hodgkin Lymphoma survivors, via the membership of HSANZ (including the Nurses Group), ALLG, RANZCR, MOGA, NZACS, NZ Lymphoma Network, and CSNA.

There were a total of 162 respondents spanning 56 different institutions across seven Australian states and New Zealand. Accepting the limitations of a survey with inherent response bias, a summary of salient findings were as follows:

A variety of **follow-up care models** for long-term HL survivors currently exist, with 65% of respondents utilizing a specialist-only based model (single in 31%, dual in 34%), and 20% adopting a shared specialist with primary care approach. Notably, 12% of long-term HL survivors are being followed solely by their primary care physician, and furthermore, in over 80% (overall 10% of respondents), the treating specialist received no further clinical updates of this group after 5 years. An annual follow-up interval was utilised in 72%.

Presented with the scenario of a well male HL survivor 5 years post treatment (non-smoker versus 10 pack year smoker), the frequency of routine blood tests including thyroid function virtually identical (63-85%), however the frequency of cardiopulmonary investigations was only marginally increased comparing the non-smoker to the smoker scenario: CXR (27% vs 45%), CT chest (6% vs 15%), pulmonary function (10% vs 17%) and echocardiography (9% vs 12%) respectively.

Similarly, in the scenario of a well female HL survivor 5 years post treatment (no mediastinal RT versus mediastinal RT), the frequency of routine blood tests was comparable in both scenarios (range 61-78%), with an increase in the frequency of breast imaging from 49% to 68% in the irradiated patient.

Of some concern, **counselling and education regarding late effects** was undertaken regarding the following areas either 'infrequently' or 'never' during follow-up: smoking status/cessation (14%), cardiovascular risk factor reduction (23%), fertility (42%) and secondary breast cancer risk/surveillance (7%).

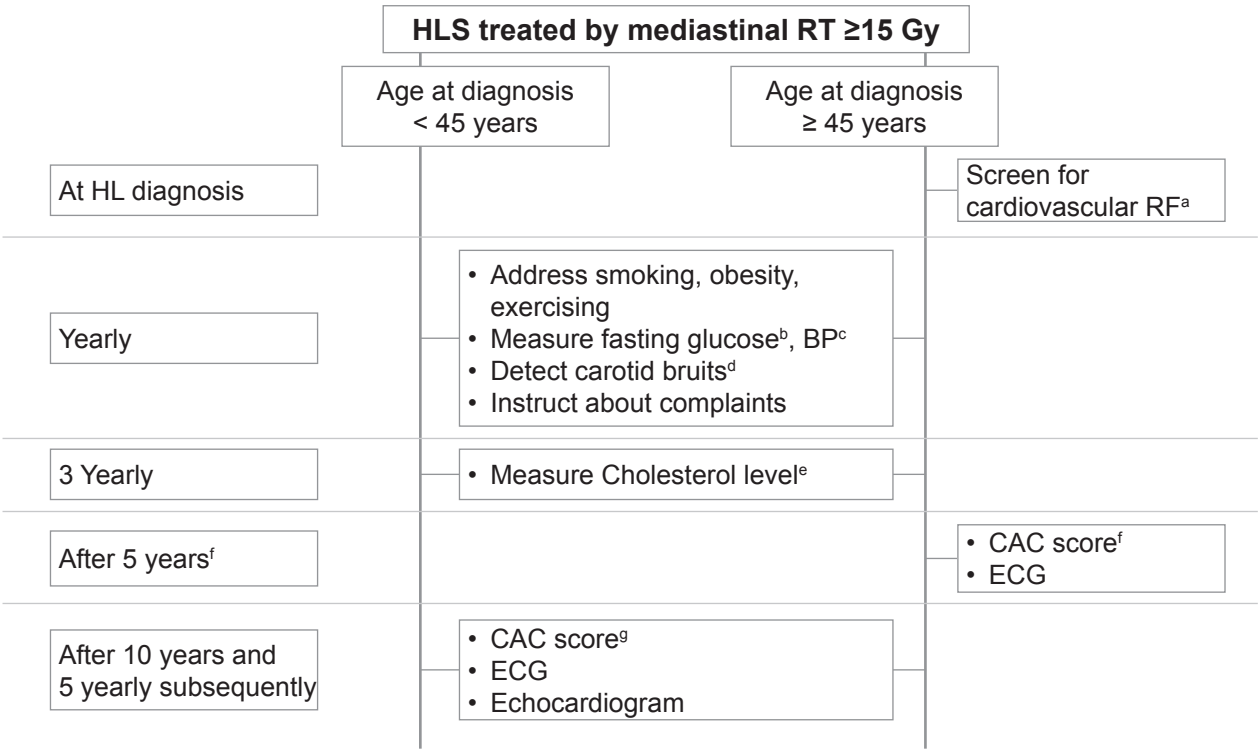
With respect to the initiation of and indications for **secondary breast cancer surveillance** in female HL survivors, these ranged widely (1 to 10 years post radiation therapy (RT), with the majority indicating 5-10 years post radiation therapy or from an attained age of 40 years, for a given 35 year old female patient receiving RT 10 years prior. Preferred modalities of breast imaging included Mammography (MMG) (64%), Ultrasound (U/S) (32%), combined MMG + U/S (47%), MRI (11%) and other (5%).

Of note, 81% of respondents had no **existing unit/policy guidelines** for management of their long-term HL survivor cohort. Although 52% (representing 45 respondents from 29 institutions) stated they had an existing database for tracking long-term HL survivors, these systems varied considerably in sophistication, and 61% had **no current tracing system** in place to facilitate longitudinal follow-up.

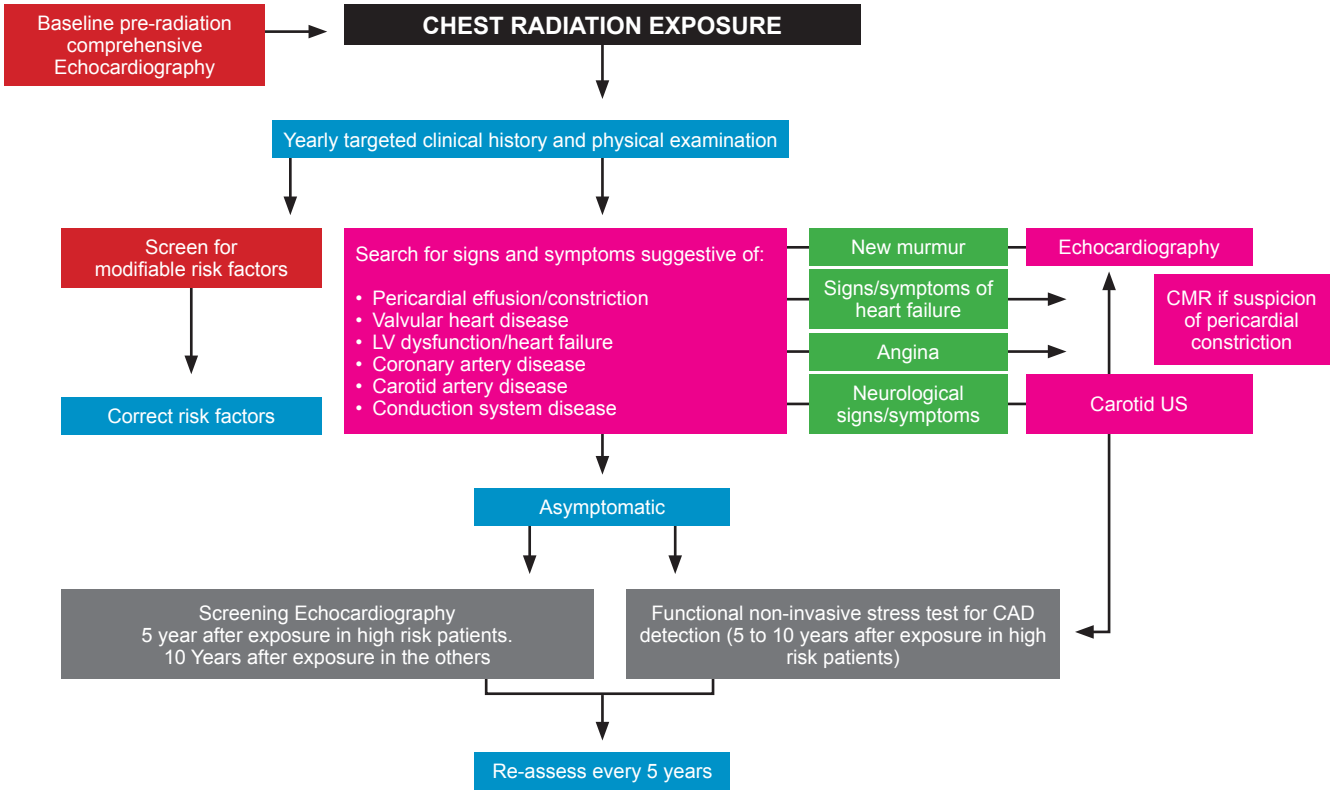
CONCLUSIONS

There is significant variability in patterns of practice for long-term HL survivors across ANZ with respect to three important areas: constituents of follow-up care, counselling and education regarding relevant late effects and secondary breast cancer surveillance strategies. Steps to address these issues will include: improved education of all relevant healthcare professionals and patients via existing advocacy groups, creation of concise national guidelines for HL and similar survivor cohorts, and developing research initiatives including addressing optimal models of care.

APPENDIX 5: CARDIOVASCULAR SCREENING PROGRAMS



Cardiovascular screening program in HLS. BP, blood pressure; CAC, coronary artery calcium; ECG, electrocardiogram; HLS, Hodgkin lymphoma survivors; RF, risk factor; RT, radiation therapy.
([a]Cardiovascular RF: hypercholesterolemia, hypertension, obesity, smoking, positive family history of cardiovascular disorders, history of cardiovascular disorders. In case of previous cardiovascular disease or a high risk profile (including cardiovascular complaints), consider treating HL without RT to the mediastinum.
[b]Treat diabetes mellitus according to the ADA/EASD guidelines,44 considering RT as one risk factor for atherosclerosis.
[c]Treat hypertension according to the JNC 7 guidelines,45 considering RT as one risk factor for atherosclerosis.
[d]In HLS treated by cervical RT.
[e]Treat hypercholesterolemia according to the NCEP ATP III guidelines,46 considering RT as a risk factor.
[f]Also perform measurements of CAC score after 5 years in HLS < 45 years at diagnosis with P2 RF for cardiovascular disease.
[g]In case of a CACscore > 0 referral to a cardiologist for ischemia detection. If no ischemia is detected on additional testing and there are no cardiac symptoms, repeat CAC-score in 5 years. In case of an augmentation of the CAC-score during subsequent testing, ischemia detection should be repeated as well.)



Algorithm for patient management after chest radiation therapy. LV: left ventricle; US: ultrasound. High-risk patients: refer to Table 1. Modifiable risk factors refer to: hypertension, tobacco use, hypercholesterolaemia, obesity, and diabetes (Lancellotti et al. 2013).

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