Endocrine health in survivors of adult-onset cancer

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Lancet Diabetes Endocrinol 2024; 12: 350–64

Published Online April 8, 2024 https://doi.org/10.1016/S2213-8587(24)00088-3

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Long-term survivors of cancer (ie, the patient who is considered cured or for whom the disease is under long-term control and unlikely to recur) are at an increased risk of developing endocrine complications such as hypothalamic–pituitary dysfunctions, hypogonadisms, osteoporosis, or metabolic disorders, particularly when intensive tumour-directed therapies are applied. Symptom severity associated with these conditions ranges from mild and subclinical to highly detrimental, affecting individual health and quality of life. Although they are usually manageable, many of these endocrine pathologies remain underdiagnosed and untreated for years. To address this challenge, a higher degree of awareness, standardised screening tools, comprehensible treatment algorithms, and a close collaborative effort between endocrinologists and oncologists are essential to early identify patients who are at risk, and to implement appropriate treatment protocols. This Review highlights common symptoms and conditions related to endocrine disorders among survivors of adult-onset cancer, provides a summary of the currently available practice guidelines, and proposes a practical approach to diagnose affected patients among this group.

Introduction

Adverse effects that occur years after malignant diseases or their treatments are increasingly relevant because the number of long-term survivors of cancer continues to grow.[1] Endocrine complications occur in 40–60% of survivors of cancer and include hypothalamic–pituitary disorders, dysregulation of steroid and peptide hormones, and dysregulation of bone and metabolism.[2] Underlying causes are multifactorial, and the risk and extent of developing hormonal issues vary depending on the individual's characteristics, the type of malignancy, and the therapy regimen.[3] Although some conditions go unnoticed, others can drastically impair quality of life and contribute to morbidity.[4] Because the degree of symptom severity shows high inter-individual variability, an individual endocrine assessment is required to estimate the individual's specific risk profile. However, data and recommendations for adult patients (aged ≥18 years) who are diagnosed with a malignancy remain scarce. In this Review, we summarise the epidemiology and aetiology of the most frequent endocrine diseases among long-term survivors of adult-onset cancer and discuss the current gold standard management of these conditions.

Common endocrine pathologies in survivors of cancer

The risk of endocrine complications in long-term survivors of cancer depends on the age of the patient, the type of underlying malignancy, and its treatment. The highest risks of hormonal disturbances are observed in survivors of malignancies treated with specific chemotherapeutics, radiation or high dose glucocorticoids, or both, as commonly seen in tumours of the central nervous system (CNS) and haematological malignancies (figure 1).

Hypothalamic–pituitary disorders

Treatment of CNS tumours and cranial radiotherapy are frequently associated with dysfunctions of the hypothalamic–pituitary axis (HPA) that can result in distinct deficiencies of one or more hormones from the anterior pituitary gland.[5] The distribution of CNS malignancies varies notably between the childhood and adult population, and patients with cancer who have a good prognosis (eg, low-grade gliomas) are at especially high risk of developing HPA disturbances.[6]

In adults, baseline blood sampling of the pituitary hormones and their corresponding hormones will typically identify severe hormone deficiencies, especially potentially life-threatening hypocortisolism. However, in some cases, stimulation tests are required to identify mild or subclinical dysfunctions of the HPA.[7,8]

Although cranial irradiation has traditionally been the major risk factor for HPA dysfunctions, hypophysitis associated with checkpoint inhibitor treatment or because of other targeted therapies is becoming increasingly prevalent.

Due to often overlapping symptoms, relevant pituitary disorders are discussed in this Review in combination with disturbances of their effector organs.

Growth hormone deficiency

In survivors of childhood-onset cancer, the growth hormone axis is most vulnerable to radiation therapy and growth hormone deficiency occurs in more than 50% of those patients.[9] In adults, growth hormone deficiency occurs in approximately 30% of patients following cranial radiotherapy.[10,11] The risk of growth hormone deficiency depends on the cumulative dose of treatment, the schedule of treatment, and the patient's age at the time of treatment. At radiation doses of more than 30 Gy, additional hormone disturbances of the HPA are likely to occur.[12] Although the estimated overall prevalence of growth hormone deficiency among all childhood cancer survivors is 12·5%,[13] this percentage could be substantially higher in individuals affected by CNS tumours receiving cranial irradiation.[14]

The prevalence of growth hormone deficiency in survivors of adult-onset cancer is unknown. Growth hormone deficiency remains underdiagnosed, which is in part explained by the diagnostic challenges of establishing

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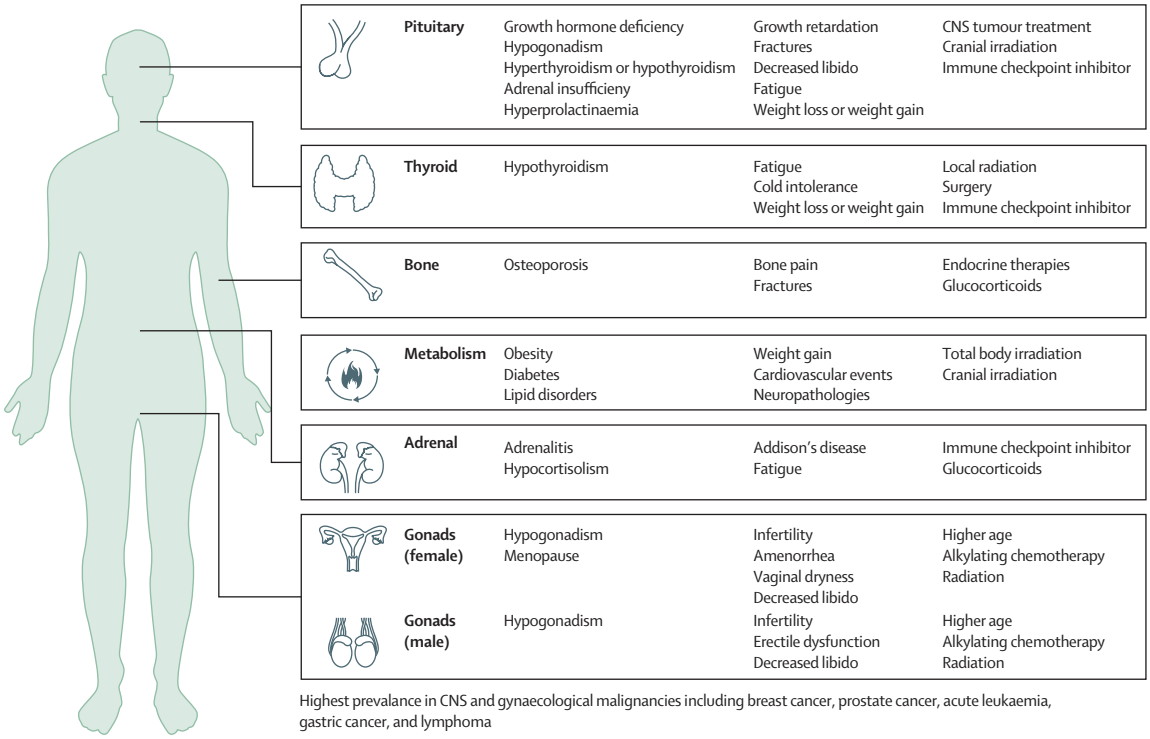

Figure 1: **Common endocrine complications in long-term cancer survivors**
CNS=central nervous system.

a definite diagnosis of growth hormone deficiency. Dynamic testing of the growth hormone axis is often not feasible and should be avoided following cranial irradiation. Likewise, serum concentrations of IGF-1 as a proxy for endogenous growth hormone axis activity can be affected by malignancy and its therapeutic sequalae.[15]

In children, growth hormone deficiency results in poor growth rate and growth hormone replacement therapy is generally recommended in these patients.[16,17] In adults, the clinical relevance of growth hormone deficiency remains under debate. Growth hormone deficiency increases the risk of fractures, and in patients with adult-onset growth hormone deficiency, replacement therapy normalises the fracture risk in both men and women.[18] Although earlier studies suggested that growth hormone deficiency is linked to excessive mortality, these findings were not supported in a study published in 2021.[19] Randomised controlled trials (RCTs) evaluating mortality upon growth hormone replacement in adults do not exist. However, there is evidence that growth hormone replacement does improve body composition and potentially the quality of life in childhood cancer survivors.[20]

The safety of growth hormone replacement in survivors of cancer is not clear. Experimental data support a pro-tumourigenic role of the growth hormone–IGF-1 system.[21,22] These observations are corroborated by the very low incidence of malignancies found in cohorts of individuals affected by rare genetic syndromes resulting in so-called growth hormone resistance (eg, growth hormone receptor mutations as found in Laron syndrome).[23] However, consensus recommendations by the European Society of Endocrinology conclude that there is no clinical evidence to support an association between growth hormone replacement therapy and primary tumour recurrence. The effect of growth hormone replacement on secondary neoplasia risk is considered minor.[15] Survivors of malignancy could thus be considered for growth hormone supplementation once tumour remission has occurred. Growth hormone replacement should be stopped in case of cancer relapse. Importantly, recommendations and expert opinions are mostly based on retrospective or observational data with a modest quality of evidence. The potential risks of growth hormone replacement should always be weighed against its benefits in an individualised manner. Growth hormone supplementation protocols follow standard recommendations and guidelines, but close vigilance is required to avoid over-treatment.

Perturbations of the thyroid axis

Secondary hypothyroidism, resulting from impaired production of thyroid stimulating hormone (TSH), is rarely an isolated finding, but typically occurs in combination with other pituitary dysfunctions.[24] Of note, chemotherapy has been described to affect growth

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hormone and TSH secretion, but it does not typically induce panhypopituitarism.[25,26]

Manifest primary hypothyroidism can occur following radiation exposure or surgical interventions in spatial proximity to the thyroid gland. Several risk factors such as being female, being White, and receiving higher doses of radiation have been defined.[27] Primary hypothyroidism is rarely observed following chemotherapy, but is a relatively common endocrine complication of immune checkpoint inhibitors.[28]

Primary and secondary hypothyroidism in survivors of cancer should be attended to following the standard guidelines for patients who do not have cancer with the aim of normalising peripheral thyroid hormones triiodothyronine (T_3) and thyroxine (T_4).[29] Of note, hypothyroidism following the treatment (surgical and radioiodine therapy) of thyroid cancer occurs in almost all patients. Substitution protocols and goals, such as TSH suppressive substitution, are different to those with other causes of hypothyroidism and excellent guidelines exist for these patients.[30]

Of note, early postoperative hypoparathyroidisms resulting in hypocalcaemia is a relevant complication, affecting about 18% of patients following total thyroidectomy for cancer.[31] Specific recommendations exist to cope with this complication.[32]

Perturbations of the adrenal axis

Adrenocorticotropic hormone (ACTH) deficiency is a potentially life-threatening condition that can lead to hypocortisolism. Clinically significant ACTH deficiency, resulting in an adrenal crisis and necessitating glucocorticoid replacement, has been reported in approximately 10% of patients following cranial radiotherapy.[11]

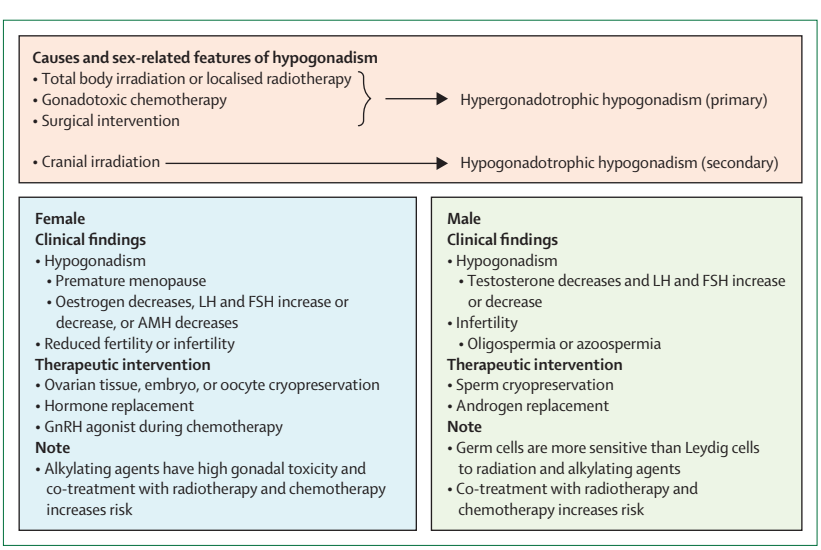

Figure 2: **Causes and clinical findings of hypogonadism in female and male survivors of cancer**
Hypogonadism is a common finding in long-term survivors of cancer. The risk of hypogonadism depends on the underlying tumour entity, but more importantly on its form of treatment. Specific forms of radiation and gonadotoxic chemotherapy have the highest likelihood of developing a hormone deficiency. AMH=Anti-Müllerian hormone. FSH=follicle stimulating hormone. LH=luteinising hormone.

Primary adrenal insufficiency can occur directly from a surgical procedure, typically after removal of both adrenal glands.[33] If long-term treatment with high-dose glucocorticoids is required, for example as an immunosuppressant in patients following allogeneic stem-cell transplantation or other haematological diseases, endogenous adrenal function could also be disturbed.[34,35] In the past decade, immune checkpoint inhibitor-mediated adrenalitis has become more prevalent.[36] Primary adrenal insufficiency presents with low cortisol concentrations and requires immediate substitution of glucocorticoids, typically hydrocortisone and fludrocortisone.[37]

Hyperprolactinaemia

Elevated prolactin concentrations can occur after cranial radiotherapy. These changes are often mild, asymptomatic, and non-persistent and thus usually do not require medical intervention,[38,39] Clinical manifestations of hyperprolactinaemia include reduced libido, erectile dysfunction in men, and amenorrhoea in females, all of which result from prolactin-mediated inhibition of the gonadal axis.[40] If symptoms persist, dopamine agonists are typically the treatment of choice.[41]

Luteinising hormone disorders, follicle stimulating hormone disorders, and hypogonadism

Hypogonadism is one of the most prominent endocrine challenges for male and female survivors of a variety of cancers. Hypogonadism arises either secondary to antitumour treatments resulting in gonadal damage (hypergonadotropic hypogonadism) or as a central dysregulation of the gonadal axis (hypogonadotropic hypogonadism). Central hypogonadism, defined by a deficiency of luteinising hormone (LH) or follicle stimulating hormone (FSH), or both, also occurs in at least a third of patients following radiation.[11,38,42] The clinical picture and individual implications of hypogonadism vary depending on the age and sex of the patient and this requires consideration in the individual assessment.

Hypogonadism

Hypogonadism in female adults

Secondary amenorrhea, as a sign of ovarian dysfunction, occurs in up to 83% of female survivors of cancer following treatment (figure 2). Older patients with diminished ovarian reserve are most prone to hypogonadism following cancer therapy.[43] Even if ovarian damage is initially incomplete, these individuals are at a high risk of premature menopause.[44] Older age is an independent predictor of ovarian insufficiency and younger patients (aged <45 years) often regain premenopausal hormone concentrations 2 years after treatment.[45] Adult patients with leukaemia, lymphoma, and those undergoing stem-cell transplantation are additional groups at especially high risk of developing hypogonadism.[46]

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Primary ovarian insufficiency leads to oestrogen deficiency and a reduction in the ovarian follicular reserve.[47] Ovarian follicles are susceptible to DNA damage induced by alkylating chemotherapeutic agents or radiation.[43]

Oestrogen deficiency can decrease libido and lead to sexual discomfort due to vaginal dryness. Unspecific symptoms including reduction in energy, fatigue, poor sleep, dry skin, and psychological problems are common symptoms associated with low oestrogen.[48,49] Additional negative effects on bone and cardiovascular health are particularly relevant as individuals age.[50] Due to its high prevalence, female survivors of cancer with an increased risk for primary ovarian insufficiency should be regularly screened for clinical signs and symptoms of hypogonadism.

Treatment of female hypogonadism

Few studies have specifically addressed the clinical benefit of hormone replacement therapy (HRT) in cancer survivors with primary ovarian insufficiency.[51]

HRT, usually consisting of a combination of oestrogens and progesterone, is recommended in female survivors of cancer with persistent hypogonadism until the normal age of menopause (appendix p 2). Of note, women with an intact uterus require concomitant progestogen to reduce the risk of endometrial hyperplasia and endometrial cancer associated with isolated oestrogen exposure.[52] An exception to HRT recommendations are survivors of breast cancer, for whom HRT is associated with a detrimental prognostic effect and is thus not recommended.[53]

Some physicians are still reluctant to prescribe HRT due to concerns of potential harm. However, hypogonadism has well documented negative effects at multiple sites in the body, including bone structure, the cardiovascular system, and on metabolism.[54] In fact, unsubstituted early natural menopause (before age 45 years) is associated with a substantially higher risk of cardiovascular mortality compared with later menopause;[55] menopause occurring before age 40 years results in a 2-year shorter life expectancy than in women for whom menopause occurs after age 55 years.[56] Primary ovarian insufficiency can also exert profound negative effects on the patients' quality of life by affecting psychosocial health and cognitive function, and by resulting in physical inactivity.[57] Accordingly, initiation of HRT in patients with primary ovarian insufficiency is key to avoid long-term negative health consequences[52] and these patients need to be evaluated from a different perspective than women naturally entering menopause.

Hypogonadism in adult males

In male survivors of cancer, hypogonadism results from gonadal damage (primary) or a disturbed HPA (secondary and tertiary). Gonadal insufficiency can occur following surgical interventions for the primary tumour (eg, bilateral orchiectomy for testicular cancer), but in most cases, hypogonadism is chemotherapy or radiotherapy related, or both.[58] Cells in the testes vary in their response to these treatments and sensitivity also changes with age. Leydig cells, responsible for LH-dependent androgen production, are relatively insensitive to chemotherapy-induced toxicity. However, there is a risk of testosterone deficiency, ranging from mild and subclinical to clinically relevant, in patients receiving extensive gonadotoxic chemotherapy or high-dose radiation.[59] Combined chemotherapy and radiotherapy further lowers the threshold for Leydig cell damage. Patients following haematopoietic stem-cell transplantation, who frequently undergo such treatment protocols, are at especially high risk of gonadal dysfunction.[60]

Androgen deficiency can have a massive negative effect on the daily life, performance, and self-perception of affected patients. Male survivors of cancer could have reduced energy, low libido, brain fog, and depressive mood. Physical findings can include weight gain, decreased muscle strength, and osteoporosis.[61] The rate of erectile dysfunction is increased in survivors of cancer and promoting factors are radiation and surgery of the spinal cord, pelvis, or prostate. Although the underlying cause is often the result of structural damage (eg, to nerves or vasculature) or testosterone deficiency, psychological aspects are also important in this setting.[62] Of note, sexual function does not directly correlate with sperm quality and has to be assessed individually.[63]

See Online for appendix

In adult males, where pubertal development cannot be used as a surrogate for androgen concentrations, symptoms related to sexual dysfunction need to be specifically assessed using standardised questionnaires and biochemical testing should be done in patients at high risk or with clinical symptoms.[64] In patients with confirmed testosterone deficiency (total testosterone below threshold in two independent samplings and measurements), measuring bone mineral density (BMD) and assessment of signs suggestive of metabolic syndrome are recommended.[65,66] Semen analyses for sperm count and quality should be performed in patients of the relevant age group.

Treatment of male hypogonadism

A wide range of different testosterone formulations are available to choose from. There are pronounced differences in the preferred formulations in different geographical regions. In adolescents and adults with confirmed androgen deficiency, testosterone should be supplemented following regional practice recommendations (appendix p 3).[64]

Fertility preservation in patients with cancer

Fertility preservation is an important topic for female and male patients who are diagnosed with a malignancy at a reproductive age. Guidelines recommend advising female patients who are at a reproductive age about the

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potential adverse effects of the planned therapies and potential strategies to counteract them before any treatment.[67] Embryo or oocyte cryopreservation is a standard strategy for fertility preservation in young patients with breast cancer or other malignancies that are at an increased risk of chemotherapy-induced or radiation-induced primary ovarian insufficiency.[68] However, cryopreservation does not protect the patient from other long-term adverse effects associated with hypogonadism. Preserving ovarian function by other means remains a major clinical ambition.

Ovarian tissue cryopreservation was first described more than 20 years ago[69] and has since become an established fertility preservation technique. By 2020, more than 200 births were reported after the auto-transplantation of frozen ovarian tissue.[70] However, there have been concerns that the graft could contain malignant cells, which appears especially relevant in haematological diseases where malignant cells were found in the ovarian tissue in up to 50% of patients.[71] Novel strategies to overcome this potential risk are being developed, although none of these are routine clinical practice yet.[72] Temporary ovarian suppression, using gonadotropin-releasing hormone (GnRH) agonists, is an option to protect ovarian function, but data for fertility outcomes (ie, pregnancy rate) remain controversially discussed. As such, current ASCO guidelines advise GnRH agonists for fertility preservation only when other techniques are not feasible or available.[68] A meta-analysis published in 2018 provided evidence for ovarian protection by GnRH agonist use, reducing the rate of primary ovarian insufficiency from 30·9% to 14·1% (p<0·001) and increasing the post-treatment pregnancy rate from 5·5% to 10·3% (p=0·030).[73] Updated 2022 guidelines from the European Society of Medical Oncology (ESMO) concur with the American Society of Clinical Oncology (ASCO) recommendation, but emphasise these additional benefits.[74]

In male survivors of cancer, infertility is more frequent than hypogonadism. The frequency of infertility is explained by a higher sensitivity of male germ cells to toxic injuries than Leydig cells, with the long-term risk of oligospermia or azoospermia depending on the type and cumulative dose of chemotherapeutic exposure (figure 2).[75] Radiation in doses of more than 7·5 Gy substantially reduces the probability of siring a pregnancy[76] and recovery rates of spermatogenesis of less than 20% have been reported in the long-term follow-up of male patients receiving total body irradiation, further emphasising the detrimental and lasting effects of radiation exposure on male fertility.[77] Accordingly, fertility preservation is a challenge in the care of male patients with cancer who are at a reproductive age. Male patients undergoing puberty and adolescents who are at high risk of developing permanent sterility from their cancer treatment (ie, testicular cancer, leukaemia, and Ewing sarcomas) should be offered the option of sperm cryoconservation.[78] If no cryoconservation was performed, patients with desire to have a child need to be addressed by a specialist, because testosterone treatment further decreases sperm quality and more complex protocols using gonadotropins are required to attain the desired outcome.[79]

***Panel 1*: Bone health in survivors of cancer**

Survivors of specific malignancies are at a high risk of bone loss and developing osteoporosis. These patients should be screened regularly. Basic measures for bone health should be applied to all patients and specific therapies should be considered if the survivor qualifies according to the relevant guidelines.

High risk tumour types
- Breast and prostate cancer
- Acute leukaemia
- Lymphoma
- Gastric cancer
- Gynaecological malignancies

Risk factors
- Endocrine therapies
- Glucocorticoids
- Radiotherapy
- Allogeneic stem-cell transplantation

Clinical findings
- Bone loss
- Fractures
- Immobility
- Pain

Basic therapy
- Vitamin D (500–2000 IU/d)
- Calcium (1–2 g/d)
- Physical activity

Specific therapies
- Amino-biphosphonates (oral alendronate 70 mg per week or intravenous zoledronate 5 mg per year)
- Denosumab (subcutaneous, 60 mg, twice per year)
- Selective oestrogen receptor modulators (oral raloxifene 60 mg per day)
- Romosozumab (subcutaneous, 120 mg per month)

Bone loss and osteoporosis

Population at risk

Survivors of adult-onset cancer are at an increased risk of bone loss and osteoporosis compared with individuals without cancer. The underlying causes are multifactorial, and the individual risk is highly variable (panel 1). The highest risk for osteoporosis and fragility fractures is typically seen in patients treated with high doses of glucocorticoids, extensive radiation therapy, or adjuvant endocrine therapies.[80] Allogeneic stem-cell transplantation is another procedure associated with a particularly prominent bone loss because risk factors often accumulate in these individuals, which include

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total body irradiation, high-dose chemotherapy, extensive glucocorticoid treatment, and adjuvant immunosuppressive agents.[81] Notably, the highest rate of bone loss occurs in the first year following transplantation, emphasising the need for early assessment and intervention. Although there is some recovery of BMD in most patients, it does not normalise and fracture risk remains elevated.[82]

Hypogonadism is an important risk factor for bone loss in male and female survivors of cancer. Even subclinical forms, such as mild Leydig cell insufficiency, which presents with normal or mildly decreased testosterone in the context of elevated gonadotropins (compensated hypogonadism), are sufficient to negatively affect bone quality.[83] In fact, FSH concentrations can potentially predict bone loss in women who are premenopausal and being treated for breast cancer,[84] and preclinical models have shown how elevated gonadotropins directly impair bone homeostasis. The importance of sex hormones on bone health becomes especially apparent in patients with breast and prostate cancer receiving adjuvant endocrine therapies.[85]

Clinical management of cancer-associated bone loss and osteoporosis

Most osteoporosis guidelines or assessment tools underestimate the fracture risk for survivors of cancer or do not address a history of cancer as an individual risk factor. To manage this clinical problem, more pro-active treatment approaches with lower therapeutic thresholds than for postmenopausal osteoporosis have been defined in ASCO and ESMO guidelines published in 2019 and 2020 respectively specifically addressing bone health in the group of patients with non-metastatic cancer (panel 2).[86,87]

Bisphosphonates and anti-RANKL antibodies (denosumab) are the two main classes of antiresorptive drugs used for the treatment of osteoporosis but a head-to-head comparison between the two drugs in survivors of cancer is missing. There are no data to support synergistic effects of the two agents and combined treatment is not recommended. Teriparatide, a bone anabolic agent, is typically not used in survivors of cancer due to historical label restrictions.[88] The newer sclerostin antibody, romosozumab, can be used in survivors of cancer. However, although there are some preclinical data suggesting a beneficial effect of blocking sclerostin for metastatic bone disease,[89] these effects remain controversially discussed[90] and there are currently no recommendations for its use in patients with a high risk of developing bone metastasis. In the case of tumours that are oestrogen-sensitive, selective oestrogen receptor modulators are an additional option.

Apart from breast and prostate cancer, there are few data on interventional treatment in cohorts of survivors of cancer of other malignancies. An analysis of 12 studies conducted in patients following allogeneic stem-cell transplantation supports the protective effect of bisphosphonates, showing an improvement in BMD after 12 months of treatment compared with control.[91] Of note, the International Osteoporosis Foundation has issued specific recommendations for managing bone health in patients following haematopoietic stem-cell transplantation, with a therapeutic threshold for pharmaceutical intervention set at a T score of less than –1·5, which is considerably lower than the threshold in general osteoporosis guidelines.[92]

There is little evidence to support the use of these antiresorptive agents in women who are premenopausal, young men (aged <50 years), or children. A systematic review published in 2020 concluded that, although there are some small studies where bisphosphonates improved BMD in children with acute lymphoblastic leukaemia, evidence is insufficient to support the routine use of bisphosphonates in this population.[93] HRT improves the BMD and reduces the risk of fractures in women with premature ovarian insufficiency and is recommended in women with hormone-irresponsive tumours and no contraindications.[94] Surprisingly, a study published in

Panel 2: **Guidelines for the management of endocrine health in survivors of adult-onset cancer**

Fertility preservation

- 2020: ESMO clinical practice guidelines (*Fertility Preservation and Post-Treatment Pregnancies in Post-Pubertal Cancer Patients*)[74]
- 2018: ASCO *Clinical Practice Guideline Update*[68]

Growth hormone replacement

- 2022: GRS and ESE consensus statement (*Safety of Growth Hormone Replacement in Survivors of Cancer and Intracranial and Pituitary Tumours: a Consensus Statement*)[15]

Hypogonadism*

- 2013: COG long-term follow-up guidelines (*Female Reproductive Health after Childhood, Adolescent, and Young Adult Cancers: Guidelines for the Assessment and Management of Female Reproductive Complications*)[158]
- 2016: NICE guideline (*Diagnosis and Management of Menopause*)[159]
- 2018: ESE clinical practice guideline (*Testosterone Therapy in Men with Hypogonadism: an Endocrine Society Clinical Practice Guideline*)[160]

Bone health

- 2020: ESMO clinical practice guidelines (*Bone Health in Cancer*)[86]
- 2019: ASCO clinical practice guideline (*Management of Osteoporosis in Survivors of Adult Cancers with Nonmetastatic Disease*)[87]
- 2021: IOF executive summary (*Osteoporosis Management in Hematologic Stem Cell Transplant Recipients*)[92]

Immune therapy

- 2022: ESE clinical practice guideline (*Endocrine-Related Adverse Conditions in Patients Receiving Immune Checkpoint Inhibition*)[146]
- 2021: ASCO guideline update (*Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update*)[161]

ASCO=American Society of Clinical Oncology. COG=Children's Oncology Group. ESE=European Society of Endocrinology. ESMO=European Society of Medical Oncology. GRS=Growth Hormone Research Society. IOF=International Osteoporosis Foundation. NICE=The National Institute of Health and Care Excellence. *No specific guidelines for survivors of adult-onset cancer.

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2024 found a numerical (non-significant) increase in fractures in men with low testosterone concentrations who were receiving testosterone supplementation.[95] Although these data cannot be directly translated into the group of treatment-associated hypogonadism in survivors of cancer, further analyses and follow-up recommendations from this study should be carefully monitored.[96]

Comorbidities

Besides overt dysfunctions of the main endocrine axes, survivors of adult-onset cancer are susceptible to developing comorbidities that arise secondary to, or are related to, endocrine dysfunction.

Metabolic complications

Metabolic homoeostasis and cancer physiology are closely intertwined. People with obesity are at an increased risk of cancer and obesity is also a negative predictor of cancer outcome in specific malignancies such as breast cancer.[97] Although cancer cachexia is of concern in many patients with an active malignancy, survivors of cancer have a higher rate of metabolic complications (eg, diabetes and obesity) than individuals without cancer.[98,99] In addition to general risk factors for overweight such as unhealthy diet, lack of exercise, and genetic predisposition,[100] cancer treatment such as cranial radiation and alkylating chemotherapy can cause endocrine disorders such as growth hormone deficiency, hypogonadism, or hypothyroidism that further increase the risk for weight gain.[101,102]

A meta-analysis of obesity in survivors of acute lymphoblastic leukaemia revealed a significantly higher BMI in this population compared with the control group.[103] Cancer treatments that include high-dose glucocorticoids or endocrine therapies can also cause weight gain or derange other parameters such as glucose or lipid metabolism, which are hallmarks of the metabolic syndrome linked to cardiovascular disease and mortality. Data from the St Jude Lifetime Cohort[104] also show an increased risk of obesity in childhood cancer survivors that was associated with glucocorticoid exposure. Untreated hypogonadism is an additional risk factor for metabolic complications of male and female survivors of cancer.[64]

Changes in bodyweight have a direct effect on social and economic factors. For example, a reduction of weight in survivors of breast cancer with obesity is associated with higher rates of return to work, although confounders might be a limitation of the work.[105] Weight loss interventions in this population are successful in decreasing bodyweight, and this leads to measurable improvements in quality of life, but there is currently not sufficient data to assess the effect on disease outcome.[106]

There is also a higher incidence of new-onset type 2 diabetes in adult patients with cancer, especially in the first year after the diagnosis.[107] Furthermore, survivors of cancer have an increased risk of cardiovascular complications that significantly affects mortality.[108] As such, young adult survivors of cancer who develop cardiovascular disease are at an increased risk of overall mortality (hazard ratio 10·9; 95% CI 8·1–14·8).[109] Of note, the risk profile varies depending on the malignancy. Whereas survivors of lymphoma are at an increased risk of valvular disease (RR 12·2), survivors of leukaemia showed an increased risk of cerebral haemorrhage (10·3) and cardiomyopathy (8·6).[110] Optimising cardiovascular risk profiles through the management of weight, blood pressure, glucose, and lipids should thus be prioritised.

Patient bodyweight and basic metabolic parameters should be closely monitored, especially during the first 5 years after the completion of cancer treatment. Early interventions such as psychological support and lifestyle modifications (eg, dietary counselling and a physical activity programme) should be offered with a low threshold and pharmaceutical interventions (such as statins or SGLT2 inhibitors) are to be initiated according to the general guidelines of the major international societies.[111,112]

Vitamin D deficiency

Vitamin D deficiency is common among patients with cancer.[113] The benefit of vitamin D supplementation, correct dosing, and optimal blood concentrations remain a topic of debate. A RCT published in 2019 argued against the idea that vitamin D supplementation reduces the risk of cancer.[114] However, there are some data from meta-analyses suggesting that vitamin D supplementation could decrease mortality among a broad range of malignancies although these findings remain controversial.[115,116] Two large RCTs in patients with gastrointestinal cancers showed no to modest effects of vitamin D supplementation on relapse-free survival.[117,118] There are relatively strong data for the positive effects of vitamin D supplementation in patients following allogeneic stem cell transplantation with respect to the occurrence of graft-versus-host disease.[119] Furthermore, a meta-analysis concluded that vitamin D deficiency is associated with adverse outcome in a range of haematological malignancies.[120] One of the reasons behind the diverging conclusions from these trials could be due to differences in the dosing of vitamin D. A meta-analysis, published in 2023, of 14 RCTs that included subgroup analyses of more than 100 000 patients revealed a significant 12% reduction on cancer mortality among patients receiving daily dosing of vitamin D, whereas no differences were seen in patients receiving bolus dosing.[121]

There is a general agreement that vitamin D deficiency should be corrected, whereby most guidelines consider 25-hydroxyvitamin D concentrations below 20 ng/mL as deficient and recommend daily vitamin D doses of 400–2000 IU. Caution should be given to high-dose supplementation schemes aimed at attaining highly supraphysiological vitamin D values, because this can lead to hypercalcaemia and other complications.

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Populations requiring special attention or monitoring

Patients receiving endocrine therapy for breast or prostate cancer

In women with oestrogen receptor-expressing breast cancer who are postmenopausal, aromatase inhibitors cause a rapid and substantial bone loss that translates into an increased risk of fractures.[122,123] An even higher rate of bone loss occurs in patients who are premenopausal, when aromatase inhibitors are combined with GnRH agonists, for whom annual BMD losses of up to 7·7% at the lumbar spine, have been reported. Furthermore, the treatment benefit in reducing cancer recurrence by endocrine therapy comes with additional side-effects that could negatively affect patients' quality of life and treatment adherence, such as sexual dysfunction.[124] Adequate counselling and proactive management of these issues are crucial components and should be pursued from diagnosis.[125] Of note, fractures in patients with breast cancer not only decrease quality of life but are also associated with a poorer overall survival.[123]

In patients with prostate cancer, endocrine treatment aimed at suppressing androgen concentrations or blocking androgen signalling to deprive hormone-sensitive prostate cancer cells from their stimulants also exerts profound negative effects on bone, increasing the risk of fractures (odds ratio 2·83; 95% CI 2·52–3·17).[126]

Antiresorptive drugs are effective in improving BMD in patients receiving endocrine therapy for breast and prostate cancer. Most studies conducted in this field were either too short or underpowered to assess fracture risk. An exemption was the ABSCG-18 trial,[127] in which adjuvant denosumab reduced the risk of clinical fractures in women with breast cancer who were postmenopausal and receiving aromatase inhibitors by half. Due to the high clinical relevance, specific recommendations on the management of aromatase inhibitor-induced bone loss have been issued.[128,129]

Importantly, in women with breast cancer who are postmenopausal, the adjuvant use of bisphosphonates has a disease-modifying effect and decreases recurrence and breast cancer-specific mortality.[130] Data for denosumab are less clear with ambiguous results with regard to the prevention of bone metastases and improving disease-free survival from two different trials, namely ABSCG-18[127] and D-CARE.[131] On the basis of these findings, many guidelines recommend that women with breast cancer who are postmenopausal should be offered a so-called off-label therapy with adjuvant antiresorptive agents (preferentially bisphosphonates) to reduce the risk of bone metastases and improve disease-free survival.[87]

Patients receiving tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKIs) are important for the treatment of malignancies in which an alteration of oncogenic pathways by tyrosine kinases has been implicated.[132] Since the discovery of imatinib for chronic myeloid leukaemia in the 1990s,[133] numerous multitarget TKIs have been approved for different conditions.[134] TKIs are generally better tolerated than standard chemotherapy, but endocrine and metabolic complications are relatively common. Approximately 20–30% of patients receiving TKIs develop thyroid disorders.[135] Of note, hypothyroidism (33·2% of patients) occurs far more frequently than hyperthyroidism (3·14% of patients).[135]

Metabolic issues such as dyslipidaemia and type 2 diabetes occur in approximately 50% and 15–40% of cases, respectively.[136] Changes in other endocrine systems (adrenal, gonadal, or hypothalamic–pituitary axes) appear less pronounced than thyroid disorders and are rarely relevant. Testing of TSH, a lipid profile, and fasting venous glycaemia are recommended before therapy and regular (ie, monthly) controls of these parameters are recommended at least for the first 6 months of treatment.[136] In addition to TSH, measurement of free T_4 could be useful, because changes of free T_4 precede TSH changes by 3–6 weeks.[134]

Patients receiving checkpoint inhibitors

Immune checkpoint inhibitors have revolutionised the therapeutic approach to many advanced malignancies and have drastically improved the prognosis of specific conditions such as metastatic melanoma or some forms of lung cancer.[137] Commonly targeted surface epitopes include CTLA4, PD1, and PD-L1, which are inhibited by immune checkpoint inhibitors such as ipilimumab, nivolumab, or durvalumab.[138] Immune checkpoint inhibitors frequently lead to long-lasting remissions, even when used in the context of metastasised disease.[139] Immune checkpoint inhibitors are associated with substantial endocrine complications that affect up to 40% of treated patients, depending on the drug used.

The diagnosis of immune checkpoint inhibitor-induced endocrinopathies might not be trivial. Many of the symptoms arising from endocrine toxicity are non-specific (eg, fatigue, weakness, tachycardia, nausea, and vomiting) and could be explained by the underlying disease or co-administered therapies.[140] Baseline hormone measurements are also often not available, thus complicating dynamic surveillance of the respective endocrine axis.

The spectrum of endocrine disorders linked to immunotherapy encompasses thyroid dysfunction (hyperthyroidism and hypothyroidism), hypophysitis with resulting pituitary insufficiency, hypogonadism, primary adrenal insufficiency, or diabetes secondary to pancreatic β-cell insufficiency.[28,141,142] Endocrinopathies linked to immune checkpoint inhibitor use can develop during drug application, with delayed onset or long after therapy has been stopped.[142] A meta-analysis of RCTs suggested that the combination of different immune checkpoint inhibitors (eg, CTLA4 and PD1 antibodies) confers the highest risk for the development of endocrine dysfunction.[143] Likewise, some endocrine glands are more likely to be affected by the use of one class of immune

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checkpoint inhibitor than another. For example, the odds ratio (OR) for the development of thyroid dysfunction is higher with PD1 compared with CTLA4 inhibitors (OR 1·89; 95% CI 1·17–3·05), whereas the opposite is true for hypophysitis (0·29; 0·18–0·49).[143] Endocrine toxicities associated with immune checkpoint inhibitors are also influenced by sex as shown by a higher risk of hypophysitis in males than in females.[144] Hypophysitis typically affects the anterior but not the posterior pituitary, which explains why diabetes insipidus is rarely observed.[143] ACTH deficiency is the most common presentation of hypopituitarism following immune checkpoint inhibitor therapy.[144] At the tissue scale, triggering an aberrant T-lymphocyte response provokes destruction of the endocrine gland, which is known as the bystander effect.[145] The resulting loss of function is mostly permanent and thus requires hormonal supplementation. Accordingly, discontinuation of immune checkpoint inhibitor therapy is usually only required temporally once endocrine toxicities develop because the dysfunction persists regardless of the presence or absence of the drug.[146] Distinguishing between primary and secondary immune checkpoint inhibitor-induced adrenal insufficiency by appropriate biochemical testing is important because the primary immune checkpoint inhibitor-induced adrenal insufficiency requires both hydrocortisone and fludrocortisone replacement. Serious immune checkpoint inhibitor-induced endocrine toxicity including severe thyroid disease or hypophysitis affecting the visual apparatus (compression of optic chiasm or nerve) could warrant high-dose glucocorticoid treatment, but current guidelines clearly advise against routine use of therapeutic glucocorticoids if manifestations are mild or modest.[146]

Biochemical surveillance of the hormonal status is key to identify immune checkpoint inhibitor-related endocrine toxicities early. According to European clinical guidelines, the minimum baseline testing includes TSH, free T_4, cortisol, glucose, and electrolytes.[146] Although recommendations for hormone testing vary slightly depending on the guideline, we propose a simple screening algorithm (appendix p 4). Attention should be drawn to potential confounders of the measured variables (eg, high dose glucocorticoid therapy) and the fact that immune checkpoint inhibitor use can trigger either primary, secondary, or combined endocrine axis dysfunction, which needs to be considered when interpreting test results.

For the **recommendations published by the IGHG** see https://www.ighg.org/

In most patients, hormonal deficits can be easily offset by supplementation, and the oncological benefit of the treatment typically outweighs the cost of such adverse events. Furthermore, several studies have shown that endocrine pathologies occurring due to immunotherapy indicate favourable outcomes among a spectrum of different malignancies.[147–149] Supplementation of hormonal deficits is done according to standard protocols and clinical guidelines. For some hormone replacements, therapeutic benefits and potential risks should be weighed against each other and informed decision making should be performed in the context of the patient's prognosis. For example, growth hormone supplementation is not indicated during active malignancy but might be considered once remission has been attained.[20] Endocrine toxicities linked to immune checkpoint inhibitor use are not rare and should be managed in an interdisciplinary way.

Older patients

There are no specific recommendations for managing endocrine conditions in older survivors of cancer and the evidence level from research and interventions is low. Nonetheless, it is widely appreciated that older patients (aged >65 years) require special attention and the execution of general recommendations should always be conducted under a clear risk-to-benefit assessment for the individual patient. Some aspects, such as bone and cardiovascular health, become more prominent in this group of patients because their risk for osteoporosis or cardiovascular events increases with age. HRT, for example, is not recommended for women once they reach the typical age of menopause and the same is true for androgen replacement in older men. Sarcopenia is a typical finding in older patients and low muscle mass is associated with a higher risk of all-cause and cardiovascular disease-specific mortality in survivors of cancer.[150] However, increasing physical activity can decrease mortality in older survivors of cancer.[151] Years after treatment, older survivors of cancer are still more likely to have age-related deficits.[152] These findings support the notion that older survivors of cancer require specific support with regard to physical, psychological, and social wellbeing.

Endocrine screening and treatment of survivors of adult-onset cancer

Current guidelines

The majority of existing guidelines for long-term cancer survivors have been published by paediatric societies or are tailored for the needs of survivors of childhood-onset or young adult-onset cancer.[153] However, there are vast differences in the populations addressed and the frequency and type of assessments recommended. The multitude of different recommendations can be confusing for attending oncologists, general practitioners, and patients. This issue has been recognised, and there are growing ambitions to harmonise the development of guidelines for childhood cancer survivors between different groups and societies. A list of recommendations published by The International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) can be found online.

There are adult survivorship guidelines for specific, highly prevalent cancer entities, for example those published by the American Cancer Society for breast,[154] colorectal,[155] prostate,[156] and head and neck cancer.[157] Survivors of adult-onset cancer can also refer to guidelines published by ASCO, ESMO, the National Comprehensive Cancer Network, and many smaller

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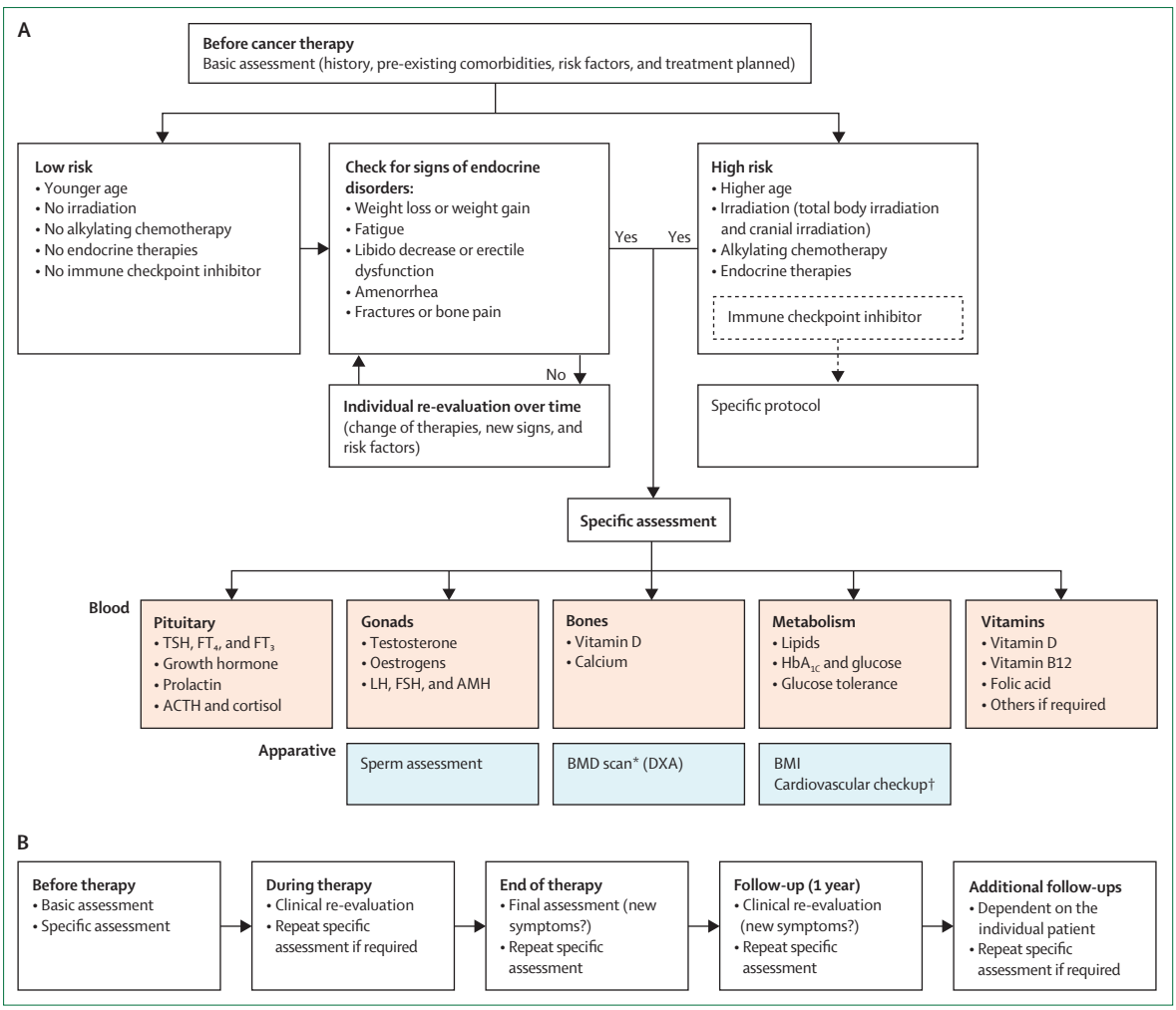

Figure 3: **Algorithm for endocrine screening in survivors of cancer**
(A) Basic assessment is required to stratify patients according to their individual risk profile. Patients with a low-risk malignancy for endocrine complications should be checked for signs and symptoms of endocrine pathologies during their routine oncological consultations. If there is no evidence for endocrine problems, no additional workup is required at that time. Patients should be repeatedly asked for new symptoms of new endocrine disorders in intervals (ie, at least once a year during the time of cancer follow-up). Patients with signs or symptoms or those with a cancer history associated with a higher risk of hormonal disturbances should receive a specific assessment. If possible, the first assessment should be conducted before therapy to obtain baseline values. Baseline blood testing will identify most relevant endocrine pathologies. Dynamic testing or special tests might be required if results are inconclusive, in which case referral to an endocrine specialist is warranted. In addition to blood testing, measurement of BMD and cardiovascular checkup is recommended at baseline. (B) Consecutive follow-up should consist of closer monitoring for new symptoms during therapy and a full assessment at the end of treatment and 1 year after treatment cessation. Additional follow-up should be conducted on an individual bases. AMH=Anti-Müllerian hormone. DXA=dual x-ray absorptiometry. FSH=follicle stimulating hormone. LH=luteinising hormone. *DXA scan is the recommended method to assess BMD. Initial assessment should be performed at baseline and repeated measurements should be conducted depending on results (earliest interval after 1 year). †Cardiovascular check-up should typically consist of at least an electrocardiogram, and echocardiogram, and assessment of vascular status.

societies. Furthermore, patients can refer to position papers by different groups that address specific issues such as HRT, bone protection, or metabolic complications. We have highlighted the most relevant guidelines for reference in panel 2.

Clinical approach to endocrine screening of a survivor of adult-onset cancer

Many of the existing guidelines are specific to populations or conditions. All guidelines emphasise the importance of an early and individualised assessment regarding symptoms and signs of endocrine pathologies. However, it is important to have simple but comprehensive algorithms to screen and evaluate a survivor of adult-onset cancer for endocrine disorders to achieve broad implementation. In an ideal setting, patients with cancer will receive an endocrine evaluation and consultation before and at the end of their cancer treatment, and any time in between and afterwards if required. However, in many regional settings, the infrastructure for a continuous interaction with an endocrinologist will not be feasible. In these cases, a standard algorithm will help the attending oncologist or general practitioner, or both, to identify patients with a specific need for an endocrine referral.

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Search strategy and selection criteria

References for this Review were identified on PubMed with a search for articles published from Jan 1, 2000, to July 31, 2024, with the terms "endocrine health", "cancer survivors", in combination with the terms "osteoporosis", "hypogonadism", "adult", "diabetes", "obesity" or "quality of life". Only guidelines, trials, meta-analyses, or original reports on survivors of cancer were included, unless there were highly relevant specific reasons for inclusion. Data reporting on metastatic disease or patients with active disease were excluded. Peer reviewed full-length articles resulting from this search strategy and key references cited in those articles were reviewed. Articles published in English and German were included.

We have summarised a proposal of recommendations that can be applied among all survivors of adult-onset cancer to help detect the most relevant endocrine conditions in figure 3. To assess an individual's risk profile, information about pre-existing medical conditions, the type of malignancy, and the planned treatment are required. If the patient has an increased risk of developing or shows signs or symptoms of endocrine disorders, we recommend a specific endocrine hormone assessment before or at the beginning of the treatment, at the end of the treatment, and 1 year after treatment completion. If a survivor of cancer is seen at a later stage and information required for risk assessment cannot be fully obtained, we still recommend a full endocrine screening (as recommended in figure 3) at least once to obtain an endocrine status and to identify potential subclinical conditions. In particular, in middle-aged and older patients, pre-existing metabolic conditions (overweight, dyslipidaemia, and arterial hypertension) are common and require additional recognition.

In addition to hormonal testing, a cardiovascular check-up (typically consisting of at least an electrocardiogram, an echocardiogram, and assessment of vascular status) is recommended at baseline. In addition, a dual x-ray absorptiometry scan to evaluate current BMD should be done at least once, with additional control scans after 1–5 years depending on the initial results and the individual risk profile for osteoporosis (especially if the patient is receiving continuous glucocorticoids or endocrine therapy).

If a patient has no relevant medical history and a low risk for developing an endocrine complication (ie, no radiation, no immunotherapy, no endocrine therapy, no chemotherapy, and no endocrine organ is affected by disease), endocrine testing might not be necessary in the absence of symptoms (figure 3).

Conclusions

The number of long-term survivors of cancer is growing and endocrine health is an important but often under-recognised topic in this population. Especially in the adult population, after successful treatment at an oncology centre, survivors of cancer are often seen by their local oncologists or general practitioners but structured programmes to ensure endocrine care are rare. To attain optimal care for our patients, a strong collaboration between oncologists and endocrinologists is warranted and local strategies for screening and detection of patients who are at risk need to be implemented as the standard of care for survivors of cancer.

Contributors

CSLR designed and wrote part of the manuscript. TDR designed and wrote part of the manuscript. NPJ wrote parts of the manuscript and performed literature research. AG designed the manuscript, revised the manuscript, and designed the figures and panel. All authors read, corrected, and approved the final version.

Declaration of interests

TDR has received payment or honoraria for lectures, presentations, speaker bureaus, or educational events from Amgen and UCB. All other authors declare no competing interests.

Acknowledgments

The work was funded as part of the priority programme (SPP-2084) µBONE by the Deutsche Forschungsgemeinschaft to TDR (RA 2151/5-1, RA 2151/7-1) and by the Deutsche Krebshilfe to AG, CLR, and TDR as part of the Mildred Scheel Early Career Center.

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