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Persistent chemotherapy-induced alopecia, persistent radiotherapy-induced alopecia, and hair growth disorders related to endocrine therapy or cancer surgery

Azael Freites-Martinez, M.D.[1], **Jerry Shapiro, M.D.**[2], **Corina van den Hurk, Ph.D.**[3], **Shari Goldfarb, M.D.**[4], **Joaquin Jimenez, M.D.**[5], **Anthony M. Rossi, M.D.**[1], **Ralf Paus, M.D., F.R.S.B.**[6], and **Mario E. Lacouture, M.D.**[1]

[1]Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY [2]The Ronald O. Perelman Dept. of Dermatology, New York University School of Medicine, New York, NY [3]Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, Netherlands [4]Breast Cancer Medicine Service, Department of Medicine - Division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center [5]Departments of Dermatology and Cutaneous Surgery, Miller School of Medicine, University of Miami, Miami, FL [6]Dermatology Research Centre, University of Manchester and NIHR Manchester Biomedical Research Centre, Manchester, UK

Abstract

With increasing survival rates across all cancers, survivors represent a growing population that is frequently affected by persistent or permanent hair growth disorders as a result of systemic therapies, radiotherapy, surgical procedures, and therapeutic transplants. These hair disorders include persistent chemotherapy-induced alopecia, persistent radiotherapy-induced alopecia, endocrine therapy-induced alopecia and hirsutism, post-surgery alopecia and localized hypertrichosis, alopecia attributed to therapeutic transplants, and to novel anticancer therapies. The information contained in this continuing medical education article should facilitate a better

Address for all communications: Mario E. Lacouture, MD, Dermatology Service, Memorial Sloan Kettering Cancer Center, 60th Street Outpatient Center, Suite 407, Room 4312, 16 East 60th St., New York, NY 10022, Phone: (646) 888-6014 | Fax: (646) 227-7274, lacoutum@mskcc.org.

Learning objectives:

To diagnose and manage hair disorders in cancer survivors.

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understanding on hair disorders in cancer survivors, so that adequate support and therapies may be provided to cancer survivors.

Keywords

Alopecia; cancer therapy; cancer survivors; endocrine therapy; persistent alopecia; persistent chemotherapy-induced alopecia; persistent radiotherapy-induced alopecia; quality of life; hypertrichosis; hirsutism; therapeutic transplants

INTRODUCTION

The National Cancer Institute defines survivorship as the focus on "the health and life of a person with cancer post treatment until the end of life."[1] It covers the physical, psychosocial, and economic issues of cancer, beyond the diagnosis and treatment phases. Survivorship also includes late effects of treatment, and quality of life (QoL).[1] Cancer survivors represent a growing population with a prevalence projected to approach 18 million by 2022 in the US,[2] and over 32 million worldwide.[3] Over the past decades, advances in cancer treatment have increased the overall 5-year survival to approximately 70% for childhood and adult cancers.[4] Currently, around one in 530 young adults is a survivor of childhood cancer,[5, 6] and approximately 1 in 30 adults have been diagnosed with cancer.[7] Moreover, these improvements in survival rates have resulted in increased attention to treatment sequelae, in areas including cardiac, endocrine, neurologic, cutaneous and psychosocial domains.[8] Approximately 1 in 4 cancer survivors reports a decreased QoL due to physical problems.[7]

Whereas the acute dermatologic adverse events (AEs) of anticancer therapies have received considerable attention, long-term dermatologic AEs such as hair growth disorders, dyspigmentation and scarring remain relatively unknown in the dermatologic community, limiting care and potential therapeutic efforts in this patient population. Indeed, the incidence of persistent or permanent alopecia after cancer was reported in 14% of 14,358 childhood cancer survivors and in 30% of adult breast cancer survivors.[9] The occurrence of alopecia and scarring in cancer survivors is notably associated with psychological disorders such as depression, anxiety and low self-esteem, eventually leading to lowering of health-related QoL.[10] The information in this article will allow clinicians to better understand hair disorders in cancer survivors so that adequate support and potential therapies could be offered, thus improving the QoL of cancer survivors.

ALOPECIA IN CANCER SURVIVORS: OVERVIEW AND CLINICAL FEATURES

Key points

- There are an estimated 15.5 million cancer survivors in the United States, equivalent to 4.8% of the population. The majority had undergone a surgical procedure as part of their diagnosis or treatment, approximately 50% have been treated with radiotherapy, and more than 60% have received systemic anticancer therapies, all of which may result in persistent or permanent hair disorders

- Breast cancer survivors treated with taxanes (paclitaxel, docetaxel) will develop persistent alopecia in 30%
- Endocrine therapies are associated with pattern alopecia similar to androgenetic type in 15-25% of cases
- Head and neck radiotherapy leads to persistent alopecia in 60% of survivors
- In childhood cancer survivors, alopecia has been associated with anxiety and depression, and adult survivors with persistent alopecia report a negative impact on their emotions

Persistent chemotherapy-induced alopecia

The total or incomplete hair regrowth 6 months following therapy completion in patients who received cytotoxic chemotherapy is defined as persistent chemotherapy-induced alopecia (pCIA).[11, 12] Also described as permanent chemotherapy-induced alopecia,[13-20] or as chemotherapy irreversible alopecia.[21-23] Whether most cancer survivors have been evaluated and treated for this type of alopecia or if pCIA is in fact permanent or irreversible has yet to be determined. pCIA has been mostly reported in breast cancer survivors treated with taxane-based chemotherapy[11, 15, 19, 24, 25] (paclitaxel and docetaxel), and cyclophosphamide-based chemotherapy,[15, 26, 27] with an incidence of 30% 36 months after completion of chemotherapy.[28] In addition, pCIA have been reported in children who have undergone a conditioning therapy with busulfan[29-35] (with a cumulative incidence of 19%), [36] and with other chemotherapies used for stem cell transplantation (e.g. thiotepa and carboplatin)[37] (Table I).

With the commonly used chemotherapy regimens combining taxanes with anthracyclines, the risk of severe pCIA was significantly higher than the combination of doxorubicin and cyclophosphamide alone (10.5 vs. 2.7%). In a questionnaire-based cross-sectional study of 265 breast cancer survivors, 7.2% reported severe pCIA (hair loss >50%).[21]

Multiple clinical features have been described for pCIA (Table I). The most common is a non-scarring, diffuse alopecia (53% of pCIA reported cases)[15, 17, 25, 31] (Figure 1), and a pattern similar to androgenetic alopecia has been reported in 46.2%.[16, 17] pCIA may also be associated with madarosis, axillary, and pubic alopecia, although the incidence of persistent alopecia in body sites other than the scalp is unknown.[18, 35]

Persistent radiotherapy-induced alopecia

Hair regrowth generally occurs within 2–4 months after radiotherapy to the head and neck. [38, 39] Persistent radiotherapy-induced alopecia (pRIA) is the total or incomplete hair regrowth 6 months following radiotherapy completion, and is commonly related to high-dose radiotherapy to the scalp.[40] In 26 patients with primary brain tumors, the doses reported to cause pRIA were correlated with radiotherapy dose to the hair follicles in a particular radiotherapy field, with a 50% risk for pRIA with a fractionated follicular dose of ≥ 43 Gy.[41] In 12 children with medulloblastoma treated with proton beam radiation in combination with high dose vincristine-based chemotherapy, pRIA was observed in 75%, and was correlated with a craniospinal radiotherapy dose above 21 Gy.[42]

Clinical presentation of pRIA includes well defined alopecic and atrophic skin confined to the area of radiotherapy, and is usually asymptomatic (Table I). Occipital, parietal, and temporal scalp are commonly focal sites of radiotherapy for brain metastases and central nervous system tumors such as glioblastoma and astrocytoma[43] (Figure 2). Diffuse pRIA is also described with whole brain radiotherapy for brain metastases,[44, 45] especially when combined with chemotherapy.[46] In addition, pRIA could be also observed in any other hair-bearing area were radiotherapy is received, such as the face, neck,[47] or the extremities in patients with other solid tumors.[48]

Endocrine therapy-induced alopecia and hirsutism

Endocrine therapies (ET) are standard of care in survivors of hormone receptor-positive breast cancer (around 70% of all breast cancers).[49] ET, including selective estrogen receptor modulators (e.g., tamoxifen, toremifene), aromatase inhibitors (e.g., anastrozole, letrozole, exemestane) and gonadotropin-releasing hormone agonist (e.g., leuprolide) are usually administered for 5-10 years in the adjuvant setting to reduce the risk of recurrence.[50, 51] Breast cancer survivors are known to have substantial AE attributed to estrogen deprivation from ET,[52] and up to 8% of survivors will discontinue therapy due to alopecia related to adjuvant therapy with aromatase inhibitors.[52]

In a hospital registry-based survey study of 851 female breast cancer survivors, 22 % of those who received aromatase inhibitors reported hair loss, and 32% reported hair thinning.[53] Additionally, a meta-analysis of 13,415 patients in 35 clinical trials including different ETs reported an overall incidence of all-grade alopecia of 4.4%, with the highest incidence (25%) in patients treated with aromatase inhibitors.[54]

In a retrospective study of 112 breast cancer patients with ET-induced alopecia (EIA), causal agents included aromatase inhibitors in 67% and tamoxifen in 33% of patients. The mean time to alopecia development was 16.8 months (range 1-91 months).[55] These patients usually present with frontoparietal hairline recession (Table I), mimicking the pattern of androgenetic alopecia (Figure 3).[56] The trichoscopic features observed in patients with EIA include the concomitant presence of vellus and terminal hairs, also a hallmark of androgenetic alopecia.[55, 57] Iatrogenic hirsutism has been reported in less than 10% of survivors receiving ET for breast cancer[58] (Figure 3).

In patients treated with cytotoxic chemotherapy followed by ET (the majority of hormone-receptor positive breast cancers), a complete medical history must be obtained to define whether alopecia is attributed to the actual ET (EIA) or to the previous chemotherapy (pCIA), or a combination of both (pCIA+EIA).

Permanent surgery-induced alopecia and localized hypertrichosis

Alopecia and scarring in cancer survivors usually arise secondary to tissue biopsies, placement of catheters, and surgeries to resect scalp primary or metastatic tumors.[59-61] In brain cancer patients, surgery is preferred for tumor removal.[62] However, complete resection is generally limited.[63] Therefore, combination therapy (e.g., radiotherapy and cytotoxic chemotherapy) is usually required;[64] these therapies combined with surgery, enhance the risk of permanent alopecia and scarring. The clinical presentation of permanent surgery-

induced alopecia includes the linear shape of the scar on the scalp. When additional radiotherapy is combined with surgery, a geometric alopecic patched confined to the area of radiotherapy is also observed (Figure 4). Hypertrophic scars may also be associated with disfigurement, pain, or pruritus.[65] Conversely, undesirable hair growth in recipient areas after reconstruction of cancer defects may be observed[66-68] (Figure 5).

Persistent hair changes induced by other anticancer therapies

Anticancer therapies such as vismodegib,[69] and immunotherapies,[70] have been reported to cause persistent alopecia after drug interruption or discontinuation. Chronic graft versus host diseases after stem cell transplants may induce both diffuse alopecia (15.6%),[31] and alopecia areata (in around 20%)[71] (Table I).

HISTOPATHOLOGY AND PATHOBIOLOGY

Key point

- Destruction of epithelial hair follicle stem cells by anticancer therapies prevents hair follicle cycling

Histopathologic features of permanent or persistent alopecia attributed to anticancer therapies are not specific. However, a non-scarring pattern is usually described in pCIA, with an increased number of miniaturized and telogen hair follicles.[30] Other reported histopathologic features of pCIA include scarring alopecia, with concentric fibrosis and a discrete perifollicular lymphoid cell infiltrate[24, 30] (Figure 2). In pRIA the predominant features are compatible with a scarring alopecia,[72] and likely similar histopathologic features are present in permanent surgery-induced alopecia (including fibrosis along with decreased numbers or absence of hair follicles). In EIA, histopathologic features similar to androgenetic alopecia have been reported.[24]

Although the cause of permanent or persistent alopecia in cancer survivors has not been identified, irreversible damage to epithelial hair follicle stem cells (eHFSC) in the bulge region of the hair follicle are thought to play a crucial role.[73] Compared with their differentiated progeny in the hair matrix, eHFSC in the bulge have a low proliferation rate and are generally less sensitive to chemotherapy,[74] but highly sensitive to ionizing radiation.[75, 76] Additionally, anticancer therapies associated with pCIA overcome the relative chemoresistance of eHFSC (for as yet not understood mechanism), and thus deplete the eHFSC pool that is vitally required for hair follicle regeneration during the next hair cycle.[73, 77]

A 50% reduction in mitotic indices of hair matrix cells was found in experimentally irradiated mice, suggesting that there is a persistent or permanent decrease in the number or growth fraction of eHFSC.[78] The effects of chemotherapy and radiotherapy on hair regrowth are related to the interval between chemotherapy sessions, dose administered, and radiotherapy exposure.[78, 79] This enhancing effect may also depend on the phase of hair follicle cycle in which the activity was arrested.[46]

Estrogens and androgens act as potent hair growth modulators.[80, 81] ET block the function and signaling of endocrine receptors, and estrogens are unable to modify the androgen metabolism in the hair follicle, increasing the amount of 5-dihydrotestosterone.[82] Indeed, androgenetic alopecia in women likely results not only from the undesired effects of androgen stimulation of androgen-sensitive hair follicles, but also from a relative lack of hair follicle stimulation by estrogens,[83] which may explain the clinical similarities between EIA and androgenetic alopecia.[24] Permanent surgery-induced alopecia results from a hair follicle ablation during the inflammatory, proliferative, and remodeling phases of scarring, which may extend beyond the field of surgical intervention, partially by pressure atrophy of the surrounding skin appendages, and by infiltration of the fibrotic-associated tissue into neighboring skin appendages.[84, 85]

QUALITY OF LIFE IN CANCER SURVIVORS WITH HAIR DISORDERS

Key point

- Persistent or permanent alopecia after cancer therapies has been associated with depression, anxiety, and increased somatization

Alopecia is often considered by health care professionals as a ‘temporary’ and ‘cosmetic’ issue in cancer survivors, even though the actual distress associated with hair loss is complex, and can be overwhelming.[86] Moreover, permanent or persistent alopecia is rarely included as an AE during clinical trials and usually underrecognized by healthcare providers.[87] Some patients also accept alopecia as a trade-off for a cure and therefore do not present with complaints of hair-related QoL issues.[88] Yet, permanent alopecia related to anticancer therapies was associated with depression, anxiety, and increased somatization.[9] In addition, head and neck scarring and permanent or persistent alopecia (after chemotherapy, surgery and or cranial radiotherapy) has been reported as the strongest predictors of distress, suggesting that outward physical appearance played a prominent role in emotional adjustment of survivors.[9, 89]

Distressing psychological consequences were common and severe among breast cancer survivors with pCIA, as reflected by the wearing hairpieces or scarves in 14 of 20 patients.[26] Additionally, in 18 breast cancer survivors with pCIA, 33% were worried about their alopecia, and it interfered with functioning in 28%.[90] Also, the satisfaction score regarding the state of their hair in breast cancer survivors with pCIA was significantly lower when compared to breast cancer patients without pCIA.[21]

The clinical severity of alopecia may not correlate with the negative impact on a patients’ QoL.[26, 91] In 112 patients diagnosed with EIA, 93% had mild alopecia (grade 1, <50% of hair loss) based on the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAEv4.0). However, these patients reported a negative emotional impact when compared to the other psychological domains.[55] Therefore, it is important to consider the distress that any grade of alopecia may have on cancer survivors’ QoL. Focus groups interviews including 25 breast cancer patients treated with taxane-based chemotherapy revealed that madarosis has a significant emotional impact.[92] Conversely, the impact of hirsutism attributed to anticancer therapies on QoL has not been defined.

MANAGEMENT

Key point

- Management of hair disorders in cancer survivors is supported by anecdotal reports and case series that fail to meet strict evidence-based medicine standards

Management of permanent or persistent alopecia in cancer survivors is mostly based on case series, case reports, and expert opinion (level of evidence, IV). Despite these limitations, we have reviewed the available information (Table II). Our pCIA experience is concordant with recent case series,[24] in which the alopecia remains stable, and few may improve with topical or systemic therapies. Therefore, prevention of persistent or permanent hair growth disorders is key in order to mitigate this untoward consequence in cancer survivors. Scalp cooling has become the most widely utilized standard for the prevention of chemotherapy-induced alopecia, showing prevention of grade 2 (>50% alopecia) in 51-67% of patients.[93, 94] However, there is no long-term follow-up data available on the efficacy of scalp cooling to prevent pCIA.

The main objectives of reactive alopecia therapy in cancer survivors are to stop or reduce the hair loss and stimulate growth. Duration of therapy should be guided by clinical response, and a laboratory analysis may help to exclude other causes of alopecia, such as thyroid disease, and vitamin or mineral deficiency.

Topical therapy with minoxidil 2 or 5% has been shown to stabilize or improve alopecia in case reports of pCIA.[24, 26] However, in 14 of 20 breast cancer survivors it was unsuccessful after >3 months of therapy.[26] On the other hand, treatment with topical minoxidil 5% daily in 46 breast cancer survivors with EIA, moderate or significant improvement was observed in 80%.[55] A case report showed that oral minoxidil improved pCIA in a breast cancer survivor.[13] In contrast, pCIA treated with spironolactone (150 mg/day, 3 months) in one breast cancer survivor showed no efficacy.[26] However, in our experience with breast cancer survivors using spironolactone alone or in combination with minoxidil 5% for pCIA and EIA, 60% of patients tend to have a moderate or significant clinical improvement as confirmed with baseline clinical and trichoscopy standardized pictures (Figure 6). These positive clinical outcomes have been mostly observed in patients with alopecia grade 1 (CTCAEv4.0). Other options should be discussed in patients with alopecia grade 2 (CTCAEv4.0), so that the expectations of alopecia improvement are realistic. There is a putative risk of hormonal stimulation of endocrine receptor-positive tumors with the use of systemic therapies for androgenic alopecia (e.g., spironolactone, finasteride), so these agents must be used with caution. Support groups may be helpful, and patients with pCIA can be directed to http://aheadofourtime.org/.

For hypertrichosis and hirsutism in cancer survivors, ruling out common causes of hyperandrogenism is important.[95] In our experience, hirsutism attributed to anticancer therapies is predominantly mild (grade 1, CTCAEv4.0) in cancer survivors, especially in postmenopausal once they have completed cytotoxic chemotherapy or in those receiving ET, and requires only reassurance and local therapies such as epilation, laser therapies, or bleaching if needed (Table II). Nd:YAG laser therapy appears to have a hair clearance of

>90% after 1-4 sessions in 5/9 patients suffering from growth of terminal hair in the oral cavity after reconstruction using a hairy donor site.[96]

Multiple scalp reconstructive options have been described to improve the appearance of the localized pRIA, including tissue expansion, and hair transplantation.[40] However, the success of these techniques will rely on the skin viability and severity of hair follicle damaged.[97] There is no reported experience using platelet-rich plasma to treat alopecias in cancer survivors, and costs may be elevated. Hair follicle neogenesis with autologous cell populations may become a future therapeutic option for pCIA and pRIA.[98, 99]

A randomized controlled trial including 20 patients treated with bimatoprost 0.03% gel for chemotherapy-induced eyelash alopecia, improvement in length (1.50 vs 0.46 mm), and thickness (3 vs 2, in a scale of 1-5) of treated eyelashes was observed, with an increase of patient satisfaction (16 vs 26) after 3 moths of therapy[100](Figure 7).

Interventions with skin camouflage (including powders, scalp micropigmentation/tattoo, hair color and hairstyle changes) can modify the concerning body image to mask skin discoloration and alopecia. This effect acts to improve the visible impact of deformity. [101, 102] When camouflage may be needed, options should be provided. Initially, most patients are reluctant to use any camouflage, but they can enhance self-confidence and QoL. [103] The market for home-use cosmetic devices is rapidly expanding, however there are no reports measuring their efficacy for hair growth disorders in cancer survivors.

The ongoing CHANCE Study (A Study of Chemotherapy-Induced Hair Changes and Alopecia, Skin Aging and Nail Changes in Women With Non-Metastatic Breast Cancer; ClinicalTrials.gov dentifier: NCT02530177) examining the incidence, risk factors, psychosocial impact, and clinical features of pCIA and EIA in 500 cancer survivors will yield additional information, critical towards the identification of preventive and treatment strategies, and similar studies in other patient populations are needed

CHALLENGES AND FUTURE PERSPECTIVES

Further efforts should be made to understand the mechanism of hair follicle alteration and to identify effective strategies for the prevention and treatment of permanent or persistent alopecia in cancer survivors. Patient counseling regarding the possibility of developing persistent or permanent hair disorders with anticancer therapies will also be important so that anticipatory coping can take place. Prospective studies evaluating patients during and after their treatments are needed to identify the real incidence and severity of these conditions. Therapeutic options remain limited in number and efficacy, and additional research is needed in order to determine optimal preventive and therapeutic approaches for the various hair disorders observed in the growing population of cancer survivors.

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ABBREVIATIONS USED

AE	Adverse event
CTCAEv4.0	Common Terminology Criteria for Adverse Events Version 4.0
eHFSC	Epithelial hair follicle stem cells
ET	Endocrine therapy
EIA	Endocrine therapy-induced alopecia
pCIA	Persistent chemotherapy-induced alopecia
pRIA	Persistent radiotherapy-induced alopecia
QoL	Quality of life

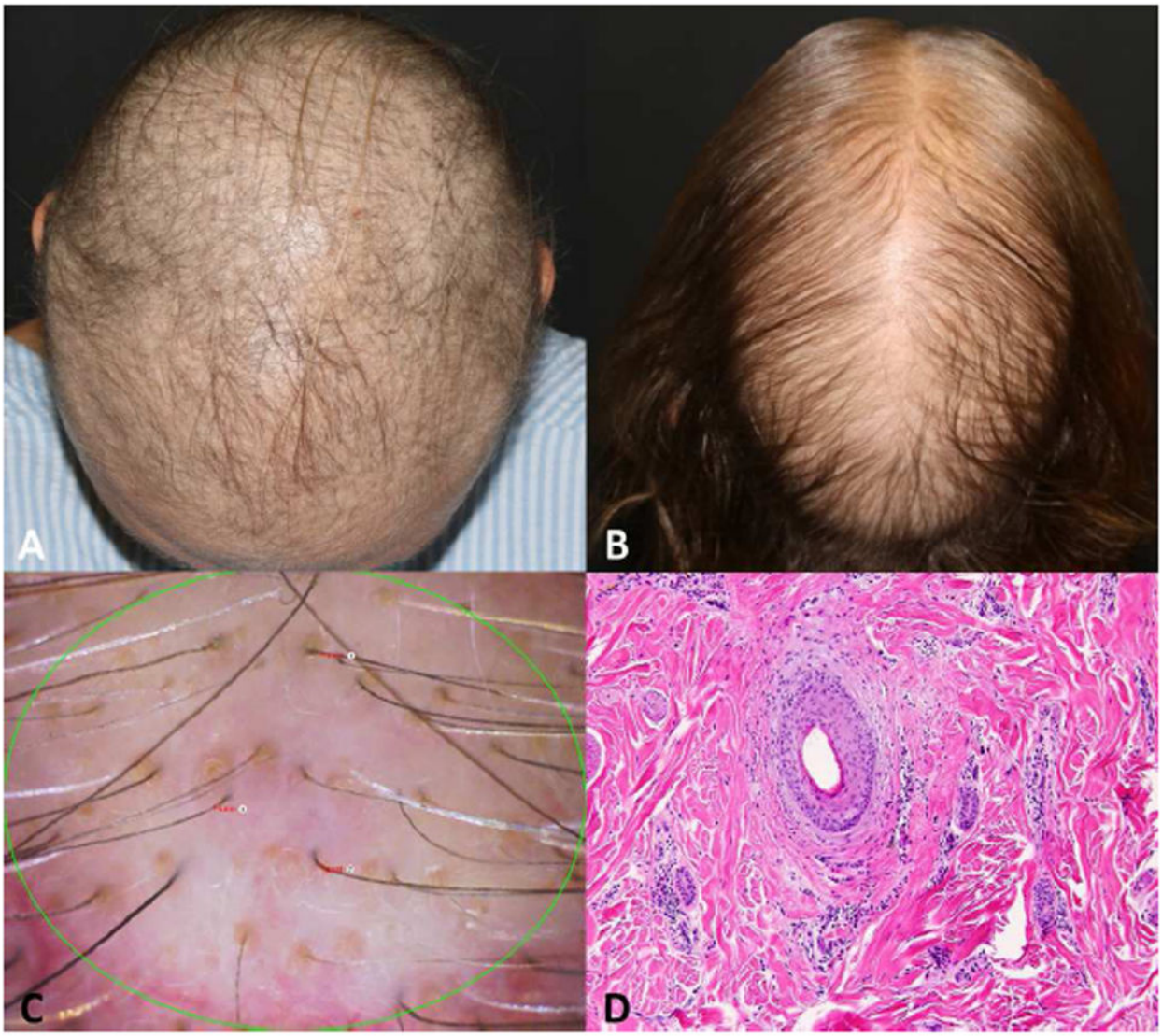

Figure 1.

Persistent chemotherapy-induced alopecia (pCIA). **A**. Diffuse alopecia in a breast cancer survivor, 2 years after taxane based chemotherapy completion. **B**. pCIA in a breast cancer survivor, 1.6 years after taxane based chemotherapy completion with similar pattern of androgenetic alopecia, predominant hair thinning on the crown area. **C**. Trichoscopy of patient in figure B, featuring hair thinning, miniaturized hairs, and yellow dots. **D**. Histology section featuring mild perifollicular inflammation and fibrosis, (hematoxylin-eosin stain).

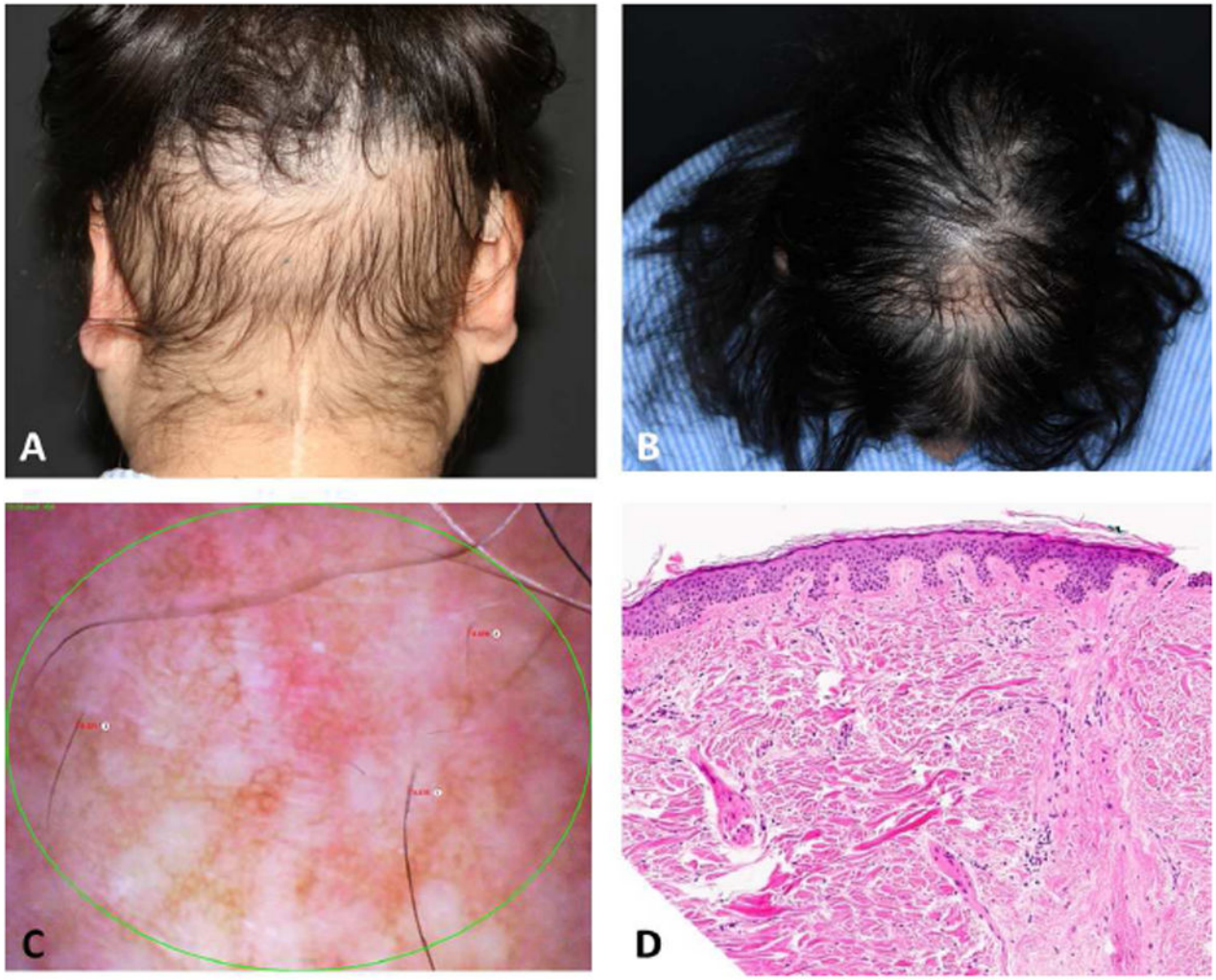

Figure 2.

Persistent radiotherapy-induced alopecia (pRIA). **A**. Localized alopecia in a childhood cancer survivor with medulloblastoma treated with surgery and traditional (photon) radiotherapy. **B**. Diffuse hair loss with hair thinning on the crown area with a central scar after traditional radiotherapy and cytotoxic chemotherapy for a SNC tumor. **C**. Phototrichogram of patient in figure A, Featuring hair thinning miniaturized hairs, and white dots. D, Histology section featuring hair follicle replaced by fibrous tract. There is no significant inflammation (hematoxylin-eosin stain).

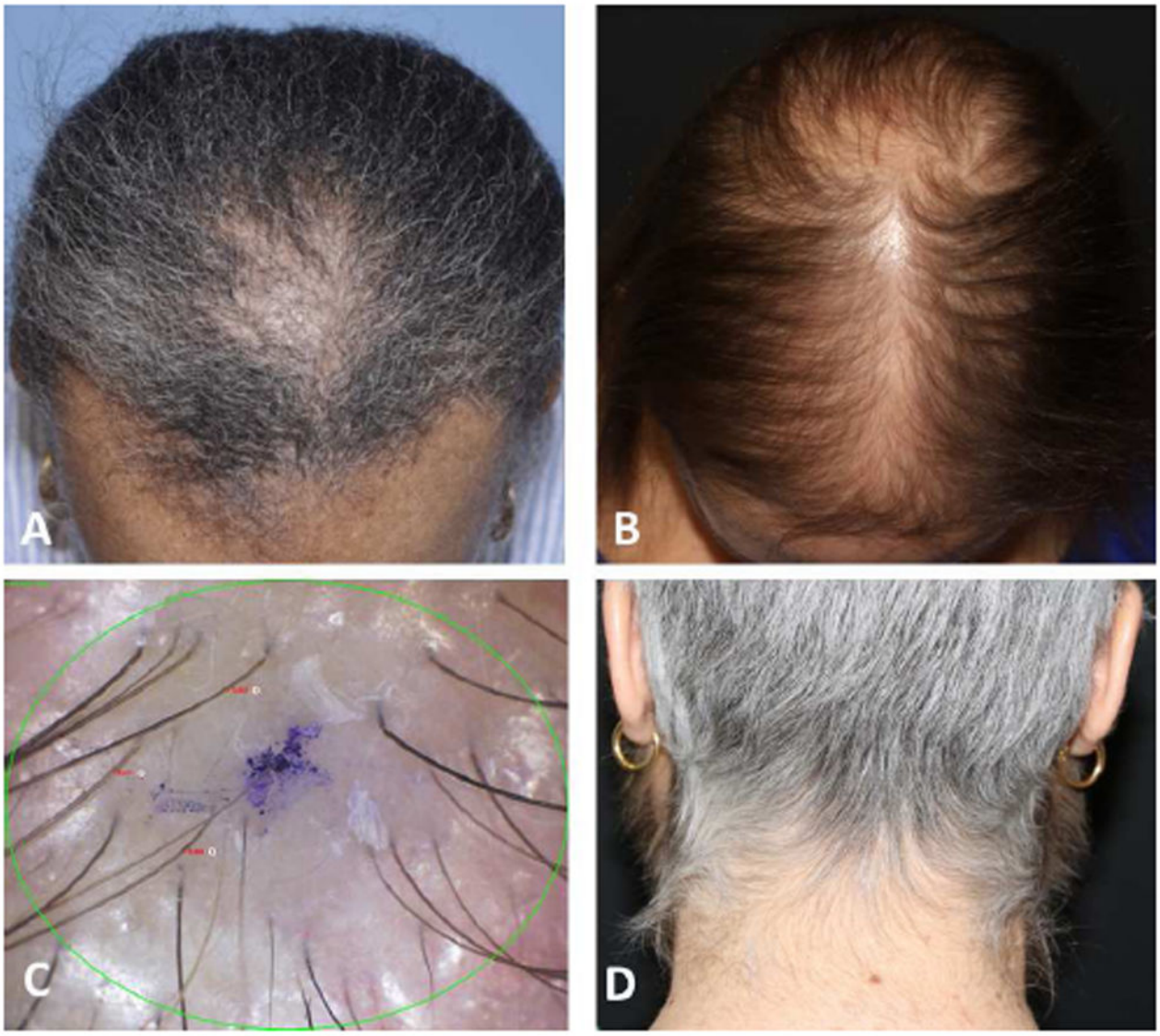

Figure 3.

Endocrine therapy-induced alopecia (EIA). **A**. EIA with similar pattern of androgenetic alopecia, predominant on the frontoparietal hair line. **B**. EIA with similar pattern of androgenetic alopecia, predominant on the crown area. **C**. Trichoscopy featuring vellus hairs, and intermediate and thick terminal hairs. **D**. Hirsutism in a patient receiving endocrine therapy.

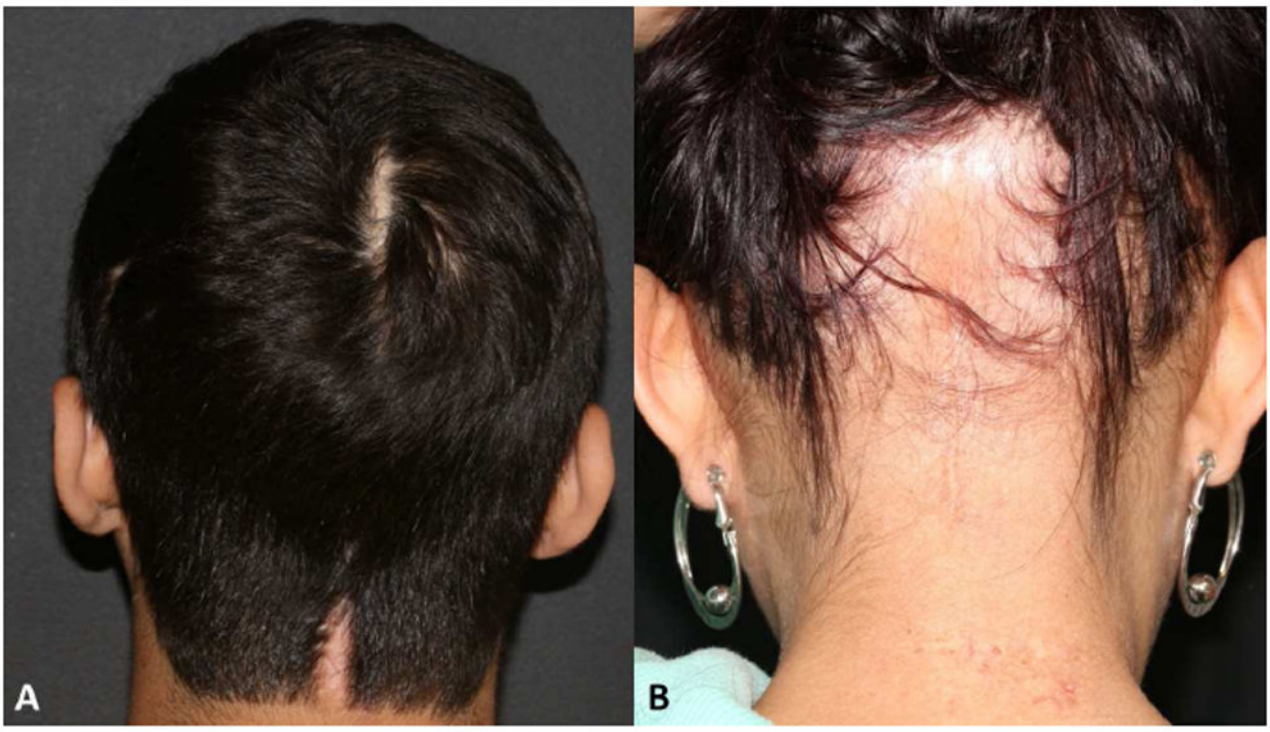

Figure 4.

A. Linear scar on the scalp after surgery of a skull base tumor. **B**. Post-surgery and persistent radiotherapy-induced alopecia.

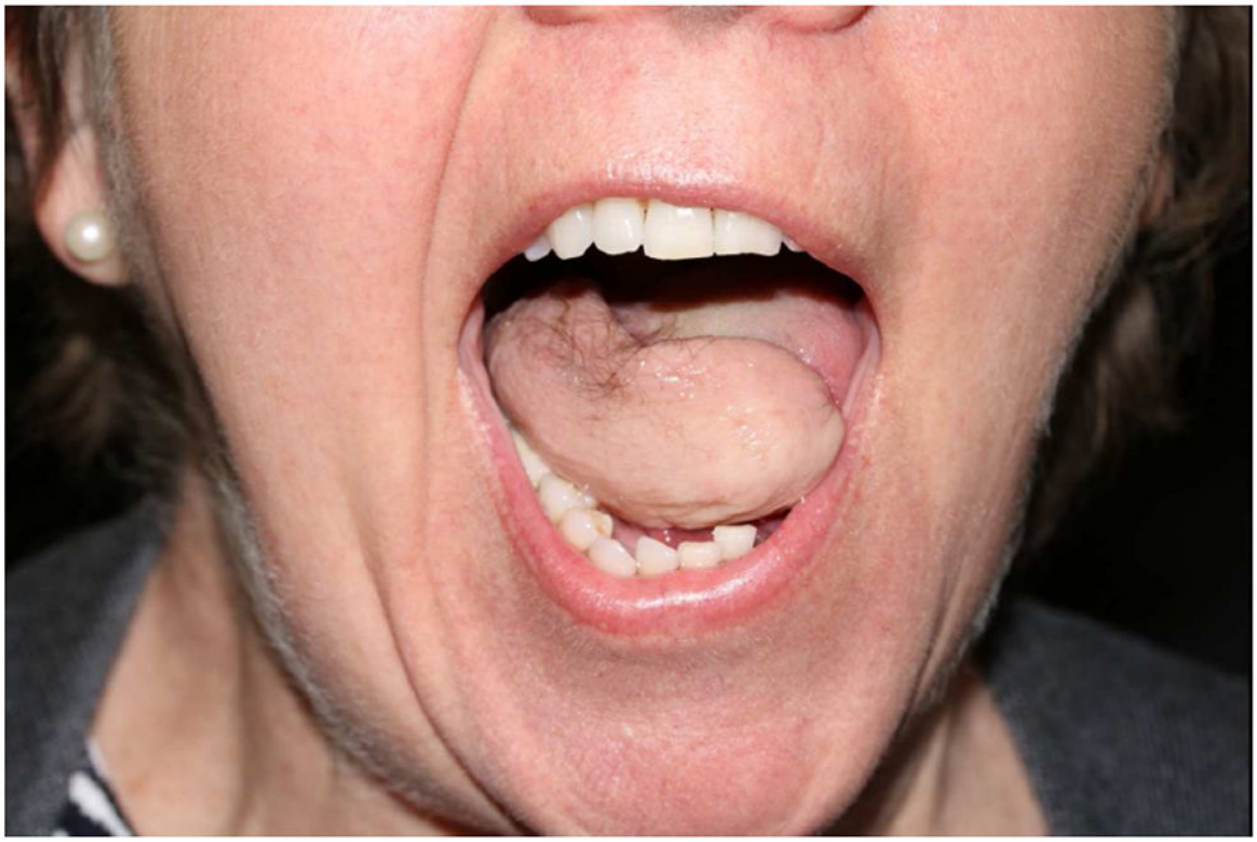

Figure 5.
Post-surgery hair disorders. Terminal hairs on the tongue after reconstruction using a hairy donor site.

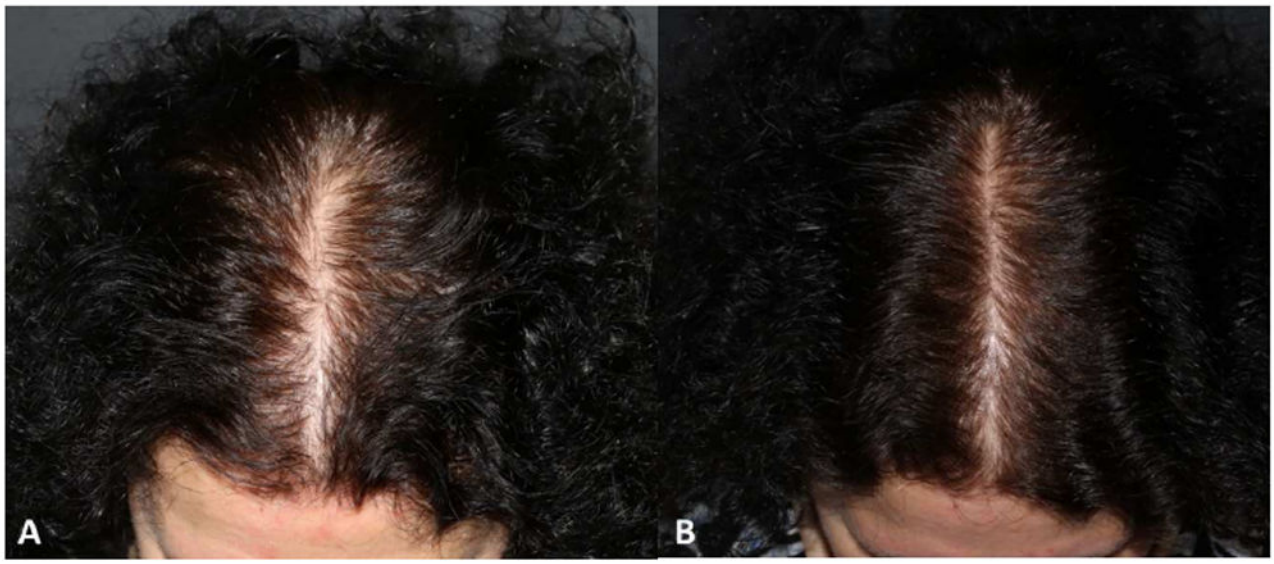

Figure 6.
Endocrine therapy-induced alopecia (EIA). **A**. Before and **B**. Six months after therapy with topical minoxidil foam 5% twice a day.

Figure 7.

Topical bimatoprost 0.03% gel for persistent chemotherapy-induced eyelashes alopecia. **A**. Before therapy and **B**. Six months after therapy.

Table I

Incidence, case reports, and clinical features of alopecia attributed to anticancer therapies in cancer survivors.

Anticancer therapies	Predominant cancer type	Reported cases and incidence	Clinical Features
Cytotoxic chemotherapy (pCIA)		**Reported cases of pCIA with described clinical features n=382 (%)**	Non-scaring alopecia, with diffuse hair thinning and lightening is reported in 53% of cases. A similar pattern to androgenetic alopecia is also described (46.2% of cases)
Taxane based chemotherapy (including combinations with cyclophosphamide, epirubicin and FEC-100)	Breast	259 (67.8%) (Incidence of 30%)	Persistent changes in texture could be observed Scarring features has been reported in 2 cases
Cyclophosphamide based chemotherapy (including combinations with doxorubicin and CTC)	Leukemias, lymphomas, solid tumors	67 (17.5%)	Eyelash, eyebrow, axillary and pubic hair could be involved
Busulphan based chemotherapy (including combinations with cyclophosphamide)	Hematologic malignancies	35 (9.2%)	
Other chemotherapies (including cisplatin, methotrexate, vincristine)	Solid tumors, hematologic malignancies	21 (5.5%)	
Radiotherapy (pRIA)			Scarring and non-scaring features may be present
Photon radiation (traditional radiotherapy)	Primary CNS tumors, metastasis	Up to 50% risk with high fractionated follicular dose of 43 Gy	Geometric shapes of atrophic skin with scarce hairs could be seen in severe cases
Proton radiation	Medulloblastoma, ependymoma	13 children reported	Diffuse hair thinning in total cranial irradiation and in combination with cytotoxic chemotherapy Commonly: occipital, parietal and temporal areas
Endocrine therapies (EIA)			
Selective estrogen receptor modulators (e.g. tamoxifen, toremifene, raloxifene)	Breast, renal cell carcinoma	~ 15%	Non-scaring features
Aromatase inhibitors (e.g. anastrozole, letrozole, exemestane)	Breast	~ 25%	Predominantly women with a similar pattern to androgenetic alopecia
Estrogen receptor down-regulator (fulvestrant)	Breast, ovarian	2.2- 7.9%	Diffuse hair thinning and lightening over the entire scalp is also reported
Luteinizing hormone-releasing hormone agonist (leuprolide)	Breast, prostate	9.5%	
Somatostatin analog (octreotide)	Growth hormone producing tumor (pituitary)	6.7%	

Anticancer therapies	Predominant cancer type	Reported cases and incidence	Clinical Features
Cancer surgery			Linear scar on the scalp Hypertrophic scars may be observed
Neurosurgical procedures (e.g. CNS tumor excisions and biopsies, scalp biopsies, catheters)	Primary CNS tumors, tumors in hair-bearing areas	Scarring/disfigurement and hair loss on the head/neck area in 3.557 (25.1%) of 14.358 cancer survivors	Could be associated with persistent radiotherapy-induced alopecia
Flaps (e.g. radial forearm flap)	Head and neck tumors		Terminal hairs in undesirable areas, such as the oral cavity or face
Immunotherapies: CTLA-4 inhibitors (e.g. ipilimumab), PD- 1 receptor inhibitors (e.g. nivolumab and pembrolizumab), PD-L1 inhibitors (e.g. atezolizumab, avelumab)	Melanoma, lung, bladder, prostate cancer, head and neck squamous cell carcinoma	2 cases with CTLA-4 inhibitors 1 case with PD-L1 inhibitor	Non-scaring alopecia with diffuse hair thinning and alopecia areata, evident 3-6 months after therapy completion
		1 case with CTLA-4 and PD-1 receptor inhibitors	Skin involvement may be present, including vitiligo, lichenoid reaction
Vismodegib	Basal cell carcinoma	4 cases	Persistent diffuse severe alopecia (CTCAEv4.0 grade 2)
SCT (acute or chronic GvHD, conditioning therapy for SCT with busulfan, and total body irradiation)	Leukemias	~ 20% of alopecia areata in chronic GvHD	More likely to develop alopecia areata. Skin involvement may be present (vitiligo, scleroderma, eczema and lichenoid reaction) Diffuse alopecia with scarring features could be observed
		Conditioning therapy for SCT: scalp alopecia with busulfan in 56% and 10% with total body irradiation	Diffuse hair loss and hair thinning

CTC, cyclophosphamide/thiotepa/carboplatin; CNS, central nervous system; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CTCAEv4.0, Common Terminology Criteria for Adverse Events Version 4.0; EGFR, epidermal growth factor receptor; FEC-100, fluorouracil/epirubicin/cyclophosphamide; GvHD, graft versus host disease; pCIA, persistent chemotherapy-induced alopecia; PD-1, programmed cell death protein 1; PDGF, platelet derived growth factor; PD-L1, programmed death-ligand 1; SCT, Stem cell transplant; TCH, docetaxel/carboplatin/trastuzumab.

Table II

Hair disorders in cancer survivors: management and recommendations.

Hair disorder	Intervention	Level of evidence
Persistent chemotherapy-induced alopecia (pCIA)	**CTCAEv4.0 grade 1:** Topical minoxidil foam 5% twice daily **CTCAEv4.0 grade 2:** Spironolactone (escalating dose up to 150mg daily) in addition to therapy recommended in alopecia grade 1 (caution due to the theoretical risk of hormonal stimulation of endocrine receptor-positive tumors) Oral minoxidil (potential adverse events should be considered)	Level IV
Persistent radiotherapy-induced alopecia (pRIA)	**CTCAEv4.0 grade 1:** Topical minoxidil foam 5% twice daily Botulinum toxin type A: 5 U per 0.1 ml saline every 3 months for 12 months **CTCAEv4.0 grade 2:** Scalp reconstruction (e.g. simple excision or flaps, tissue expansion) Hair transplant (if not severe skin damage)	
Endocrine therapy-induced alopecia (EIA)	**CTCAEv4.0 grade 1:** Topical minoxidil foam 5% twice daily **CTCAEv4.0 grade 2:** Spironolactone (escalating dose up to 150mg daily) in addition to therapy recommended in alopecia grade 1 (caution due to the theoretical risk of hormonal stimulation of endocrine receptor-positive tumors)	
Hirsutism and hypertrichosis	**CTCAEv4.0 grade 1 (mild hair growth):** Local therapy such as epilation, waxing, depilation, bleaching **CTCAEv4.0 grade 2 (prominent thick hairs, associated with psychosocial impact):** Laser or intense pulsed light Spironolactone appeared to be as effective as flutamide and finasteride (avoid in hormonal-sensitive tumors) Other physiologic causes of hirsutism may be ruled out Laser (Nd:YAG) for hair in unwanted areas (e.g., oral cavity)	
Permanent surgery-induced alopecia	**First line:** Management of scar symptoms if present (topical or intralesional steroid, laser and light-based treatment) **Second line:** Hair transplant Scalp reconstruction (e.g. simple excision or flaps, tissue expansion)	
Eyebrow and eyelashes alopecia	Topical bimatoprost gel 0.03%	Level IB

Hair disorder	Intervention	Level of evidence
SCT (Chronic GvHD, conditioning therapy for SCT with chemotherapy and/or total body irradiation)	In GvHD depends upon the organs involved and severity of symptoms Topical and intralesional steroid for alopecia areata (Level II-III), and in steroid resistant; janus kinase (JAK) inhibitors (Level IV)	Level II-IV
	Conditioning chemotherapy and/or total body irradiation; follow the interventions of pCIA and pRIA respectively	Level IV
Immunotherapies: CTLA-4 inhibitors (e.g. ipilimumab), PD-1 receptor inhibitors (e.g. nivolumab and pembrolizumab), PD-L1 inhibitors (e.g. atezolizumab, avelumab)	Potent topical steroid, and orthosilicic acid	Level IV
Vismodegib	Not reported	No evidence
General recommendations	Therapy should be discussed to have realistic expectations of therapy outcome Follow-up at least 3 months after alopecia therapy started Laboratory analysis including, ferritin, Vitamine D, Zinc levels, and thyroid function may be requested if other causes of alopecia (e.g., androgenetic, telogen effluvium, thyroid-related) are suspected Camouflages techniques should be provided (e.g. crayons, powder, volumizers, hair weaves/hair extension, scalp micropigmentation/tattoo and hairpieces) If emotionally affected; psychological counseling is recommended Involve nurses and other health care providers in the cancer survivors care	

CTCAEv4.0, Common Terminology Criteria for Adverse Events Version 4.0; CTCAEv4.0 grade 1 for alopecia, Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage; CTCAEv4.0 grade 2 for alopecia, Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; SCT, Stem cell transplant; Nd:YAG, neodymium-doped yttrium aluminium garnet; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.