Hair disorders in cancer survivors

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- 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*

- There are an estimated 15.5 million cancer survivors in the United States, equivalent to 4.8% of the population

- Approximately 50% have been treated with radiotherapy, and 60% have received systemic anticancer therapies

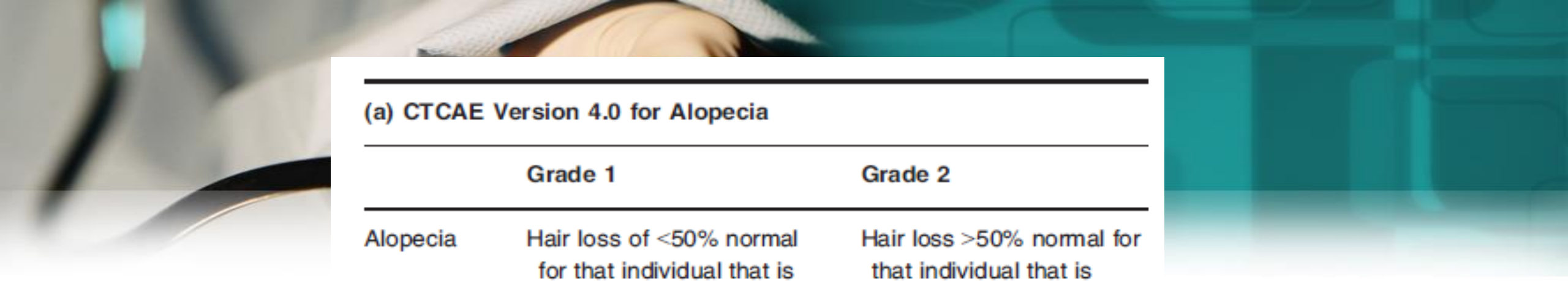
- Approximately ***1 in 4*** cancer survivors reports a decreased QoL related to physical conditions
- An estimated ***65%*** of patients undergoing classic chemotherapy will experience hair loss, which is an extremely upsetting adverse event for many.
- the incidence of persistent or permanent alopecia after cancer was reported in ***14%*** of 14,358 childhood cancer survivors and in ***30%*** of adult breast cancer survivors

- **Acute Dermatologic Adverse Events (AEs) of anticancer therapies have received considerable attention, long-term dermatologic AEs, such as**
  - ***hair growth disorders, depigmentation and scarring***

- The effects of chemotherapy and radiotherapy on hair regrowth are related to the:
- *interval between chemotherapy sessions, dose administered, drugs mechanism of action, radiotherapy exposure, patient age, nutritional and hormonal status*

QUALITY OF LIFE IN CANCER SURVIVORS WITH HAIR DISORDERS

- Persistent or permanent alopecia after cancer therapies has been associated with depression, anxiety, and increased somatization
- head and neck scarring and permanent or persistent has been reported as the:
  - ❖ **strongest predictors of distress, suggesting that outward physical appearance played a prominent role in emotional adjustment of survivors.**
- The clinical severity of alopecia may not correlate with the negative impact on a patient's QoL
- Madarosis has a significant emotional impact



(a) CTCAE Version 4.0 for Alopecia

	Grade 1	Grade 2
Alopecia	Hair loss of <50% normal for that individual that is not obvious from a distance but only on close inspection; a different hairstyle may be required to cover the hair loss, but it does not require a wig or hair piece to camouflage	Hair loss >50% normal for that individual that is apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact

(b) Modified Dean's Alopecia Scale for Hair Loss

Dean score	Percentage of hair loss
Grade 0	No hair loss
Grade 1	>0 to ≤25% hair loss
Grade 2	>25 to ≤50% hair loss
Grade 3	>50 to ≤75% hair loss
Grade 4	>75% hair loss

Persistent chemotherapy-induced alopecia

- CIA usually begins 1–3 weeks after the initiation of chemotherapy, with hair regrowth occurring after a delay of 3–6 months

Texture and color may be different after the regrowth

The total or incomplete hair regrowth 6 months after completion of therapy

- *pCIA has been mostly reported in breast cancer survivors treated with **taxane-based** chemotherapy and **cyclophosphamide-based** chemotherapy*

- In addition, pCIA has been reported in children who have undergone conditioning regimens with **busulfan**, and with other chemotherapies used for **stem cell transplantation**, such as thiotepa and carboplatin

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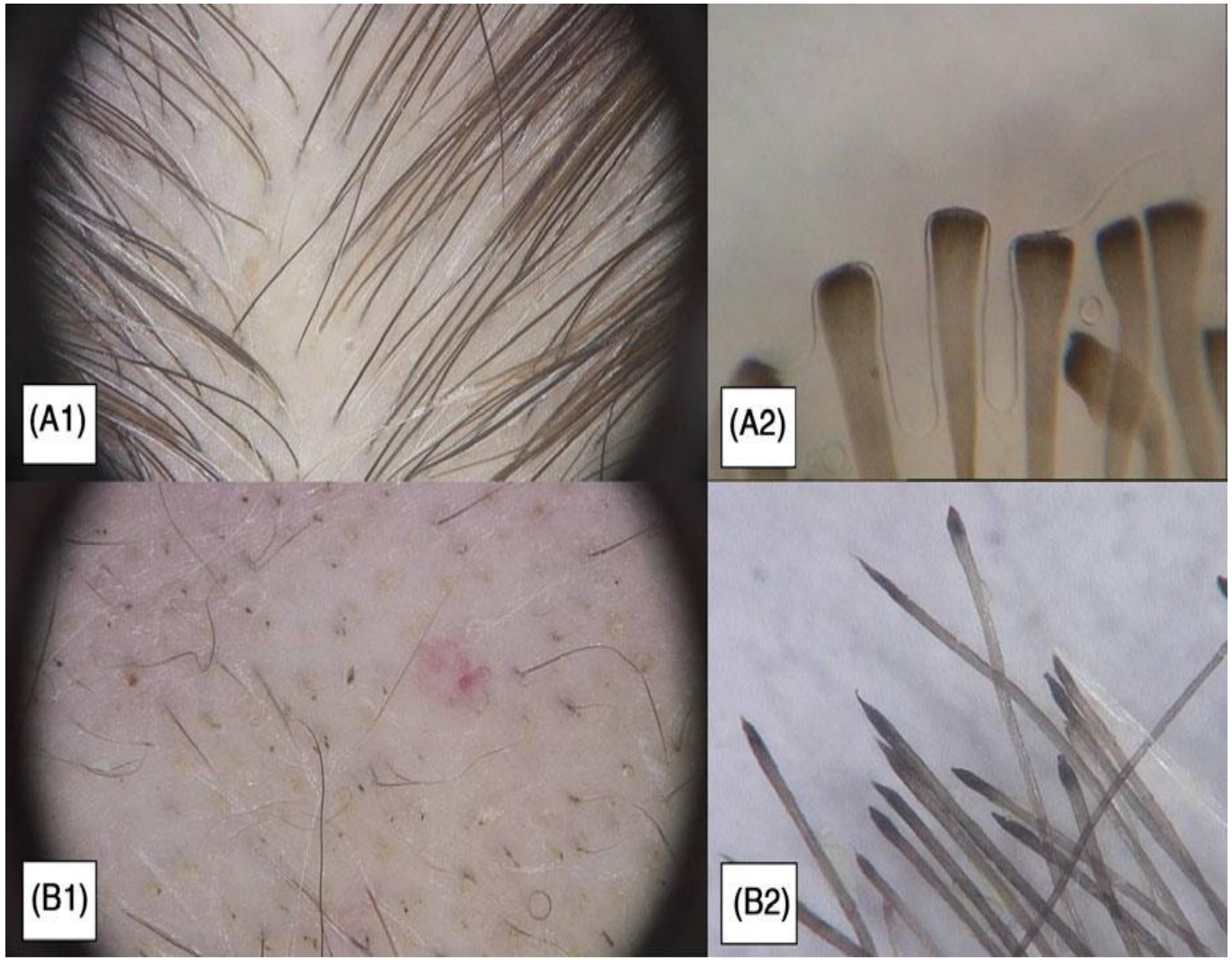
Clinical features have been described in pCIA

- The most common is *a nonscarring, diffuse alopecia* (53% of pCIA reported cases)
- A pattern *similar to androgenetic alopecia* has been reported in 46.2%of cases.
- *Frontal and occipital* hairlines are frequently involved and seem to be more sensitive compared to other areas of the scalp
- pCIA may also be associated with *madarosis and axillary and pubic alopecia*

Table 3 Chemotherapeutics and targeted therapies that cause chemotherapy-induced alopecia (CIA)[9,19,20]

Classic chemotherapeutic drugs		
Type of agent	**Type of alopecia**	**Frequency**
Classic Chemotherapeutic Therapies		
Antimicrotubule agents		
• Vinca alkaloids: Vincristine, vinblastine, vinorelbine, vinflunine.	• Nonscarring, diffuse.	80%
• Taxanes: Paclitaxel, docetaxel.	• Cases of permanent alopecia with taxanes.	
Topoisomerase inhibitors		
• Topoisomerase I inhibitors: Topotecan, irinotecan.	• Nonscarring, diffuse.	60–100%
• Topoisomerase II inhibitors: Etoposide, teniposide, mitoxantrone.		
Alkylating agents		
• Nitrogen mustards: Bendamustine, cyclophosphamide, estramustine, ifosfamide, mechloretamine, melphalan.	• Nonscarring, diffuse.	>60%
• Platinum analogs: Carboplatin, cisplatin, oxaliplatin.		
• Triazenes: Dacarbazine, procarbazine, temozolomide.		
Antimetabolites		
• Folate antagonist: Methotrexate.	• Nonscarring, diffuse.	10–50%
• Purine antagonist: 6-Mercaptopurine, 6-thioguanine, azathioprine, fludarabine.		
• Pyrimidine antagonist: 5-Fluorouracil, capecitabine, cytarabine.		
Targeted therapies		
EGFR inhibitors		
• Monoclonal antibodies to EGFR: Cetuximab, panitumumab	• Nonscarring, diffuse.	50–90%
• Tyrosine kinase inhibitors specific for EGFR: Erlotinib, gefitinib.	• Cases of erlotinib-induced cicatricial alopecia.	
• Dual kinase inhibitors of EGFR and HER2: Lapatinib		
• Inhibitors of erbB receptors: Canertinib.		
Tyrosine kinase inhibitors		
• Inhibitors of tyrosine protein kinases: Sorafenib.	• Nonscarring, diffuse.	5–21% (sunitinib)
• Multitargeted receptor tyrosine kinase inhibitors: sunitinib, pazopanib	• Hair depigmentation.	8–10% (pazopanib)
RAF inhibitors		
• B-Raf/MEK step interruption on the B-Raf/MEK/ERK pathway: Vemurafenib, dabrafenib	• Grade 2 nonscarring alopecia, +/− hair curling.	Up to 30%
MEK inhibitors		
• Trametinib, cobimetinib, binimetinib, selumetinib.	• Nonscarring, diffuse, usually grade 1. • Eyelash trichomegaly. • Hair depigmentation.	Up to 17%
Hedgehog signaling pathway inhibitors		
• Vismodegib	• Nonscarring, reversible.	58–63% (all grades) 10–14% (grade 2).



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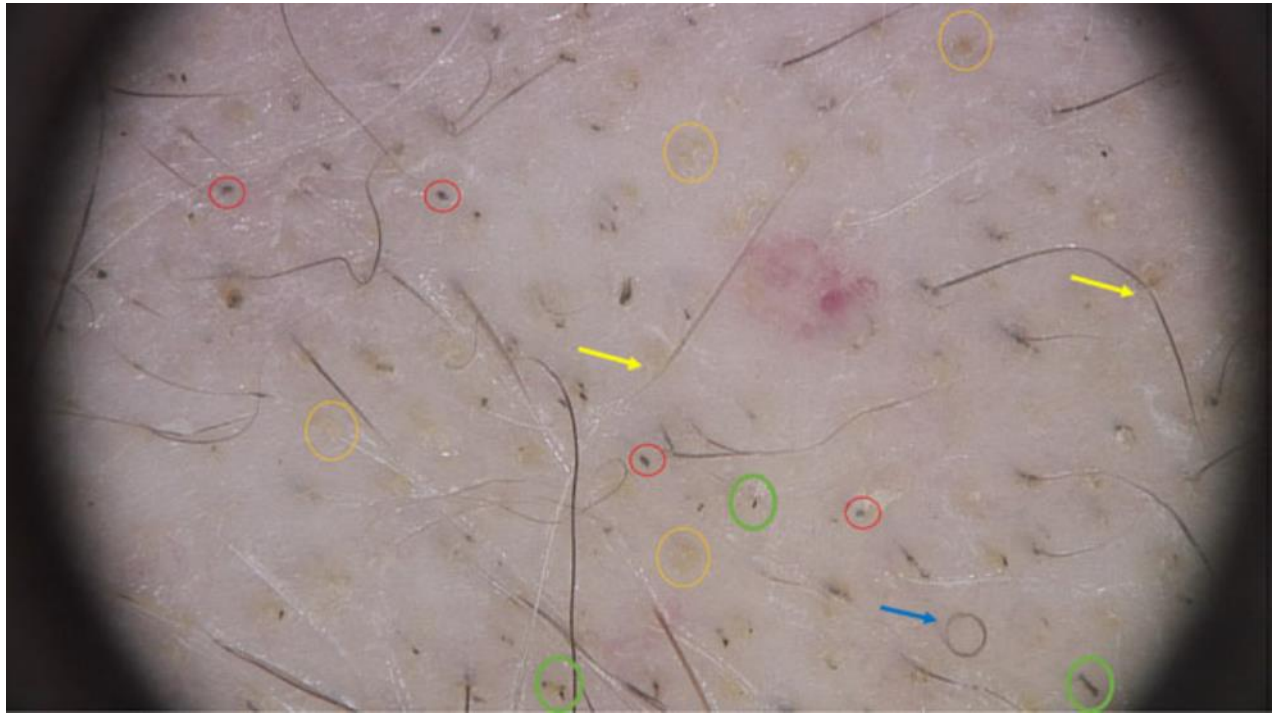
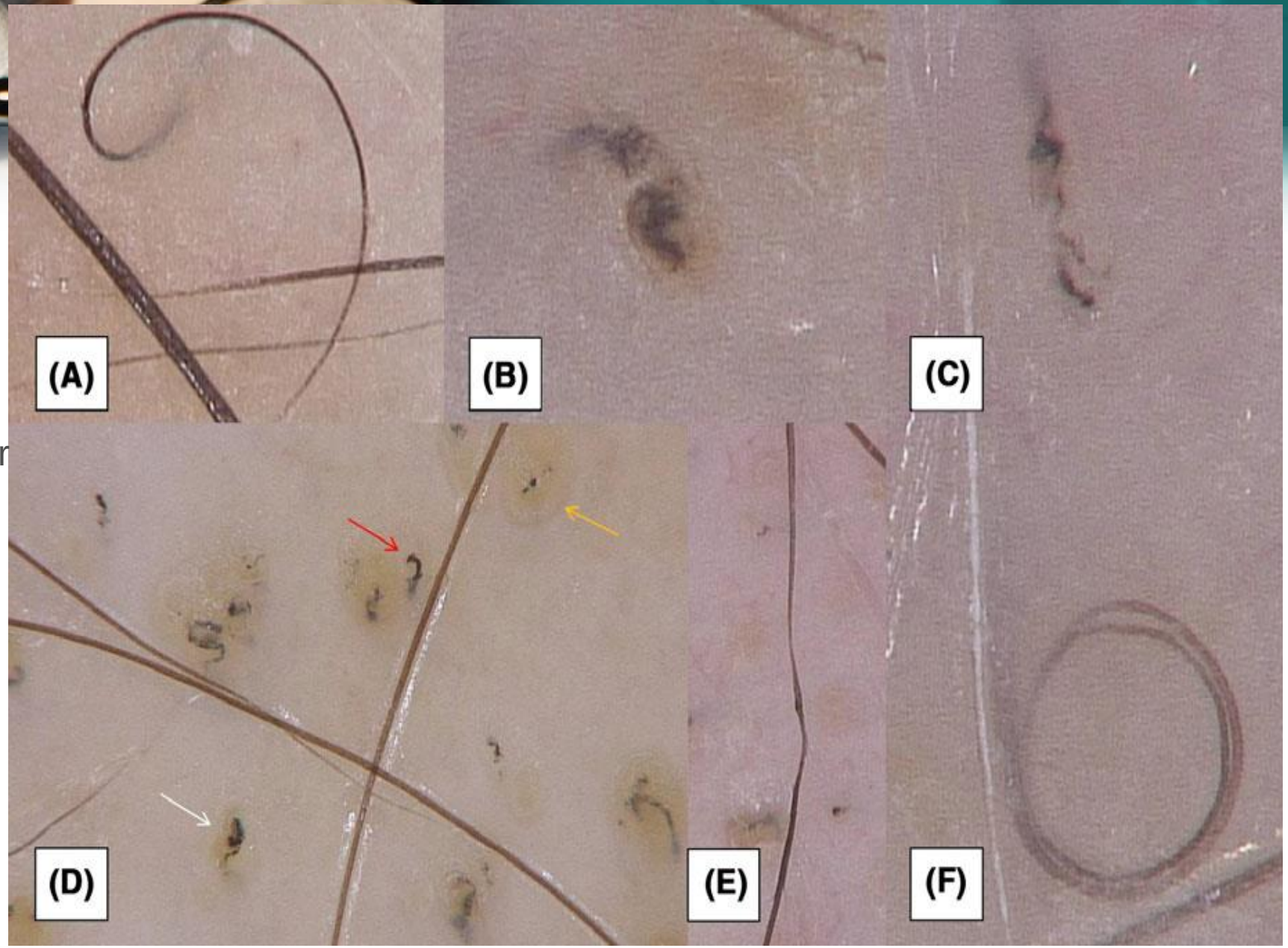
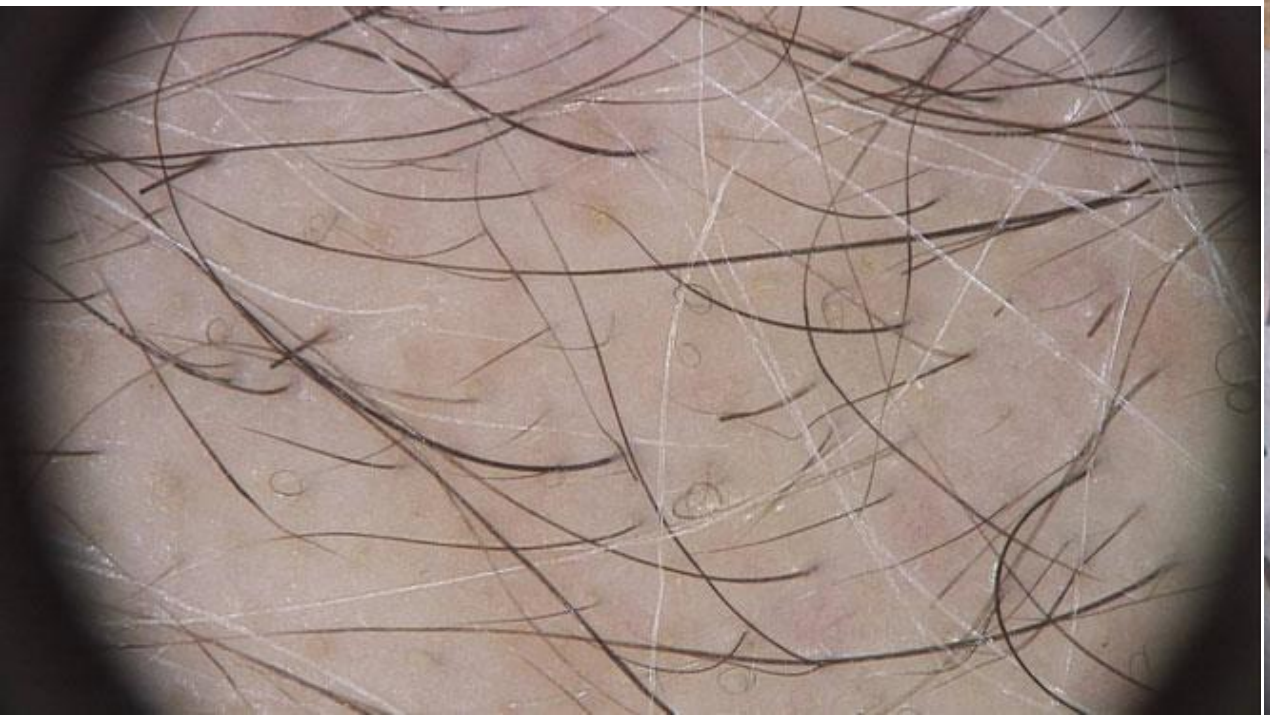
During Chemotherapy

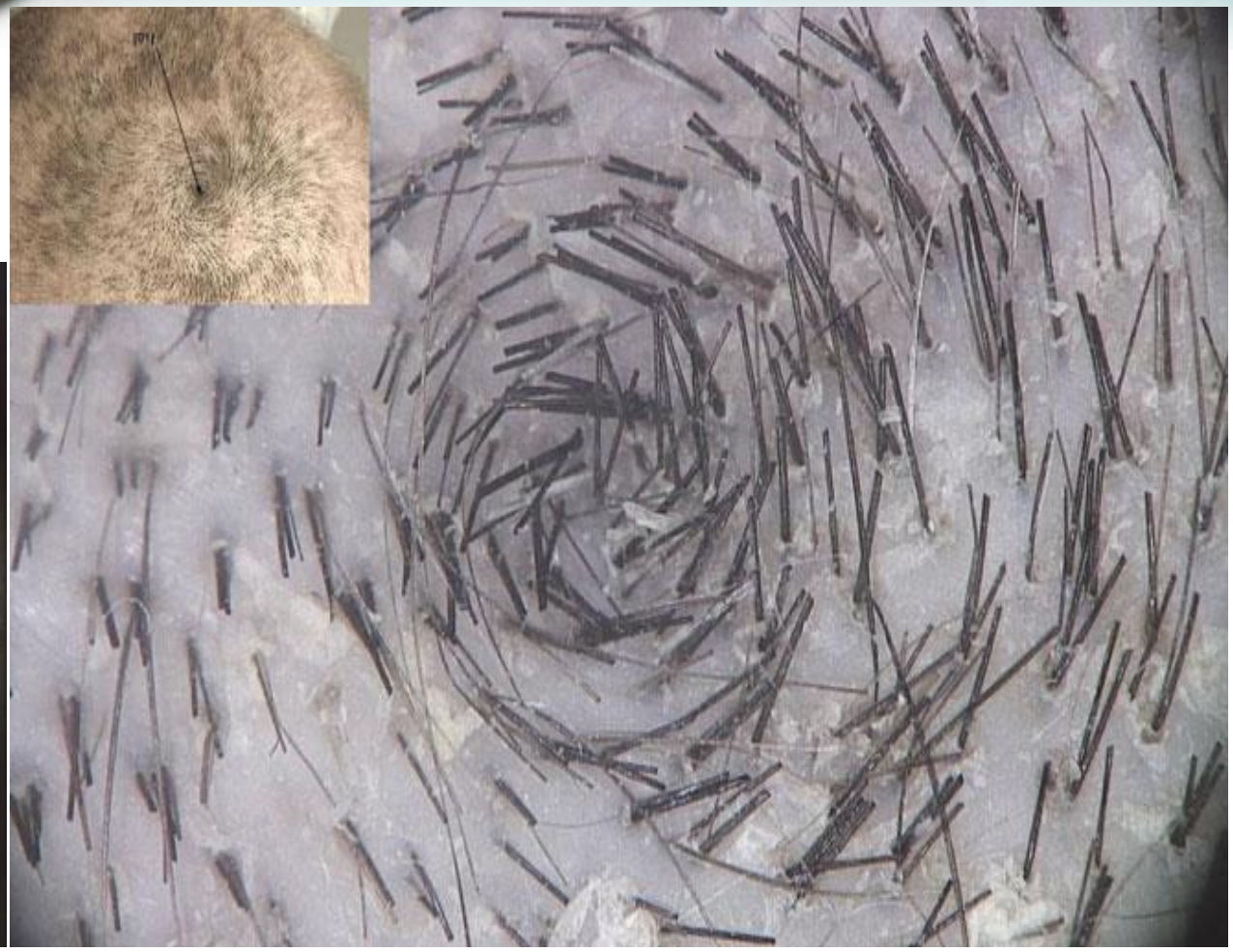


Some of the most typical CIA trichoscopical findings: pig tail hair (A), ingrown circle hair (F), flame hair (B, C, and D white arrow), comma hair (D, red arrow), yellow 3D dot (D, yellow arrow), pohl pinkus (E)



After Chemo





International Journal of Dermatology

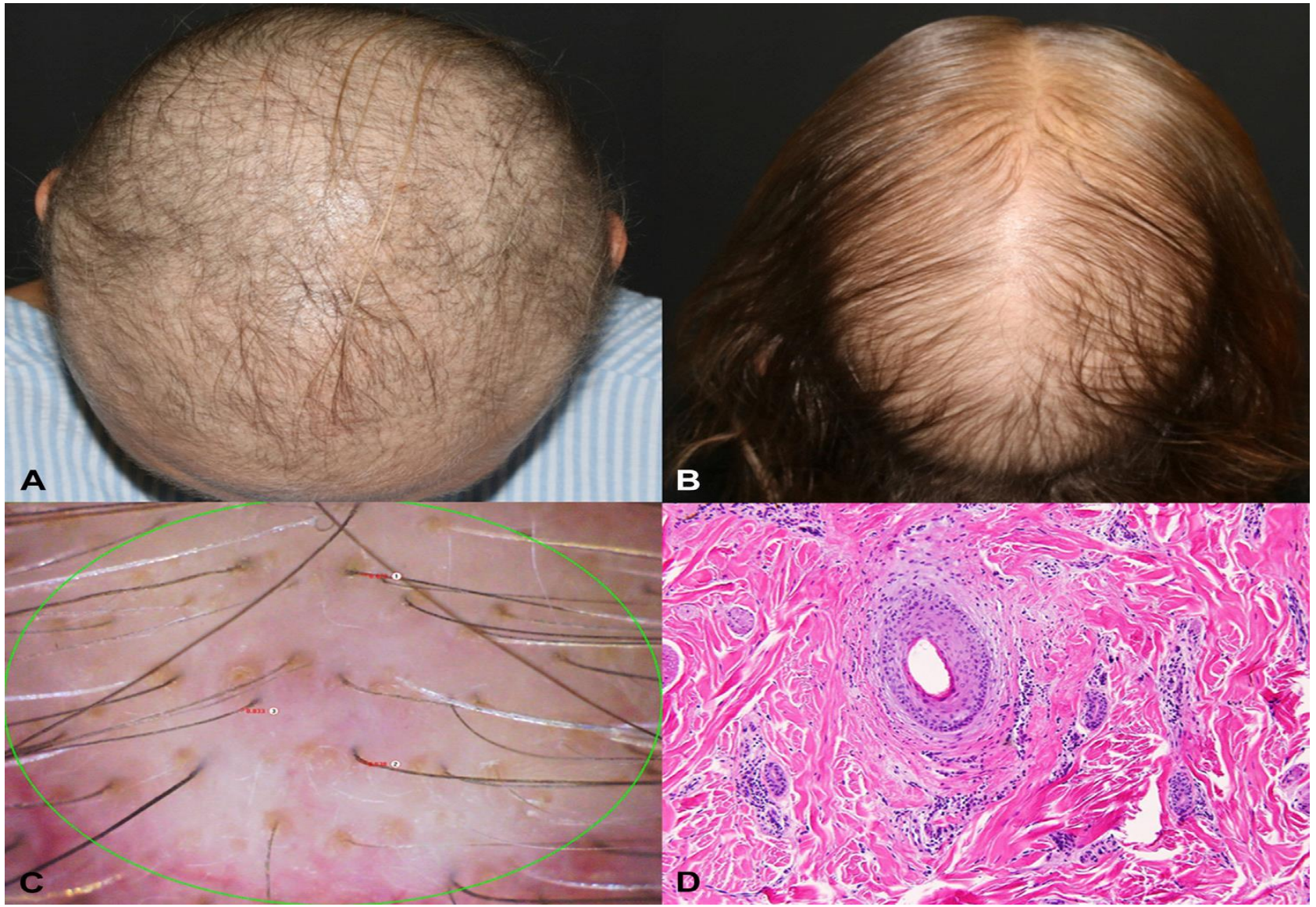
Review

Pathogenesis and treatment options for chemotherapy-induced alopecia: a systematic review

Belen Rubio-Gonzalez[1], MD, Margit Juhász[2], MD, Jamie Fortman[2], MSc, and Natasha Atanaskova Mesinkovska[2], MD, PhD

Table 2 Trichoscopic patterns[12]

Follicular patterns	Hair shaft characteristics	Interfollicular patterns
White dots Yellow dots Black dots	Specific features seen in hair shaft with various physical, genetic, and inflammatory disorders. Examples include: (1) Hair shafts of various lengths in trichotillomania. (2) Beaded hair shaft in monilethrix. (3) Brush-like hair fractures in trich-orrhexis nodosa. (4) Exclamation hairs in alopecia areata. (5) Peripilar tubular casts in lichen planopilaris.	Vascular patterns (interfollicular simple red loops, interfollicular twisted loops, arborizing red lines) Pigment patterns



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HISTOPATHOLOGY AND PATHOBIOLOGY

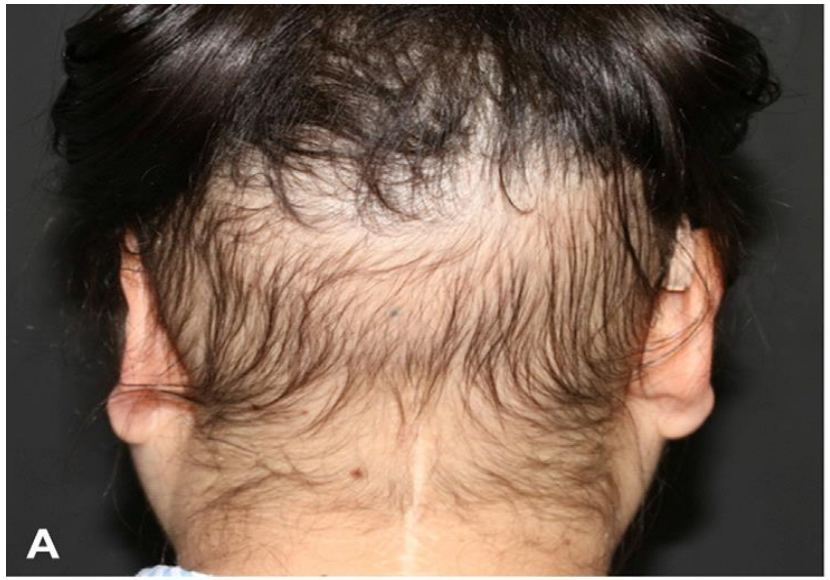
- A nonscarring pattern is usually described in pCIA, with an *increased number of miniaturized and telogen hair follicles*
- Other reported histopathologic features of pCIA include: *scarring alopecia with concentric fibrosis and a discrete perifollicular lymphoid cell infiltrate*

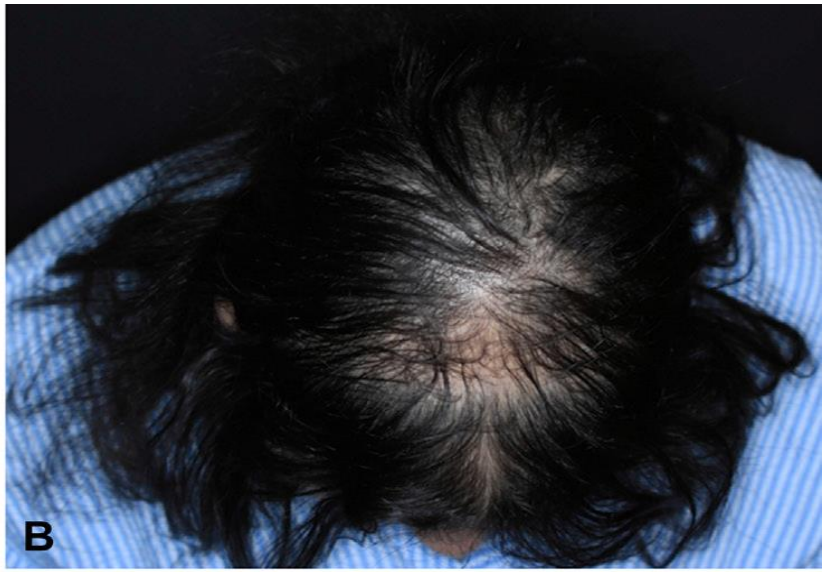
Persistent radiotherapy-induced alopecia

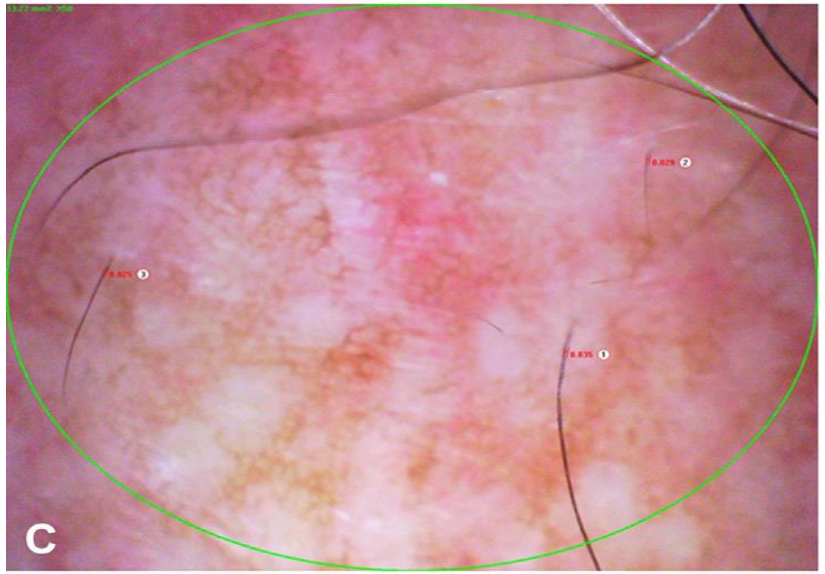
- Hair regrowth generally occurs within 2 to 4 months after radiation to the head and neck.
- pRIA is the total or incomplete hair regrowth 6 months after the completion of radiotherapy and is commonly related to high-dose radiotherapy to the scalp
- correlated with radiotherapy dose to the hair follicles in a particular radiotherapy field(a 50% risk of pRIA with fractionated follicular dose of >43 Gy)

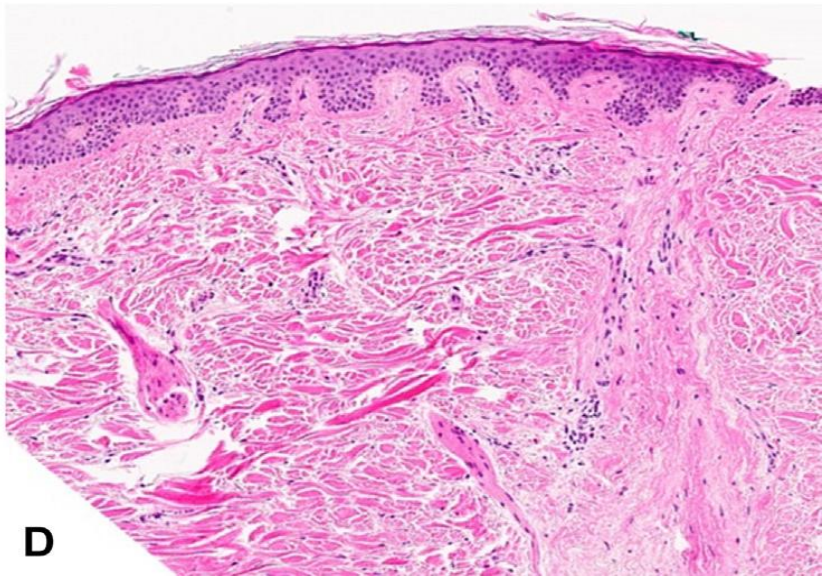
- Clinical presentation of pRIA includes *well defined alopecic and atrophic skin confined to the area of radiotherapy* and is usually asymptomatic

- *Occipital, parietal, and temporal* scalp are commonly focal sites of radiotherapy for **brain metastases** and central nervous system tumors, such as **glioblastoma and astrocytoma**









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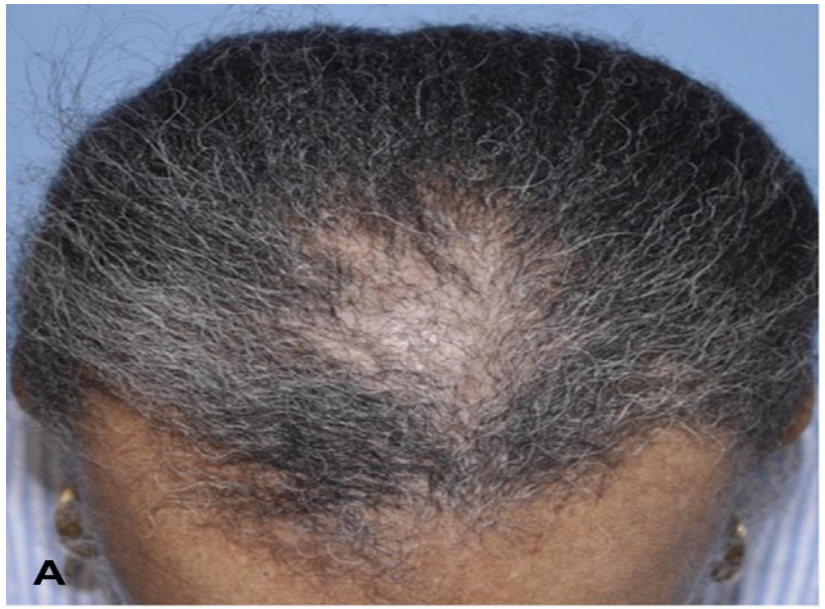
- In pRIA the predominant features are compatible with a scarring alopecia and it is likely that similar histopathologic features are present in permanent surgery-induced alopecia (*including fibrosis along with decreased numbers or absence of hair follicles*).

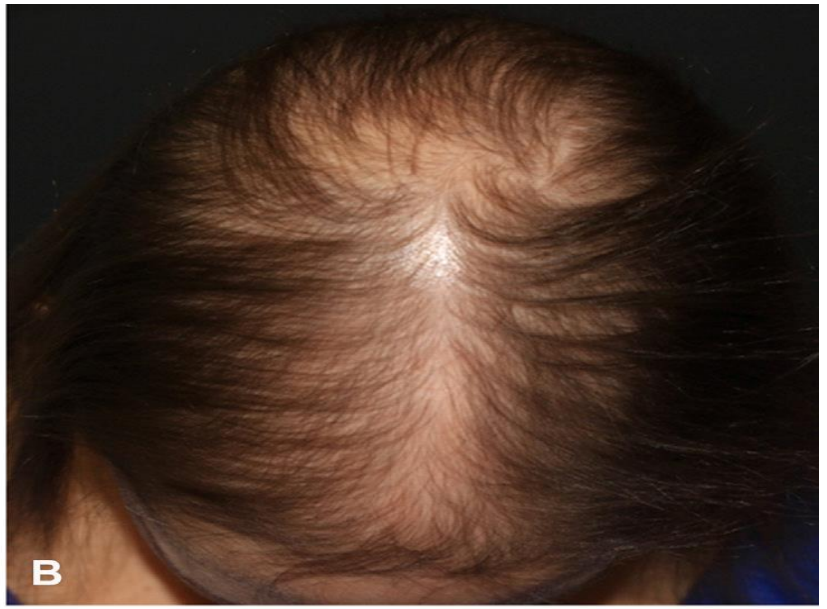
Endocrine therapy- induced alopecia and hirsutism

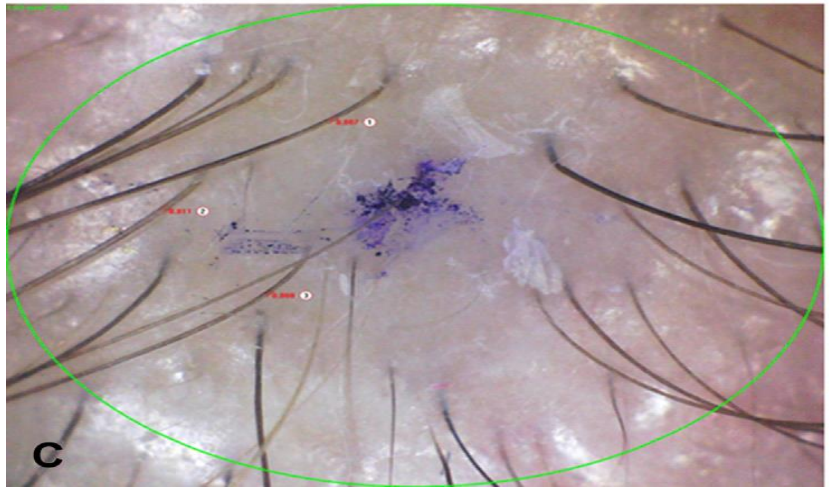
- Endocrine therapies (ETs) are standard of care in survivors of hormone receptor-positive breast cancer
- ETs, including :
- selective estrogen receptor (ER) modulators (eg, *tamoxifen and toremifene*)
- ER antagonists (*fulvestrant*)
- Aromatase inhibitors (eg, *anastrozole, letrozole, and exemestane*) {**the highest incidence (25%)**}
- Gonadotropin-releasing hormone agonists (*leuprolide*)
- usually administered for 5 to 10 years in the adjuvant setting to reduce the risk of recurrence

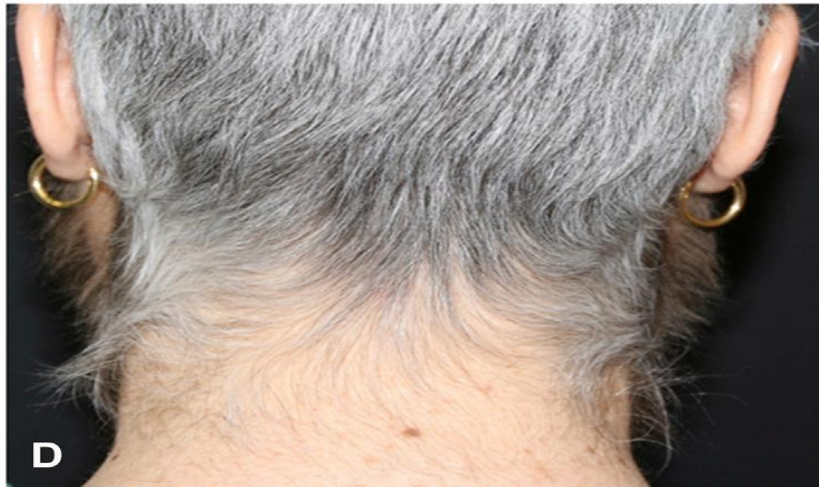
- In a retrospective study of 112 breast cancer patients with EIA, causal agents included aromatase inhibitors **in 67%** and tamoxifen **in 33%** of patients. The mean time to alopecia development was **16.8 months** (range 1-91 months).
- These patients usually present with ***frontoparietal hairline recession***
- Trichoscopic features observed in patients with EIA include the concomitant presence of vellus and terminal hairs, also a ***hallmark of androgenetic alopecia.***
- Iatrogenic **hirsutism** has been reported **in<10%** of survivors receiving ET for breast cancer

- In patients treated with cytotoxic chemotherapy followed by ET (the majority of hormone receptore 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).**









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Postsurgery-induced alopecia and localized hypertrichosis

- Alopecia and scarring in cancer survivors usually appears in sites from which
  - *biopsy specimens were obtained, placement of catheters, and surgeries to resect scalp and brain primary or metastatic tumors.*
- The clinical presentation of surgery induced alopecia includes the *linear shape of the scar on the scalp*
- When additional radiotherapy is combined with surgery, a *geometric alopecic patch confined to the area of radiotherapy* is also observed

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- Results from a hair follicle ablation 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
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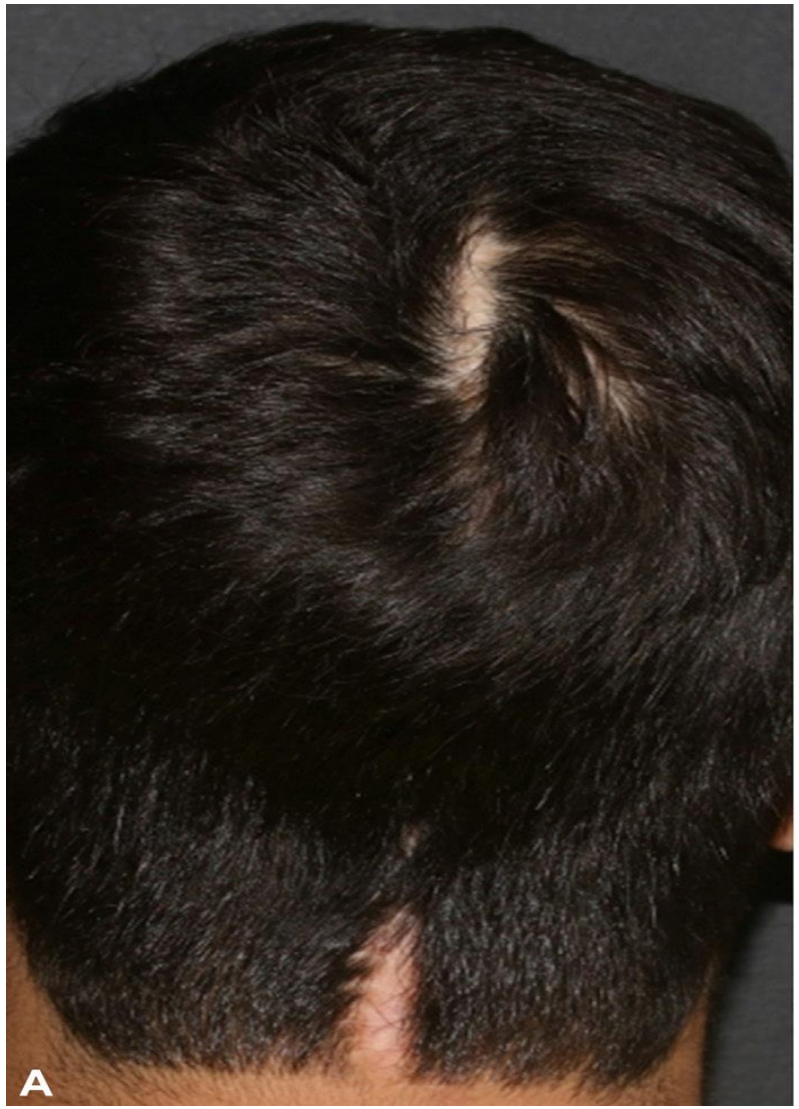

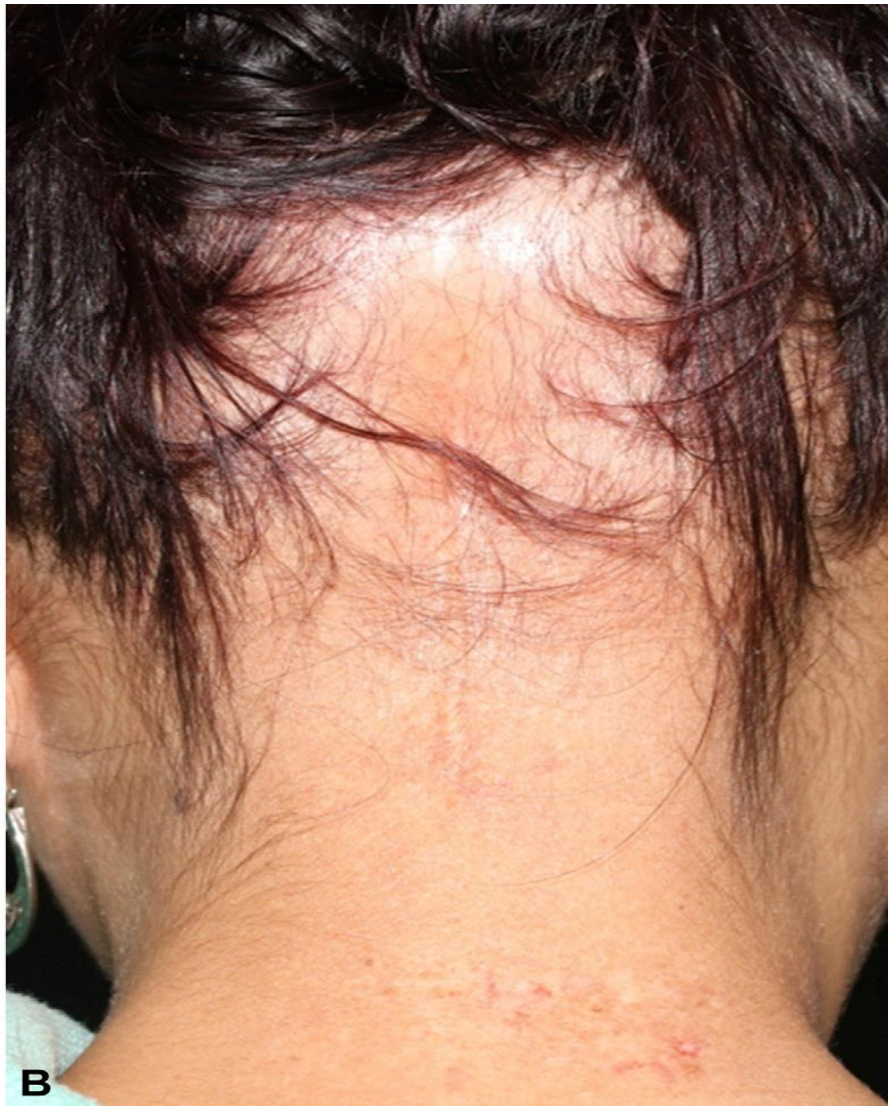

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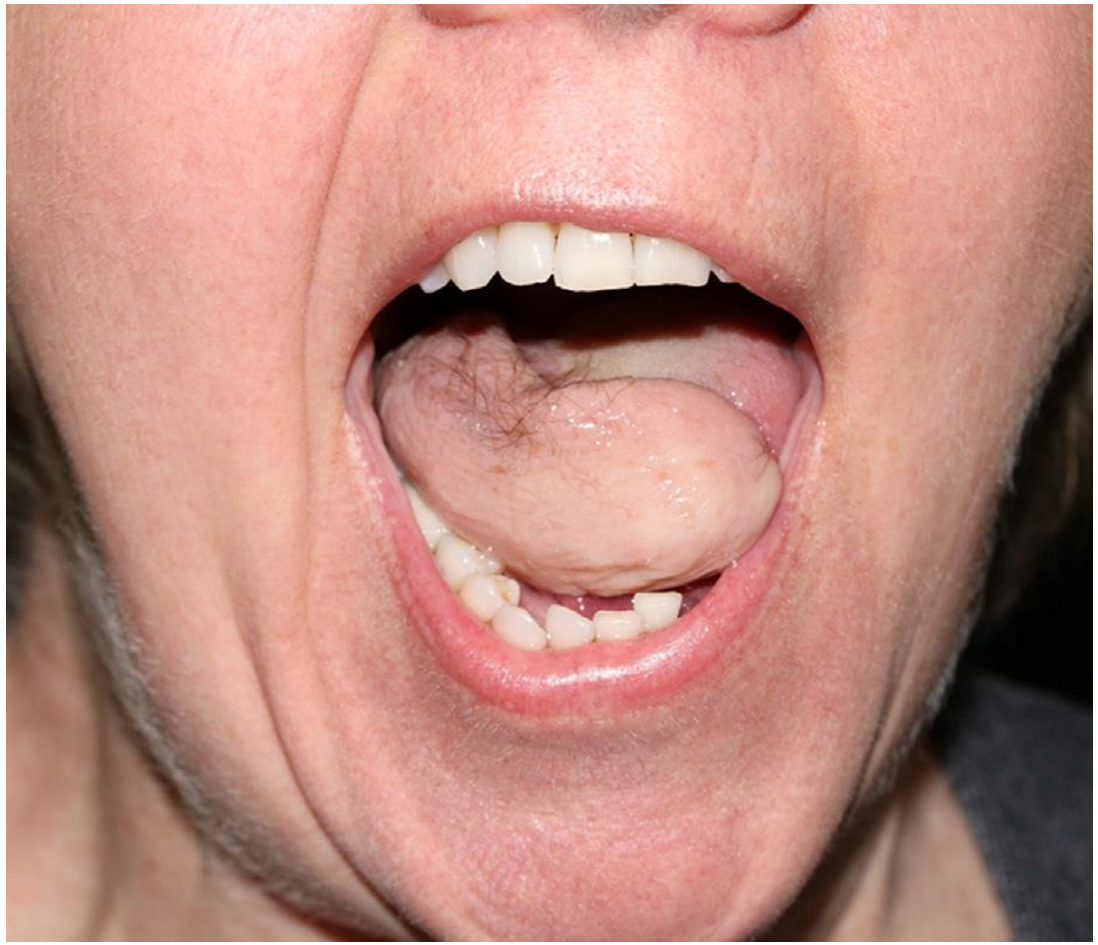

Persistent hair changes induced by other anticancer therapies

- Anticancer therapies, such as **Vismodegib, and Immunotherapies** have reportedly caused persistent alopecia after drug interruption or discontinuation.

- **Chronic Graft Versus Host Disease** after stem cell transplantation may induce both *diffuse alopecia (15.6%) and alopecia areata (20%)*

The pathogenesis of Alopecia

- Direct toxicity to the *highly proliferative matrix keratinocytes, as well as the follicular pigmentary system* (As the hair matrix and dermal papilla are very sensitive to toxins, some chemotherapeutics may lead to rapid apoptosis.)
- *irreversible damage to epithelial hair follicle stem cells (eHFSCs)* in the bulge region of the hair follicle are thought to play a crucial role in PCIA.

- **eHFSCs** in the bulge have a **low proliferation rate** and are generally **less sensitive to chemotherapy** but are highly **sensitive to ionizing radiation.**

- anticancer therapies associated with pCIA deplete the eHFSC pool that is vitally required for hair follicle regeneration during the next hair cycle.

- **Estrogens and Androgens** act as potent hair growth modulators
- 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*

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)			
Taxane-based chemotherapy	Breast	259 (30)	Nonscarring diffuse alopecia and lightening in 53% of cases; a pattern similar to androgenetic alopecia in 46.2%; persistent changes in texture are common; scarring has been reported in 2 cases; eyelash, eyebrow, axillary, and pubic hair frequently associated
Cyclophosphamide-based chemotherapy	Leukemias, lymphomas, and solid tumors	67 (17.5)	
Busulphan-based chemotherapy	Hematologic malignancies	35 (9.2)	
Other chemotherapies (including cisplatin, methotrexate, and vincristine)	Solid tumors and hematologic malignancies	21 (5.5)	
Radiotherapy (pRIA)			
Photon radiation	Primary CNS tumors and metastasis	227 (in ~70)	Scarring and nonscarring features depending on dose; geometric alopecia and atrophic skin; diffuse alopecia in total cranial irradiation and when combined with cytotoxic chemotherapy; commonly affects the occipital, parietal, and temporal areas
Proton radiation	Medulloblastoma and ependymoma	13 (75)	
Endocrine therapies (EIA)			
Selective estrogen receptor modulators (tamoxifen, toremifene, and raloxifene)	Breast and ovarian cancers	625 (in ~15)	Nonscarring features; predominantly women with a pattern similar to androgenetic alopecia; diffuse hair thinning and lightening over the entire scalp is also reported
Aromatase inhibitors (anastrozole, letrozole, and exemestane)	Breast and ovarian cancers	223 (in ~25)	
Estrogen receptor downregulator (fulvestrant)	Breast and ovarian cancers	17 (in ~5)	
Luteinizing hormone–releasing hormone agonist (leuprolide)	Breast and prostate	28 (in ~10)	
Somatostatin analog (octreotide)	Growth hormone–producing tumor (pituitary)	3 (in ~7)	
Surgery			
Neurosurgical and scalp procedures (CNS and scalp tumor biopsy and excisions, catheter placements)	Primary CNS tumors and tumors in hair-bearing areas	Scarring/disfigurement 1143 (in ~100)	Linear scar on the scalp; hypertrophic scars may be observed; could be associated with persistent radiotherapy-induced alopecia
Flaps (eg, radial forearm flap)	Head and neck tumors		Terminal hairs in undesirable areas, such as the oral cavity or face

General recommendations

- have realistic expectations of therapy outcome
- follow-up at least 3 months after alopecia therapy started
- laboratory analysis including, **ferritin, vitamin D, zinc levels, and thyroid function** may be requested if other causes of alopecia (eg, androgenetic, telogen effluvium, or thyroid-related) are suspected
- **camouflage techniques** should be provided (eg, 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 survivor's care

Scalp cooling

- Two recent studies, a randomized control trial by Nangia et al, and a prospective cohort study by Rugo et al, showed that more than ***50%*** of patients maintained more than ***50%*** of their hair after treatment using scalp cooling machines .

- Efficacy of scalp cooling varies based on multiple factors, including *chemotherapy type, regimen, cycles, and "capper" expertise*

Scalp cooling

- Scalp cooling devices are postulated to prevent CIA via 2 mechanisms:
- (1) vasoconstriction causing decreased delivery of cytotoxic agents to hair follicles, and
- (2) reduction in metabolic and biochemical activity of the hair follicle, resulting in less damage and turnover

- **scalp cooling does not increase the incidence of scalp metastases**
- SC should be considered a potential preventive option for CIA **in patients with solid tumors who are receiving high-risk CIA regimens.**
- Given its risk for scalp skin metastasis, Should be avoided in:
  - *patients with hematological malignancies (lymphoma, leukemia)in patients with cold agglutinin disease, cryoglobulinemia, and posttraumatic cold injury*
- Caution in patients with liver dysfunction because of reported poorer efficacy

Manual Scalp Cooling or Cold Caps	Machine Scalp Cooling Systems
-Rented by the patient and brought to infusion center by patient -Stored in either freezers provided by the facility or dry ice coolers provided by patients -Typically requires changing caps ~ every 20- 30 minutes before, during, and after chemotherapy treatment -Brands include: Penguin Cold Caps™, Arctic Cold Caps™, Wishcaps™, Warrior Caps™, Chemo Cold Caps™ -Usually rented on a per monthly basis	-Purchased by the facility and maintained at the infusion center -Requires one-time cap fitting -Machine delivers a coolant throughout the cap, keeping the scalp at a constant temperature -Patient wears cap ~30 minutes before, during, and typically 90 minutes after chemotherapy with no cap changes required -Brands include: DigniCap™ or Paxman™ (FDA approved in 2015 and 2017, respectively) -Pay for use of machine +/- facility fee

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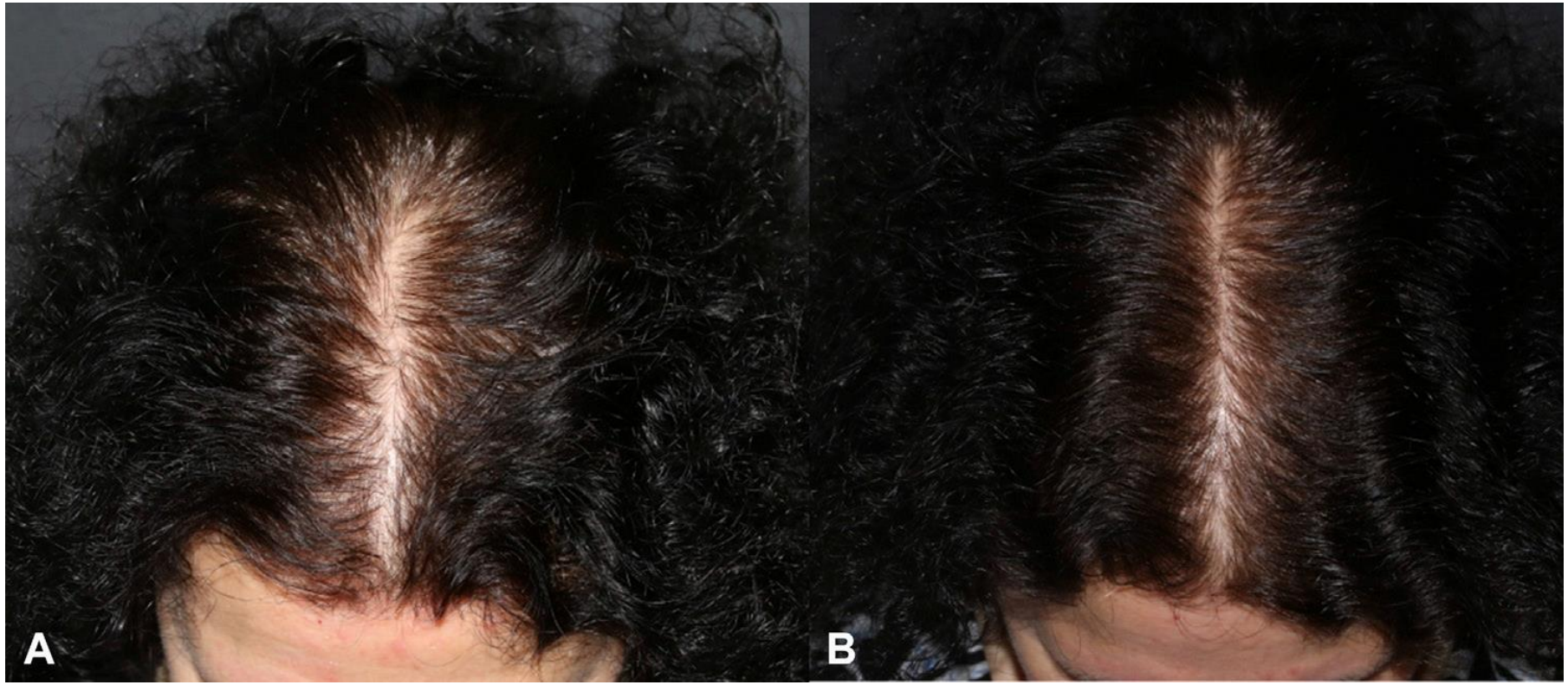
Minoxidil

- One study assessed the efficacy of minoxidil 2% applied twice daily in preventing alopecia in patients with solid tumors treated with doxorubicin-containing chemotherapy.
- In a second trial performed in breast cancer patients receiving adjuvant chemotherapy with fluorouracil,doxorubicin, and cyclophosphamide supplemented with methotrexate and vinblastine, topical 2% minoxidil did not prevent alopecia, ***but it did speed up the regrowth of hair.***

(A) baseline and (B) 6 months after therapy with topical minoxidil foam 5% twice a day



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Bimatoprost

- Topical bimatoprost (0.03%) is a prostaglandin analog that successfully enhances eyelash growth in patients with alopecia areata affecting the eyelashes.
- In a randomized trial of 130 patients with idiopathic or chemotherapy-induced eyelash loss. Clinical improvement was noted in the 37.5%
- Results were most pronounced at 12 months from the baseline assessment

Topical bimatoprost 0.03% solution for pCIA of the eyelashes (A) baseline and (B) 6 months after therapy.

- Soref et al. evaluated the efficacy of topical epinephrine and norepinephrine in preventing radiotherapy and chemotherapy-induced hair loss in mouse studies
- **Hypoxia signaling may help follicular cells to maintain their function and promote neogenesis, as well as reduce the amount of chemotherapeutic reaching the hair bulb.**
- Topical vasoconstrictors have the advantage of easier and long-lasting administration, typically once a day for several days

Drugs Under Investigation

- cyclin-dependent kinase-2 (CDK-2)
- topical cyclosporine
- systemically and topically administered EGF and FGF
- Pharmacologic strategies to block p53

Table II. Hair disorders in cancer survivors: Management and recommendations

Hair disorder	Intervention	Level of evidence
pCIA	CTCAEv5.0 grade 0: Alopecia prevention with scalp cooling	IV
	CTCAEv5.0 grade 1: Topical minoxidil foam 5% twice daily	
	CTCAE v5.0 grade 2: Spironolactone (escalating dose ≤200 mg/d) in addition to therapy recommended in alopecia grade 1 (caution because of the theoretical risk of hormonal stimulation of ER-positive tumors)	
	Oral minoxidil (potential adverse events should be considered)	
pRIA	CTCAE v5.0 grade 1: Topical minoxidil foam 5% twice daily, botulinum toxin type A: 5 U per 0.1 mL every 3 months for 12 months	
	CTCAE v5.0 grade 2: Scalp reconstruction (eg, simple excision or flaps, tissue expansion)	
	Hair transplant (if no fibrosis)	
EIA	CTCAE v5.0 grade 1: Topical minoxidil foam 5% twice daily	III
	CTCAE v5.0 grade 2: Spironolactone (escalating dose ≤200 mg daily) in addition to therapy recommended in alopecia grade 1 (caution because of the theoretical risk of hormonal stimulation of ER-positive tumors)	
Hirsutism and hypertrichosis	CTCAE v5.0 grade 1 (mild hair growth): Local therapy, such as threading, electrolysis, lasers	III
	CTCAE v5.0 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 (eg, oral cavity)	
Postsurgery alopecia	First line: Management of scar symptoms if present (topical or intralesional steroid, laser and light-based treatment)	IV
	Second line: Hair transplants	
	Scalp reconstruction (eg, simple excision or flaps, tissue expansion)	IIB
Eyebrow and eyelash alopecia	Topical bimatoprost solution 0.03%, hair transplants, microblading (medical tattoo)	
SCT (chronic GvHD, conditioning therapy for SCT with chemotherapy, 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 JAK inhibitors (level IV)	II-IV
	Conditioning chemotherapy or total body irradiation; follow the interventions of pCIA and pRIA, respectively	IV
Immunotherapies: CTLA-4 inhibitors (eg, ipilimumab), PD-1 receptor inhibitors (eg, nivolumab and pembrolizumab), PD-L1 inhibitors (eg, atezolizumab and avelumab)	Potent topical steroids	IV
Vismodegib	Not reported	No evidence

Continued

MANAGEMENT

Table 4 Current preventive and therapeutic approaches for chemotherapy-induced alopecia (CIA)[21–48]

Preventive approaches to reduce CIA		
Proven efficacy	**No proven efficacy**	**Currently under investigation**
• Scalp hypothermia "DigniCap" "Paxman"	• Topical calcitriol • Topical minoxidil (2% or 5%) • α-Tocopherol	• Topical vasoconstrictors; Epinephrine Norepinephrine • Cyclin-dependent kinase-2 • Interleukin-1 • p53 inhibitors • Epidermal growth factor • Fibroblast growth factor
Therapeutic approaches to speed regrowth after CIA		
• Topical minoxidil 2% • Bimatoprost ophthalmic solution 0.03%		