Eye Care in the Shadow of Cancer

COPE Course : 54531-SD

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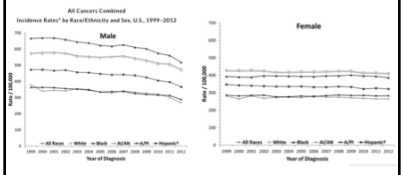
Financial Disclosure

I have nothing to disclose

Top 10 cancers in the US

1. Skin
2. Lung
3. Prostate
4. Breast
5. Colorectal
6. Kidney
7. Bladder
8. Non-Hodgkin's Lymphoma
9. Thyroid
10. Endometrial

Who gets cancer?



Lifetime risk of developing cancer in U.S.*

	Men	Women
All invasive sites	1:2	1:3 ←
Lung	1:14	1:17
Colon	1:21	1:23
Breast	1:769	1:8
Prostate	1:7	---
Skin Melanoma	1:38	1:61

* Surveillance Epidemiology and End Result (SEER) database 2010-2012

Lifetime risk of dying from cancer in U.S.*

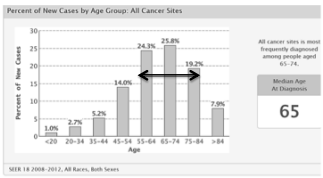
1:4 deaths in the US is attributed to cancer

	Men	Women
All invasive sites	1:3	1:5 ←
Lung	1:16	1:20 ←
Colon	1:50	1:55
Breast	1:3333	1:37
Prostate	1:39	---
Skin Melanoma	1:233	1:476

* Surveillance Epidemiology and End Result (SEER) database 2010-2012

When are people diagnosed with cancer?

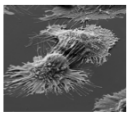
70% of patients diagnosed with cancer are between ages 55 and 85

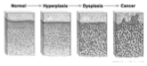


Distribution for cancer diagnosis by state

What is cancer?

- not 1 specific "disease" but a group of diseases



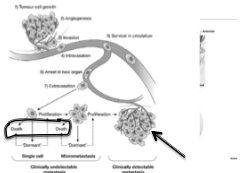


- characterized by uncontrolled/ abnormal growth of cells

Cancer spread

Locally by invasion of surrounding tissue

Distally t bloodstr lymphat circulati



How often does systemic cancer affect the eye

0.7% reported by Godtfredsen in 1944
4.7% reported by Albert et al in 1967

Between 15- 42% have known primary

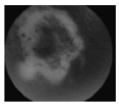
1/3 of patients with orbital metastasis have no previous diagnosis of cancer

Metastatic involvement to the eye

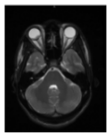
Metastasis site	Primary Site	Symptoms	Primary cancer already diagnosed?	Systemic metastases	Survival Rate	Reference
FROM LUNG	TO: Choroid 88% Iris 10% CB 2%	Blurry vision 73% Asx 23% Pain 14% Floaters 6%	NO: 44% YES: 56%		Mean: 12 months Med: 6, range 1-110 mo) 54% died within one yr of dx of ocular mets	Shah (2014) N = 374
FROM BREAST	TO: Choroid 85% Iris 3% CB + 1%	Blurry vision 75% Asx 7% Floaters 6% Photopsia 5%	NO: 3% YES: 97% in 14%, uvea was first metastatic site	92% had associated systemic mets One-year mets diagnosed; incidence of brain mets increased from 6% to 28%	Survival rate: 65% at 1 yr 34% at 3 yrs 24% at 5 yrs Avg 21 months	Demirci (2003) n= 264
TO IRIS	Breast 33% Lung: 27% Cutaneous: 12% Renal: 7%	Pain 32% Blurry vision 30% Asx 18% Mass 12%	NO: 13% YES: 81% Simultaneous: 6%	AFTER: 60% BEFORE: 30% Simultaneous: 10%	Mean time to death: 24 months	Shields CL, Kaliki S (2014) N = 106
To UVEA Choroid 88% Iris 9% CB 2%	Breast 47% Lung 21% Unknown 17% GI tract 4%	Blurry vision 70% Flashes/floaters 12% Asx 11% Pain 7%	NO: 34% YES: 66% Eventual primary site: 35% lung 7% breast 1% GI, prostate 51% unknown	70% had other mets • 38% disseminated • 20% lung • 14% bone • 12% liver	Of those without known primary, 45% eventually died of diffuse metastatic disease 34% doing well no other mets	Shields CL and Shields JA (1997) n = 520
To EYE & ORBIT	Breast 40% (77% of F) Lung 30% (40% of M) Kidney 4% Unknown 18%	Blurry vision 80% Pain 22% Exophthalmos 11% RD 11%	NO: 46% YES: 59% Simultaneous: 3%	15% developed mets < 1 yr after dx of primary 12% 1-2 years 2.7% > 10 yrs	85% died at mean follow up of 7 months	Ferry AP, Font (1974) N = 227

Direct involvement by metastasis

Choroid most common ocular structure involved

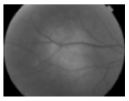


90% of choroidal metastasis in posterior pole



>70% are single lesions but may have multiple

Choroidal melanoma

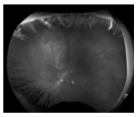


Varying pigmentation (creamy to heavily pigmented)

Elevated with dome shape

Overlying and/or adjacent serous detachment

Ultrasonography "hollowness"



August 2009

Choroidal Nevus Transformation Into Melanoma

Analysis of 2514 Consecutive Cases

Carol L. Shields, MD; Minoru Furuta, MD; Edwina L. Berman, BS; et al

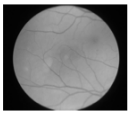
> Author Affiliations | Article Information

Arch Ophthalmol. 2009;127(8):981-987. doi:10.1001/archophthalmol.2009.151

2% in 1 year

9% in 5 years

13% in 10 yrs



Nevus vs. Melanoma TFSOM Mnemonic

T = Thickness >2 mm

F = Fluid

S = Symptoms

O = Orange pigment

M = Margin touching ONH

1 feature has 38% chance of growth in 5 years

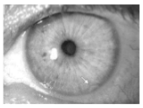
2 or more have 50% chance of growth in 5 years

Iris metastasis

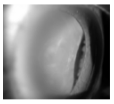
Solid in appearance with Cream/pink in color

Frequently seen in isolation

Frequently seen inferiorly due to shedding of tumor cells

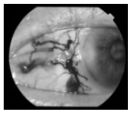


Ciliary Body metastasis



Displaces the iris root forward

Feeder vessels may be observed



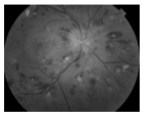
May only be visible after pupillary dilation

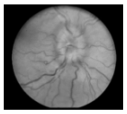
Poor prognosis due to dx at late stage

Optic nerve involvement

Disc swelling c/s retinal hemes

Significant drop in VA





VA improves with treatment

Poor prognosis given advanced disease status

Orbit. 2009;28(2-3):153-9.

Orbital metastasis: clinical features, management and outcome.

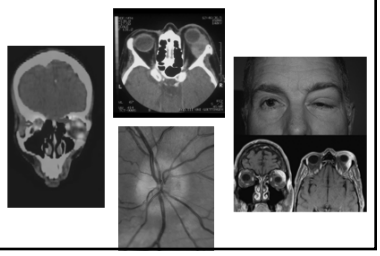
Valenzuela AA[1], Archibald CW, Fleming B, Ong L, O'Donnell B, Crompton J J, Selva D, McNab AA, Sullivan TJ.

Clinical symptoms		Primary	
Diplopia	48%	Breast	29%
Pain	42%	Melanoma	20%
	%		%

Reported survival was 28% at 18 months following diagnoses of orbital metastases

Clinical findings		CT Location	
Proptosis	63%	Orbital fat	43%
Strabismus	62%	EOM	28%
Vision loss	49%		

Orbital metastasis considerations



Blurred vision and dry eye

41 yo WF experiencing gradual blur OU when reading for 3 mos which started after her last exam 5 mos prior to exam

States use of lubricant drops w/o any improvement of vision

Chemotherapy treatment for stage 4 breast cancer x 2 years

Pertinent clinical findings

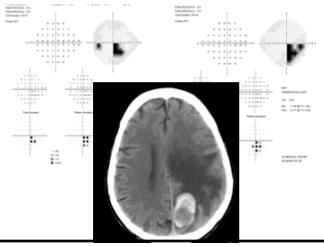
Perrl (–) APD

No motility abnormality

BVA OD: 20/30 (subjective blur OD/OS)
OS: 20/30 (was 20/20 OD/OS 5 mos earlier)

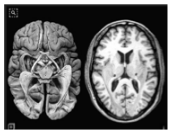
Confrontation VF : Some facial blur OD /OS

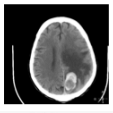
Anterior segment and fundus: Unremarkable



Intracranial metastasis considerations

Optic radiations





72 yo WM with 2 day onset of horizontal diplopia evaluated in local ER previous day

Discharge diagnosis:
- right VI nerve palsy from diabetes
- recommend eye evaluation if it gets worse

2 year history of DM

1 year history of Stage 4 squamous carcinoma of soft palate s/p surgery, chemotherapy and radiation

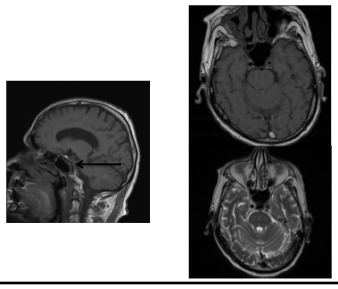
OD eso posture with left abduction deficit

No APD

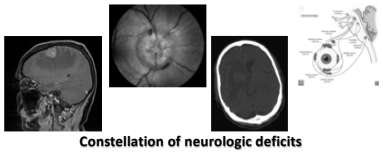
BVA 20/30 OD
20/20 OS

Mild ptosis OS

Dilated exam:
Sharp disc margins
No diabetic retinopathy



Intracranial Involvement



Constellation of neurologic deficits

Elevated ICP, CN palsy, motility

Paraneoplastic syndromes

Seen in less than 1% of cancer patients.

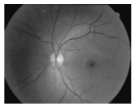
Most commonly associated with lymphoma, lung, ovarian and breast cancers

Results from humoral OR antigenic response to the cancer

Ocular involvement of PNS

CONDITION	ANTIGENIC TARGET
Carcinoma associated retinopathy (CAR)	photoreceptors (cones)
Melanoma associate Retinopathy (MAR)	bipolar cells
Bilateral diffuse melanocytic uveal Proliferation (BDUMP)	uveal tissue

CAR



May precede dx of cancer by months to years

Painless vision loss over weeks to months

Relatively normal appearance to fundus/ possible disc pallor

Photoreceptor loss on OCT macular scan

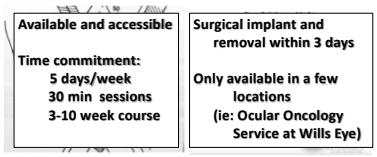
Basics of cancer treatment

Curative treatment options are offered when possible.

The primary goal of treatment for metastatic disease is to control the rate of growth and offer symptomatic relief when possible

Most people that die of cancer, succumb to their metastatic disease

Radiation of ocular structures



Available and accessible	Surgical implant and removal within 3 days
Time commitment: 5 days/week 30 min sessions 3-10 week course	Only available in a few locations (ie: Ocular Oncology Service at Wills Eye)
External beam radiation	Radio plaque implant

Radiation terminology

Rad: amount of energy absorbed by 1 Kilogram of living tissue

Gray (Gy)= 100 Rads

1 Gy= 100 cGy

Chest x-ray= 1 cGy

Dosages for radiation treatment

Tissue	Dose, cGy
Brain	6000
Spinal Cord	4500
Heart	4500
Intestine	4500
Liver	3000
Lung	2000
Kidney	2000
Bone Marrow	250

Ocular tissue tolerance of radiation

Table 1. Tolerance doses of the optic nerve, retina, ocular surface and lens.

Ophthalmic structure	Manifestation of toxicity	TD 5/5 (Gy)	TD 50/5 (Gy)
Optic nerve	Optic neuropathy	> 55	> 65
Retina	Retinopathy	45–50	55
Ocular surface	Severe dry eye	35	50
Lens	Cataract	10	18

TD = tolerance dose.

Ophthalmic and adnexal complications of radiotherapy. Shane R. Durkin,Daniel Roos, Braden Higgs, Robert J. Casson and Dinesh Selva. ACTA Ophthalmologica Scandanavia 2007.

Ophthalmic and adnexal complications of radiotherapy

ACTA SCANDANAVIA 2007

Shane R. Durkin,[1] Daniel Roos,[2] Braden Higgs,[2] Robert J. Casson[1,3] and Dinesh Selva[1,3]

[1]Department of Ophthalmology and Visual Sciences, University of Adelaide, Royal Adelaide Hospital, Adelaide, South Australia, Australia
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[3]Department of Medicine and Surgery, University of Adelaide, Royal Adelaide Hospital, Adelaide South Australia, Australia

ABSTRACT.
The role of radiotherapy in ophthalmic practice continues to grow. This growth has seen an expansion of indications for radiotherapy, a refinement of the modalities that can be used and a reduction in the ocular and adnexal complications that result from this form of therapy. The compendium of indications for radiotherapy in ophthalmology continues to grow and now includes many conditions such as the treatment of lid and adnexal disease, ocular surface disorders and both benign and malignant disease of the posterior segment and optic pathways. The radiotherapeutic modalities employed to manage these conditions are numerous and include both radioactive plaques (brachytherapy) and external beam radiation techniques. New techniques such as stereotactic radiosurgery are delivering benefits in the management of conditions such as optic nerve sheath meningioma, where the treatment of this bleeding and occasionally life-threatening intracranial neoplasm now results in fewer adverse effects. The purpose of this review is to give a brief overview of the indications and treatment modalities, and a more in-depth discussion of the potential side-effects when radiotherapy is used for ocular and periorbital disease.

The efficacy of radiotherapy is determined by aspects of radiation delivery and the biological consequences to the tumour and normal tissues. By giving radiation doses over a number of fractions, damage to normal tissues can be reduced due to the repair of sublethal damage between fractions and repopulation of cells during the course of treatment. Although the radiosensitivity of different tumours varies considerably (Steel 1997), in general tumour cells are more susceptible to radiation than normal tissues as they are less able to reduce the amount of DNA damage inflicted by radiation and have less fidelity of DNA repair.

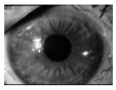
Just as tumour cells differ in their vulnerability to ionising radiation, so

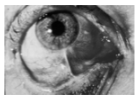
Eyelid involvement from radiation treatment

Condition	Duration
Erythema	Temporary
Malposition (entropion/ectropion)	Temporary or permanent
Madarosis	Temporary (possible permanent >50Gy)
Trichiasis	Variable

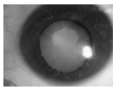
Ocular sequella of local radiation

Anterior segment:
Eyelids
Lacrimal system
mild to KCS





Conjunctiva
Cornea
Sclera
Lens

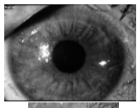


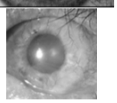
Time to onset of ocular xerophthalmia

< 30 Gy: not commonly seen

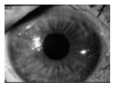
30–45 Gy: 4–11 years

> 57 Gy: corneal NV/ apparent 10 mos





Potential xerophthalmia treatments



Ocular lubricant gtts/ung

Restasis/Xiidra?

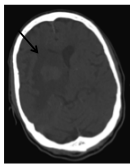
Surgical procedures
ie: Tarsorraphy ?

Autologous serum drops?

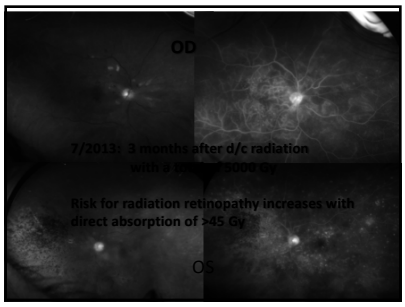
Manifestation of radiation damage

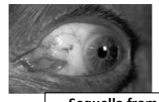
63 yo BM with known CNS lymphoma

Had head radiation over 13 month period



		OD	OS
	9/22/2006	20/20	20/20
	8/24/2009	20/20	20/20
	3/10/2012	20/25	20/25
	(dx with CNS Lymphoma, radiation started)		
6 mos → after rad	10/24/2012	20/40	20/40
	4/22/2013	20/80	20/80
	(Last dose of radiation received 04/2013)		
	7/1/2013	20/400	20/400
	9/9/2013	CF	CF
	5/23/14	CF	CF

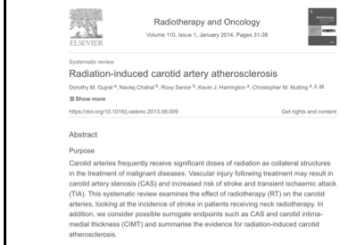




Scleral atrophy 10 yrs post brachytherapy

Sequella from previous radiation treatment may manifest months to years following completion of radiation treatment in distant past.

1 yr post orbital radiation



Radiotherapy and Oncology

Volume 110, Issue 1, January 2014, Pages 31-38

Systematic review

Radiation-induced carotid artery atherosclerosis

Dorothy M. Gujral [a], Navtej Chahal [b], Roxy Senior [b], Kevin J. Harrington [a], Christopher M. Nutting [a,*]

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https://doi.org/10.1016/j.radonc.2013.08.009 Get rights and content

Abstract

Purpose

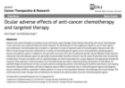
Carotid arteries frequently receive significant doses of radiation as collateral structures in the treatment of malignant diseases. Vascular injury following treatment may result in carotid artery stenosis (CAS) and increased risk of stroke and transient ischaemic attack (TIA). This systematic review examines the effect of radiotherapy (RT) on the carotid arteries, looking at the incidence of stroke in patients receiving neck radiotherapy. In addition, we consider possible surrogate endpoints such as CAS and carotid intima-medial thickness (CIMT) and summarise the evidence for radiation-induced carotid atherosclerosis.

Chemotherapy and the eye

Incidence of complications from chemotherapy

38% of reported involvement is rare

16.4% common or somewhat common



Ocular adverse effects of anti-cancer chemotherapy and targeted therapy

No reported incidence- however under-estimation and under-reporting is suspected due to other life threatening situations

Chemotherapy

53 yo BF diagnosed with breast CA 1 year ago

Treated with tamoxifen for past year

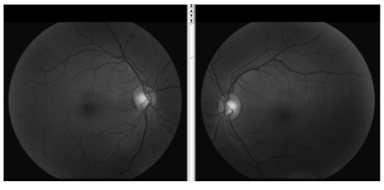
Wants glasses for reading

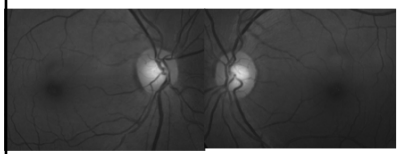
Pertinent case findings

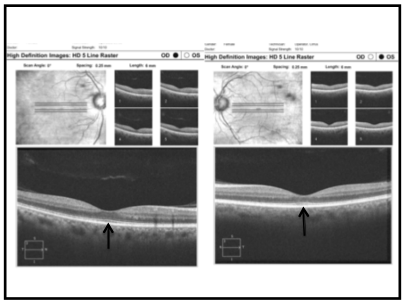
BVA 20/20 OD
20/20 OS with subjective blur

No APD

Fundus findings…….







2011

2017

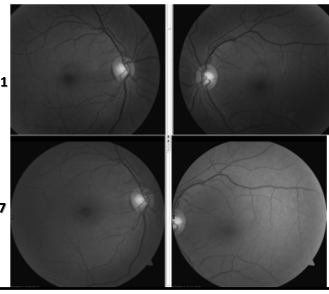


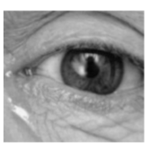
Photo courtesy of Lynn E. Harman, MD. Point Reyes Beach North.

Recognizing ocular complications of chemotherapy before they result in irreversible injury involves taking a clinical history and performing a basic eye examination.

Ophthalmic Complications Related to Chemotherapy in Medically Complex Patients

Lynn E. Harman, MD

Medscape 2016: Cancer Control. 23 (2):150-6. ISSN 1526-2359



Epiphora

Table 5. — Clinical Inferences Associated With Excessive Tearing

Relevant History and Finding	Clinical Inference	Potential Drug Implication
Excessive tearing associated with mass in medial canthal region	Consider mechanical obstruction of nasal-lacrimal outflow Swelling in medial canthal region may or may not show signs of inflammation	No drug implications In context of cancer treatment, consider infection or metastatic tumor
New-onset tearing associated with mild red eyes, ocular discomfort, or photophobia	Consider secondary to ocular surface disorder (keratitis or conjunctivitis) Diagnosis of drug-related keratitis or conjunctivitis is process of exclusion	5-fluorouracil[18,20] Capecitabine[5,21] Cytosine arabinoside[23-25] Deoxycoformycin[6] Chorambucil[6] Docetaxel[26,27]
Pre-existing symptoms associated with itching, or past "problems" with eyelids	Consider ocular allergies, trichiasis, or abnormalities of eyelid position	Same medications that exacerbate dry eyes can worsen pre-existing allergy symptoms
Pre-existing symptoms worse in certain environments like air-conditioned rooms or under fans Mild foreign body sensation	Reflex tearing due to dry eyes	Often exacerbated by antihistamines and other common medications

Table 1. — Somewhat Commonly Occurring Adverse Events of Cytotoxic Chemotherapies

Adverse Event	Drug	Route of Administration
Arteriovenous shunts (central nervous system)	Carmustine	Intra-arterial
Blurred vision	Busulfan	Intravenous
	5-fluorouracil	Intravenous
Conjunctivitis	5-fluorouracil	Intravenous
	Deoxycoformycin	Intravenous
Corneal opacity	Cytosine arabinoside	Intravenous
Cranial nerve palsies	Plant alkaloids	Intravenous
Epiphora	5-fluorouracil[8]	Intravenous
Eye pain	5-fluorouracil	Intravenous
Focal demyelination of the optic nerve	Carmustine/cisplatin	Intra-arterial
Foreign body sensation	Cytosine arabinoside	Intravenous
	5-fluorouracil	Intravenous
Keratitis	Cytosine arabinoside[8]	Intravenous
	5-fluorouracil	Intravenous
Keratoconjunctivitis sicca	Cyclophosphamide	Intravenous
	Busulfan	Intravenous
Macular pigment	Cisplatin	Intravenous
Papilledema	Carmustine	Intra-arterial
Periorbital edema	5-fluorouracil	Intravenous
	Methotrexate	Intravenous
Photophobia	5-fluorouracil	Intravenous
Ptosis	Plant alkaloids	Intravenous
Retinal arterial narrowing	Carmustine	Intra-arterial
Retinal hemorrhages	Carmustine	Intra-arterial

Table 3. — Chemotherapeutic Agents Associated With Cranial Nerve Palsies or Diplopia[a]

Complication	Select Example	Route of Administration
Bilateral lateral rectus palsy	Cytosine arabinoside and mitoxantrone[15]	Intravenous
Cavernous sinus syndrome	Cisplatin[14]	Intra-arterial
Cranial nerve palsy	Vinca alkaloids[10,11]	Intravenous
Diplopia	Chlorambucil[5]	Intravenous
Disturbance in oculomotor function	5-fluorouracil[12]	Intravenous
Fibrosis of extraocular muscles	Carmustine Nitrosoureas[8,13]	Intra-arterial Intravenous
Internuclear ophthalmoplegia	Methotrexate Nitrosoureas[8,9]	Intra-arterial Intrathecal
Oculomotor nerve palsy	Interferon α[5]	Intravenous

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Ocular adverse effects of anti-cancer chemotherapy and targeted therapy

Parul Singh[1*] and Abhishek Singh[2]

Abstract

Systemic anti-cancer therapies can produce acute and chronic organ damage. Ocular toxicity induced by anti-cancer chemotherapy is not uncommon, but underestimated and under-reported. The development of more aggressive regimens, use of newer agents and combination chemotherapies have resulted in a significant increase of reported cases of chemotherapies induced ocular side effects. Visual changes have been attributed to a number of chemotherapeutic agents such as antimetabolites, alkylating agents, taxanes and platinum agents. In addition to the eye itself, structures of the skin including the eye lids may be affected. Ocular toxicities induced by chemotherapeutic agents are generally not preventable; therefore clinicians must be aware of potential vision threatening complications. Prompt consultation with an ophthalmologist can lead to early detection, proper diagnosis and appropriate therapeutic measures. Dose reduction or discontinuation of incriminated drugs may help in reducing severity and duration of side effects. An ophthalmologist should be part of team caring for patients undergoing systemic chemotherapy for baseline examination and ongoing assessment. Baseline examination will help to diagnose adverse effects caused later due to chemotherapeutic agents and; diagnose any pre-existing conditions, especially in elderly patients. It is easy to miss association between chemotherapy and visual changes. This article document ocular changes that are believed to be related to the administration of certain chemotherapeutic agents.

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Parul & Abhishek. Journal of Cancer Therapeutics & Research 2012, http://www.hoajonline.com/journals/pdf/2049-7962-1-5.pdf

Visual/Ocular involvement of chemotherapy

Ocular Adverse effects	Common drugs associated
→ Blurred vision	Cisplatin
	Oxaliplatin
	Cyclophosphamide
	Ifosphamide
	Methotrexate
	Paclitaxel
	Capecitabine
	Imatinib
	Tamoxifen
	Rituximab
	Mitomycin-C
	Busulphan
	Carmustine
	Fludarabine
	Pentostatin
	Cytosine arabinoside
→ Photophobia	5-Florouracil (5-FU)
	Methotrexate
	Fludarabine
	Cytosine arabinoside
	Pentostatin
→ Conjunctivitis	Oxaliplatin
	Cyclophosphamide
	Ifosphamide
	Methotrexate
	5-FU
	Docetaxel

Ocular Adverse effects	Common drugs associated
	Doxorubicin
	Capecitabine
	Rituximab
	Panitumumab
	Nilotinib
	Erlotinib
	Carmustine
	Busulphan
	Pentostatin
	Everolimus
→ Cataract	Tamoxifen
	Anastrazole
	Busulphan
→ Abnormal lacrimation	Oxaliplatin
	Cyclophosphamide
	5-FU
	Docetaxel
	Doxorubicin
	Cytosine arabinoside
	Pentostatin
	Panitumumab
→ Dry eye	Cyclophosphamide
	Imatinib
	Nilotinib
	Pentostatin
	Busulphan

→ Keratitis	5-FU
	Capecitabine
	Tamoxifen
	Cetuximab
	Erlotinib
	Chlorambucil
	Cytosine arabinoside
→ Optic neuropathy	Cisplatin
	Carboplatin
	Methotrexate
	Paclitaxel
	Vincristine
	Tamoxifen

	Alemtuzumab
	Carmustin
	Cytosine arabinoside
	Fludarabine
→ Retinopathy	Cisplatin
	Carboplatin
	Methotrexate
	Etoposide
	Tamoxifen
	Carmustin
	Pentostatin
	Leuprolide
→ Cortical blindness	Cisplatin
	Vincristine
	Fludarabine
→ Eye pain	Oxaliplatin
	5-FU
	Carmustine
	Cytosine arabinoside
→ Accelerated growth of eyelashes	Cetuximab
	Panitumumab
→ Limitation of ocular motility	Carboplatin
	Methotrexate

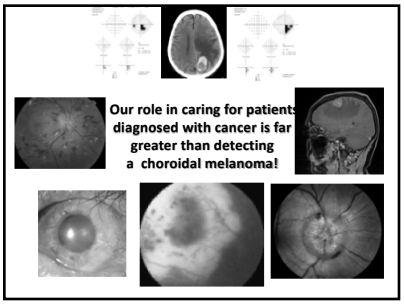
Patient education and preemptive Tx

Table 6. — Preemptive Strategies for Common Ocular-Related Adverse Events of Chemotherapy

Agent	Adverse Event	Strategy[a]
5-fluorouracil	Conjunctivitis (noninfectious)	Cool compresses Topical methylcellulose drops Topical corticosteroids[4,37]
Cyclophosphamide	Dry eyes	Artificial tear treatment[4,7]
Cytosine arabinoside	Keratitis	Topical corticosteroid drops started prior to treatment and tapered[33-36] Topical artificial tears[33-36] Topical 2-deoxycytine drops prior to therapy[33,36]
Docetaxel	Canalicular fibrosis Secondary epiphora	Temporary intubation of lacrimal puncta in patients with early symptoms[31]
Methotrexate	Keratitis Photophobia	Artificial tear treatment[32]

Immunotherapy approach to treatment

BCL-2 is a protein involved in the apoptotic process and certain forms of cancer (ie: CLL) modifies the BCL-2 functionality thereby preventing the body to kill off the cancer cells.



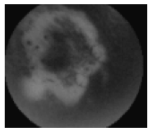
Our role in caring for patients diagnosed with cancer is far greater than detecting a choroidal melanoma!

Optometry role in caring for patients with cancer diagnosis

Patient education
- Potential ocular/visual involvement
- Need for prophyllactic management

Palliative care
- Provide prophylactic lubricants
- Known radiation
  total dose and ocular involvement
- known chemotherapy

Thank you!



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