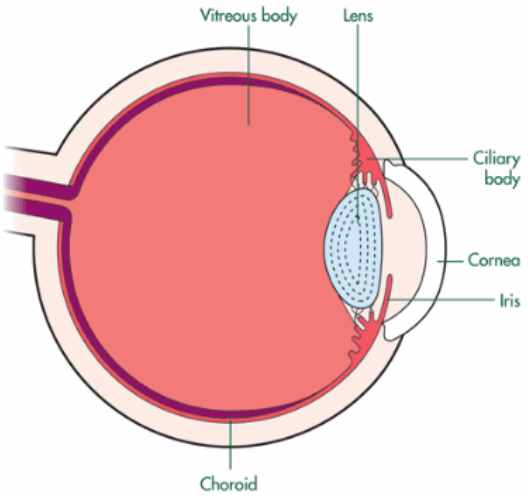
Ocular Melanoma

The eye is an essential organ to the human population. It allows us to perceive detail and to carry out tasks which would otherwise have been impossible. We can see both objects that are distant and those that are very close, for example, the minute detail such as pores in fabric in-between each thread. It is therefore debilitating when this sense is lost or otherwise hindered. There are many factors that can go wrong with regards to our sight, from simple myopia and hyperopia to ocular melanoma. This essay will look at ocular melanoma in detail and will fall into several sections. They are the incidence, the symptoms, detection, current and future therapies as well as survival rates.

The eye

The eye is a round (sometimes oval) structure composed of the cornea on the outside. Underneath the cornea lies the iris, which is able to contract and dilate to control the amount of light it lets into the eye. The lens is held up by ciliary bodies attached to ciliary muscles. The inside is filled with vitreous humour. The choroid is a dark lining in the eye which prevents any light from reflecting on the inside. Melanoma is a cancer that develops a type of cells called melanocytes. These cells produce a dark pigment called melanin. Melanin is found in many parts of the body such as the skin, the hair, the lining of internal organs and the eye.



Macmillan Cancer Support. (2009). *Melanoma of the eye (ocular melanoma).* Available: http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Eye/Melanomaoftheeye.aspx. Last accessed 2/3/11.

The choroid, ciliary body and the iris make the uveal tract of the eye, and this is predominantly affected by melanoma. Uveal melanoma is the most common type of ocular melanoma and the main focus of this essay ,though other types such as conjunctival melanomas can also develop (thin lining of the eye, the conjunctiva, or the eyelid) (Macmillan, 2009).

Incidence

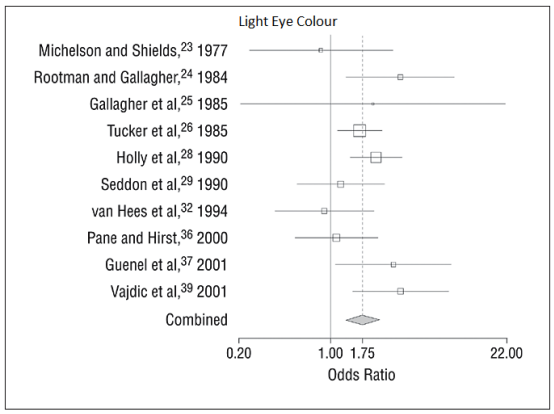
According to Singh *et al* there are approximately 4.3 new cases of ocular melanoma per million people in the United States, this is an age adjusted incidence which has remained constant over the past 50 years (2005). Singh *et al* further state that approximately 85% of ocular melanomas are uveal in origin, where conjunctival and orbital melanomas are rare. Furthermore in approximately 50% of patients being treated, malignant posterior uveal melanoma metastases to the liver within 15 years of diagnosis.

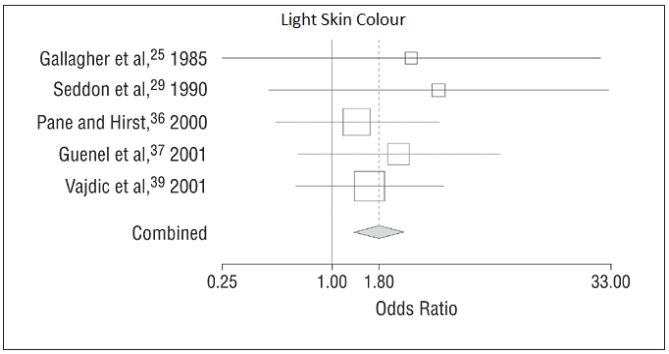
Macmillan states that within the UK there are 500 new cases of ocular melanoma diagnosed each

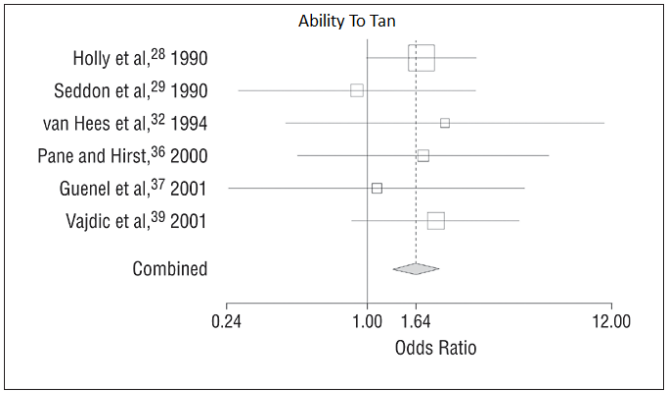
year. The incidence increases with age and most cases are diagnosed in patients who are over 50 years of age (2009). According to Singh *et al* (2005) the incidence peaks at the age of 70.

An individual is more susceptible to ocular melanoma if they are Caucasian, have light eye colour, light skin colour and can tan easily (Singh *et al 2005,* Weis *et al* 2006).

A meta-analysis carried out by Weis *et al*, 2006, looked at the relationship between uveal melanoma and the above susceptibility factors;







They had found that the odds ratios for light eye colour, light skin colour and the ability to tan were 1.75, 1.80 and 1.64 respectively all at 95% confidence intervals. Weis *et al* state that those with light eye colour, blue or gray, are associated with a 75% increased chance of developing uveal melanoma as opposed to those with dark eyes. White people are 80% more likely to develop uveal melanoma in comparison to people with dark skin. There is a 64% increase in the likelihood of developing uveal melanoma in people who sunburn easily compared to those that tan well (2006).

Weis E, Shah CP, Lajous M, et al.: The association between host susceptibility factors and uveal melanoma: a meta-analysis. Arch Ophthalmol 124 (1): 54-60, 2006.

A systematic review carried out in 2003 by Singh and Topham looked at the incidence of primary uveal melanoma in the United States over a 25 year period, between 1973 and 1997. They have concluded that "the age adjusted incidence rate of uveal melanoma has remained stable for the past 25 years." They have found that 97.8% of cases occurred in the white population and that there was significant variation between genders; at a 95% confidence interval, the probability for males being 4.9 and 3.7 for females. There was no significant variation of incidence by geographic location.

<u>Symptoms</u>

Ocular melanomas often show no signs and symptoms. They are frequently diagnosed by an optician during a routine sight test. Some of the symptoms may include blurred vision, flashing lights and shadows. These are however common to other eye conditions. Patients have also reported floating objects in their vision (floaters) (Macmillan, 2009)

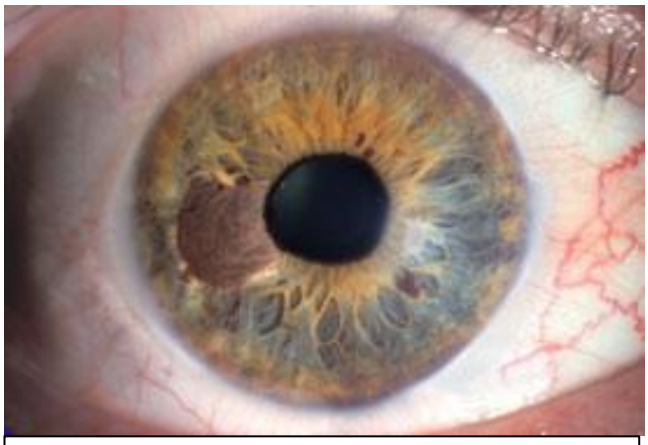
Melanoma in the choroid can often cause structural deformities based on its location.

If the choroidal melanoma is situated towards the front of the eye, it can push on the lens causing blurred vision and irregular astigmatism. Furthermore it can leak fluid beneath the retina. This is the cause of flashing lights and floating specks as the retina can detach.

The choroidal melanoma can develop in the centre of vision, the macula, and so grow beneath the fovea. This causes far-sightedness. If the choroidal melanoma continues to develop it can damage and destroy the fovea causing distortion, changes or loss in colour perception and even loss of vision.

Finger P. (1998-2011). *Choroidal Melanoma.* Available: http://www.eyecancer.com/Patient/Condition.aspx?nID=62&Category=Choroidal+Tumors&Condition=Choroidal+Melanoma. Last accessed 2/3/11.

Anterior uveal melanoma can cause a discolouration of the iris, it can also cause a brown spot on the outside of the eye, an irregular pupil and glaucoma (Finger, 1998-2011).



Royal Liverpool University Hospital. (2009). *Ocular Tumours.* Available: http://www.eyetumour.co.uk/images/iris_melanoma.jpg. Last accessed 4/3/11.

<u>Detection</u>

As previously stated ocular melanomas are predominantly detected during a routine sight test because there are predominantly no symptoms. The ocular melanoma can be detected and diagnosed using a number of different techniques;

Opthalmoscopy uses an opthalmoscope (handheld lens) to look on the inside of the eye.

An ultrasound scan can be used to build up a picture of the inside of the eye, where the ultrasound head is run over the skin around the eye area.

Colour fundus photography takes photographs of the fundus (the back of the eye). These are often useful in determining what the melanoma looks like pre and post treatment. In this procedure, the pupil is dilated and a specialised camera is then used.

A biopsy may sometimes be obtained and analysed under a microscope. In most cases this is not required however due its characteristic properties (Raghavan *et al*, 2006)

Although the above procedures are effective in aiding the diagnosis of ocular melanomas, other, less frequently used diagnostic techniques may also be used;

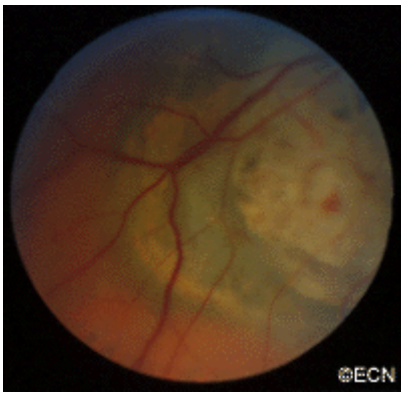
Fluorescein angiography uses a dye called fluorescein which travels to the vessels inside the eye (injected via the arm). A filtered camera selective for the dye is then used to take an image of the inside of the eye as the dye circulates through the retina and the choroid.

A *CT* scan can be used to take anx-ray image of the inside of the eye, similarly to the fluorescein angiography a dye may also be used to highlight the vessels.

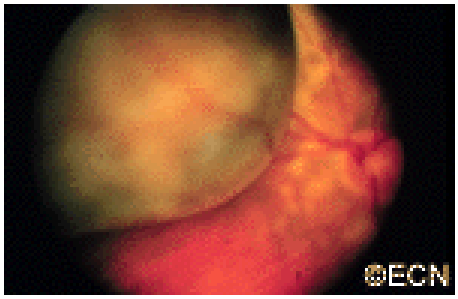
An *MRI* scan also builds up an image of the inside of the eye. Unlike the CT scan, an MRI scan uses magnetic resonance to build up the image. It is safer as no radiation is absorbed by the body. It does however take much longer than a CT scan, and the patient has to remain absolutely still during the scan. A contrast medium may also be used during this procedure (Souhami *et al, 2005)*.

According to Finger (1998-2011) and Gragoudas *et al* (2009), uveal melanomas have very characteristic features. These include pigmentation, thickness, low or moderate internal ultrasound reflectivity, orange pigment on the surface of the choroid and retinal detachment.

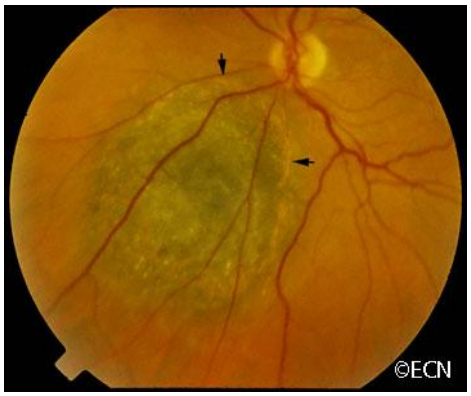
Finger P. (1998-2011). *Choroidal Melanoma.* Available: http://www.eyecancer.com/Patient/Condition.aspx?nID=62&Category=Choroidal+Tumors&Condition=Choroidal+Melanoma.



A collar-button shaped choroidal melanoma with orange pigment, subretinal fluid, and thickness greater than 2 mm: all consistent with choroidal melanoma.



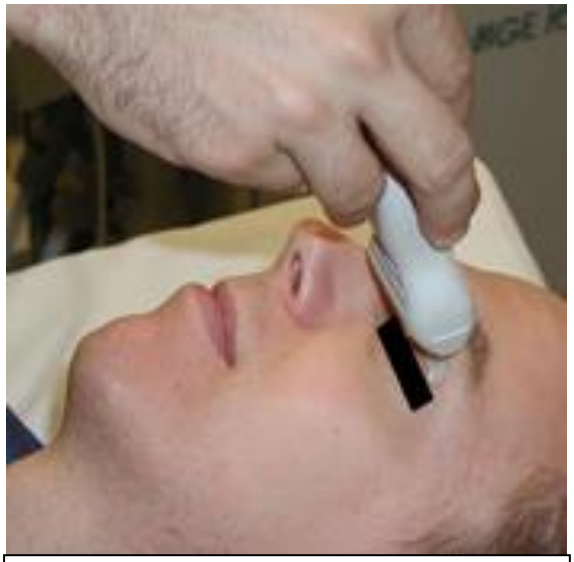
Dome shaped Choroidal melanoma



Choroidal Melanoma with Orange Pigment

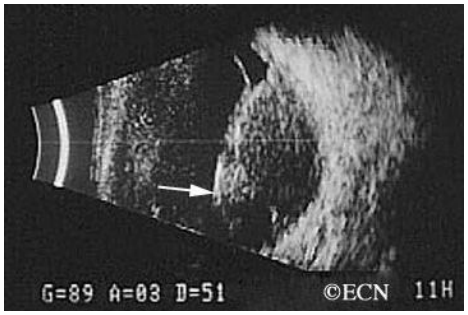
Choroidal melanoma pigment is present due to melanin present from the naturally occurring melanocytes cells in the choroidal layer. Choroidal melanoma is usually pigmented, but it can also be variably pigmented and even amelanotic. Amelanotic melanoma is usually as a result of the proliferation of melanocytes that have lost their ability to produce melanin.

If there is orange pigment found on the uveal melanoma, the cells are dying on the tumours surface. The orange pigment is called lipofuscin.



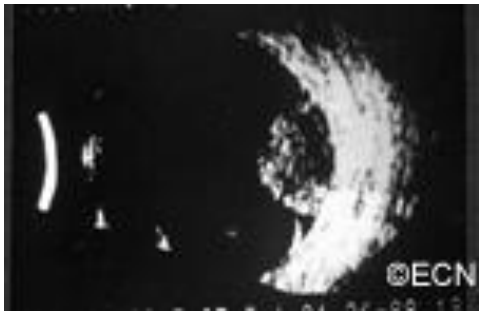
Srikar R. Adhikari, M.D., RDMS. (2008). *Small Parts- Ocular ultrasound.* Available: http://www.sonoguide.com/smparts_ocular.html. Last accessed 4/3/11.

Ultrasounds show that choroidal melanomas can take on two main shapes, a dome or a mushroom.



Ultrasound of a collar-button shaped Choroidal Melanoma

Finger P. (1998-2011). *Choroidal Melanoma.* Available: http://www.eyecancer.com/Patient/Condition.aspx?nID=62&Category=Choroidal+Tumors&Condition=Choroidal+Melanoma.



Ultrasound of a dome shaped Choroidal Melanoma

Leakage around the melanoma indicates that the tumour is eroding through the overlaying membranes that separate the leaking choroid from the retina. Leakage behind the retina can cause it to detach, where the severity of detachment varies from a small cap over the tumour to a large serous retinal detachment (Souhami *et al* 2001, Finger 1998-2011, Raghavan *et al* 2006).

<u>Current and Future therapies</u>

The main goal of therapy is to;

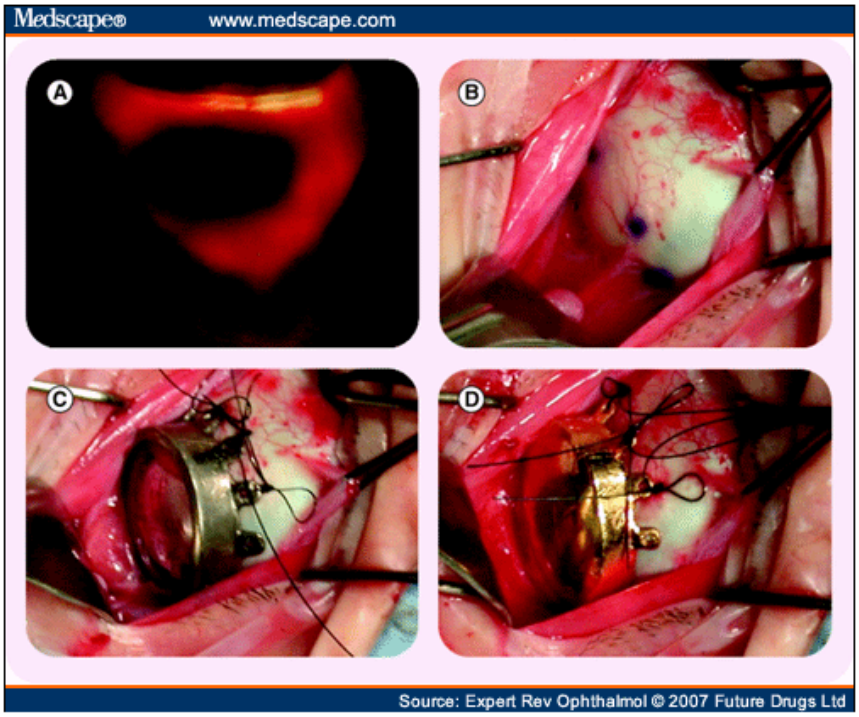
- Reduce the risk of metastasis
- Prevent further growth and destruction of ocular tissue
- Preserve as much vision as possible
- Achieve a cosmetically acceptable appearance.

Upon diagnosis of the primary uveal melanoma, the optician may suggest a tumour. This is usually in individuals who have a low life expectancy. These include the elderly and the infirm (Ramayia *et al* 2007).

Brachytherapy, or plague radiotherapy, is the most common treatment for posterior uveal melanoma. It allows a high-dose radiation to be delivered to the site with minimal radiation spill over to the surrounding extraocular tissue. This procedure involves the insertion of a radioactive plague on the globe of the overlaying area of the tumour. It is left for several days, and delivers a radiation dose of 80-100 Gy. Following the surgical procedure therapy, the patient is usually seen in a follow up every three months for the first year, every four months for the second year and then every six months for the next two to three years. After that, the patient is seen annually. The USA uses a plague ^{125}I which can be used to treat tumours that are 10-12mm thick, the plaque emits gamma rays. Europe uses a plaque which treats tumours of approximately 5mm height, the plaque is ^{106}Ru and emits less powerful beta radiation (Ramayia *et al* 2007)

Complications associated with this procedure are;

- Cataracts
- Retinopathy
- Papillopathy
- Neovascular Glaucoma
- Scleral necrosis
- Lipid exudation
- Local Tumour recurrence (Laube *et al, 2003)*



Surgical technique for episcleral radioactive plaque placement. **(A)** Transillumination of the globe is used to identify the tumor location. **(B)** The margins of the tumor are marked on the sclera. **(C)** The scleral marks are used to suture a 'dummy' plaque to the sclera. **(D)** Once satisfactory location of the dummy plaque is confirmed using intraoperative ultrasonography, it is removed and replaced by the radioactive plaque, which is secured to the sclera with the preplaced sutures.

Teletherapy uses an external beam radiation system to irradiate the tumour. There are various types of teletherapy;

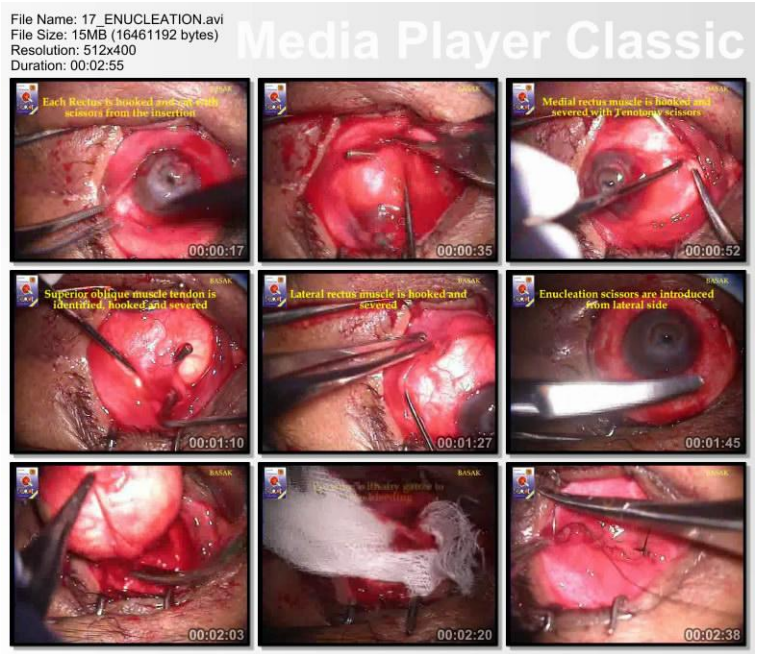
- Gamma knife RT
- Charged particle RT
- Stereotactic RT
- External Beam proton therapy

A case study on an 82-year -old patient who had undergone teletherapy found that the male patient developed several ocular complications post-therapy; just three days after his therapy, he presented with right optic neuritis with some posterior improvement. Five years after his therapy, he developed ischemic retinopathy and severe dry eye syndrome (Sanabira *et al,* 2007)

Transpupillary thermotherapy (TTT) damages the tumour by increasing its temperature using a low energy, low duration infrared laser diode. Tumour destruction has been demonstrated to a depth of 3.9mm. Although this technique was developed to be used in conjunction to plaque therapy, some medical institutions use TTT as a primary treatment for uveal melanomas and it is one of the most rapidly developing treatments. The complications associated with this treatment include macular traction, retinal vascular occlusion, macular edema , macular pucker, renital hemorrhage, iris burns and cataracts amongst others. The visual outcomes for eyes treated with TTT as opposed to plaque therapy are not significantly different (Ramayia *et al* 2007).

It has now become possible to treat small to medium melanomas using stereotactic radiotherapy (xray therapy) with acceptable dose distributions and target localisations. This should provide a better alternative to proton therapy. The primary issue in the treatment of ocular melanoma by stereotactic radiotherapy is the reproducibility of the eye position at CT and during each fractionated treatment (Gragoudas *et al* 1982, Dieckman *et al* 2001).

Should all of the available procedures fail, enucleation is performed. Enucleation is the removal of the eye. It is the best options for patients with large tumour sizes, optic nerve invasions, anterior segment invasion, orbital extension, lack of access to other treatments and also if the patients prefers this treatment (Ramayia *et al* 2007)



http://www.filefactory.com/file/90ef4d/n/0388_17_ENUCLEATION_rar Last Accessed: 4/3/11

The above list of the treatment options is not exhaustive. There are new constantly developing techniques and procedure used experimentally.

Some therapy procedures aim to slow the progress of the tumour and its development. Resections often try and remove the cancer offending areas (Peyman *et al, 1998*)

Because the ocular tumour can be malignant, it can metastasise to other parts of the body. If this is the case, chemotherapy is used to treat the patient. There are many chemotherapy programmes available to patients, and the best one is usually selected following a consultation

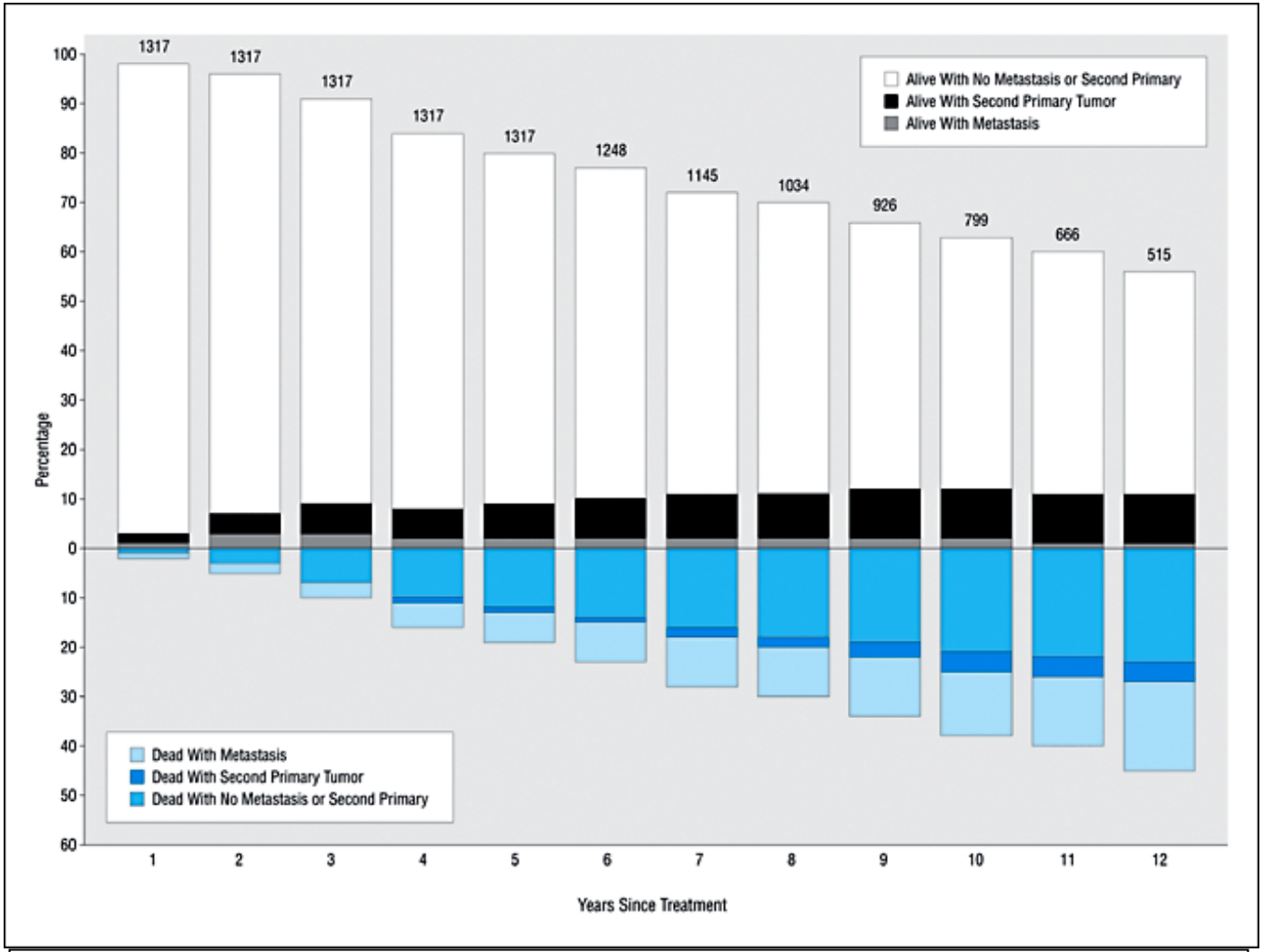
The drugs used in cancer chemotherapy include alkylating agents such as cyclophosphamide and cisplatin, antimetabolites like methotrexate and gemcitabine, antiobiotics such as docorubicin and bleomycin. Furthermore Topoisomerase inhibitors (etoposide, teniposide), microtubular inhibitors (vinca alkaloids, taxanes) and hormones (oestrogens and progesterones) may be used depending on the location of the secondary, tertiary and all other cancers. Today's programmes usually involve using three chemotherapy agents and one anti-inflammatory agent (Murray *et al*1997, Macmillan 2009).

Survival

According to Garcia-Valenzuela and Pons (2009) approximately 30-50% of patients diagnosed with choroidal melanoma will die within 10 years from prognosis and treatment. This is usually as a result of distant metastases, where the risk increases in larger tumours.

In patients whose tumour is confined to the eye the five year survival rate is approximately 80%, this is in stark contrast to those with secondary metastases, where the five year survival rate is just 15% (Cancer.org 2010).

According to the American Cancer Society there are approximately 230 deaths from this cancer each year, which breaks down to 120 men and 110 women (2010).



Dahr. (2008). *Eye melanoma.* Available: http://eyemelanoma.com/What_is_my_prognosis_with_uveal_melanoma.html. Last accessed 4/3/11.

The graph to the left demonstrates the percentage of patients with a specific melanoma status at the end of each year as followed by Dr Dahr, Oklahoma 2008. We can see that the percentage of alive patients constantly decreases with time and the development of a Second Primary Tumour develops as time progresses. Mortality increases with time primarily due to metastasis.

It should be noted that sometimes the second tumour can be unrelated to the ocular melanoma, this is often prostate, lung or breast cancer.

2473 Words

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