Module 1 – Decision making and the cancer MDT

Learning objectives

- Understand how patients are referred into oncology
- Know about 'Red-Flag' symptoms and how to deal with them
- Understand the principles of cancer staging
- Consider the importance of co-factoring for patient morbidity
- Follow the principles of survival analysis used in clinical trials

Cancer pathways

In the UK we are very fortunate to have well-structured cancer services. It wasn't always like this. When I was at medical school, a GP or surgeon might resect or biopsy a lesion and obtain a cancer diagnosis, and it was up to them to decide what to do next. Improvements in cancer services were driven by Prof Sir Mike Richards, director of the first DoH cancer plan. These were driven by two main targets:

- A patient with a suspected malignancy should see a specialist within 2 weeks
- A patient should start treatment within 28 days of a cancer diagnosis being established

The targets were driven by the fact that the UK was slipping places in the league tables for cancer survival statistics, but more importantly the targets were backed up by real investment into cancer services.

The Cancer MDT

Decisions on how to treat (or not treat) patients with malignancy are now made by multidisciplinary teams (MDTs). These contain all the necessary expertise to ensure that patients receive optimal treatment. Clinicians may dial in from other units to join the discussion. The precise makeup of an MDT will vary from disease to disease but typically include the following:

- Surgeons
- Medical oncologists & clinical oncologists
- Pathologists
- Radiologists
- Specialist nurses
- Speech and language therapists
- Dieticians

Click here to watch a YouTube video about a tumour board (American speak for Cancer MDT) [3'28"]

MDTs should ensure that all patients get a balanced and holistic view on different treatment options for their malignancy. *Cynics of the system say that an MDT means no-one makes a decision and no-one takes*

on responsibility for the patient. It is certainly worth attending some MDTs when you are a student as the clinic-pathological correlation makes a good teaching experience. Later in your career you know when your team trusts you when they let you present or respond in an MDT!

As a junior doctor you will be charged with making a referral to a specific MDT. In Addenbrooke's we run over 30 different cancer MDTs per month, and they all have different rules for making a referral. You can always get advice from the MDT coordinator – give them a call and they will tell you how to make a referral.

Red-Flag symptoms

Sometimes, the most important thing you can do is to consider a cancer diagnosis in an unwell patient who comes in with an apparently unrelated condition. This is one of the reasons why establishing a differential diagnosis is so important in your clerking of a patient. There are some symptoms that are particularly suspicious for an underlying cancer diagnosis, which are known as 'Red Flag' symptoms. Each of these on its own has a positive predictive value of over 25% for an underlying malignancy. That's why some of the messages make it onto bus stands and above men's urinals in motorway service stops.

Some are patient focussed

- Hoarseness of the voice for more than 2 weeks
- Cough lasting more than 3 weeks

Some are physician focussed

- Anaemia – in men with Hb ≤ 12g/dl aged 20 and older and women with Hb ≤11 g/dl aged 50 and over
- Blood in urine – in men and women aged 60 and over
- Coughing up blood – in men over 55 and women over 65
- Difficulty swallowing – men over 55
- Breast lump or mass – in women aged 20 and older
- Post-menopausal bleeding – in women aged 75-84
- Abnormal rectal examination – in men 40 and older
- Rectal bleeding – in men and women aged 75 and older

Approach to a patient with suspected malignancy

So what do you need to do if you see someone with one of these red flag symptoms? It is wise to always consider the following approach:

- Treatment the patients symptoms, and explain what is happening.
- Confirm a diagnosis of malignancy. This is nearly always needed before cancer therapy can be started.
- Stage the disease

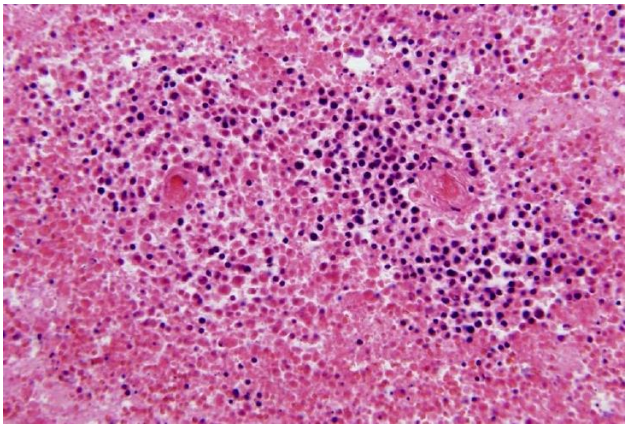
Treating immediate symptoms

Sometimes when you see a patient come in on-take with a suspected malignancy, there can be such a rush after the post-take round to get the diagnosis that you forget to address the patient's symptoms. Remember the symptoms are what likely brought the patient into hospital. The commonest symptoms are:

- Acute Pain
- Headache

- Breathlessness
- Bleeding
- Visceral obstruction

Remember to offer treatment for these symptoms and explain what you are doing. It's worth just thinking a moment about corticosteroids. We use corticosteroids extensively to help with acute pain from visceral compression, raised intracranial pressure, and breathlessness. For most solid tumours, obtaining a biopsy whilst on steroids will not alter the diagnostic accuracy. The only notable exception is a suspected lymphoma. In some high grade lymphoma, steroids can induce marked apoptosis making diagnosis of the tumour more difficult.



'Ghost tumour' - this H&E stain is of a biopsy from a nodal mass from a patient with suspected lymphoma, who had been started on corticosteroids. The purple stain is intact nuclei. Look at how most of the cells have already lost their nuclei as they have apoptosed.

Confirm a malignant diagnosis

In general, oncologists will want a confirmation of malignancy before starting cytotoxic therapy or radiotherapy. Generally this means obtaining histology, and you might think this is a surgeon's job but not always:

Physicians obtain histology
- Skin biopsy
- Aspiration cytology
- Bronchoscopy / endoscopy
- Blood film / bone marrow
- Radiologically guided biopsy

Surgeons obtain histology
- EUA
- Primary surgery

Marker based diagnosis
- Germ cell tumour (positive bedside pregnancy test in a male with a testicular mass)

Radiological diagnosis
- MRI appearances for brainstem glioma, optic nerve sheath meningioma where risk of neurosurgical complications from biopsy outweighs benefit

Did you know that beyond the immediate diagnosis and implications for treatment, a number of things happen when a cancer diagnosis is made:

- A cancer registration event is received by the national cancer registration service. This is part of the department of health and they maintain statistics on cancer burden throughout the country
- For some cancer diagnoses, a minimum information dataset is generated for reporting of pathology
- Patients can use the diagnosis to activate healthcare insurance policies
- Various benefits related to social care become immediately accelerated
- Patients receive free prescriptions, so that medications needed as adjuncts to their cancer care are freely provided.

Stage the disease

Oncologists love staging. Maybe not as much as cancer surgeons, but still probably more than they should. Staging means using scans and sometimes clinical evaluation to assess the extent of spread of the condition. There are three really important (and one less important) reason why oncologists love staging:

1. Staging is a common dialogue amongst cancer specialists. If you have a patient in front of you, and you have to disturb a thoracic surgeon half way though her morning round of golf, if you say to her "I have a fir 56 year old non smoker with an rT3N2M0 lung cancer that needs a VATS biopsy" they know instantly and exactly what you are talking about. The classifications are generally widely accepted (UICC TNM, FIGO for gynaecological tumours).
2. Staging systems (Stage groups in particular) are linked to the prognosis of the patient. This means that when you stage a patient, you have some idea of what the outcome will be for this patient.
3. Staging defines similar patients for clinical trials. They allow you to define a 'relatively' homogeneous group of patients if you want to assess the efficacy of a new therapy. The corollary to this is that staging identifies the optimum 'evidence-based' treatment for a patient.
4. When you know your staging, it makes you sound clever, and possibly more attractive to oncologists!

On the portal, you will find some worked examples of cancer staging. You don't need to learn staging systems in their intricate detail (except if reason 4 is really important to you) but it is useful to understand the principles of the TNM system:

- **T = Tumour**. (T0-T4) This generally quantifies the size of the tumour, and its relationship with the organ of origin. T3 often means spread beyond the organ of origin, and T4 often means invasion into critical surround tissues making it unresectable.
- **N = Nodes.** (N0-N3) This describes the extent of involved lymph nodes.
- **M = Metastasis.** (M0-1) This describes whether the disease is localized or has metastatised or other locations in the body.

From the TNM stage there are various disease stage groupings where the disease may have similar behavior or treatment options. An example of lung cancer stage groupings is given in this youtube.

Purists will state that the TNM stage should always be prefixed to indicate how the staging was established rT2N0M0 for a radiological staging might become pT2N1M0 from a post-operative pathological staging.

Co-factoring and performance status

So now you have diagnosed and staged the tumour, it is clear that we have only half of the story. We need to understand a bit more about the tumour's host before deciding upon a treatment strategy. We call this process co-factoring and we use it extensively in oncology.

The first thing we use is the performance status. This is a global assessment of function, and tends to focus on mobility. In the UK and Europe we use the World Health Orgnisation performance status. In the US they use the ECOG scale (which is functionally the same as WHO PS) and Karnofsky performance status (KPS). KPS runs from 0 to 100 where 0 is dead and 100 is perfect health. Some people like it because it overs a wider range of values, and there are algorithms for adjustment according to KPS.

Performance Scores[2,3]

Grade	WHO / ECOG
0	Fully active, able to carry on predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office)
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Death

In older patients with cancer, co-morbidity becomes more important. Specific co-morbidities may exclude certain types of cancer therapy. For example, some chemotherapy drugs are nephrotoxic and contraindicated in patients with renal failure. Patients with poorly controlled hypertension or diabetes or patients who are actively smoking tend to have more normal tissue reactions from radiotherapy.

The Charlson Co-morbidity index is a really useful co-factoring tool. Based on comorbidities and patient age, it calculates the 10 year survival probability of a patient, and this can be very useful in making decisions, especially around the use of adjuvant therapies. Try it out here:

http://www.pmidcalc.org/?sid=7722560&newtest=Y

Like staging, performance status helps divide patients in the published evidence base, as clinical trials will typically only treat patients from a specific performance status window.

Establishing treatment intent

We now have quite a lot of information about our patient and their tumour, and we can think about an optimum treatment strategy that is right for the patient. One of the really important things to consider at this point is treatment intent. Are we delivering a radical (curative) treatment or a palliative (supportive) treatment. The treatment intent influences greatly how we look after the patient downstream:

For patients being treated with **radical intent**

- Examples include benign conditions (meningioma), localized tumours, or treatment sensitive metastatic tumours (lymphoma, germ cell tumour)
- We accept significant acute toxicity if cure is possible
- It is important to consider long term effects of therapy, including second malignancy
- We have to support the patient through side effects, even if this requires ITU admission

For patients being treated with **palliative intent**

- Examples include metastatic disease (solid tumours), locally advanced disease, or patient co-factors which preclude curative treatment
- We may still need intensive therapy to achieve palliation (e.g. Head & Neck Cancer)
- It is important to balance side effects of treatment with their quality of life. This is particularly important when giving palliative chemotherapy
- We must set a ceiling of supportive care that is appropriate for the patient

Having established treatment intent, there are several **treatment scenarios** that we must consider:

- Primary treatment : using Chemo or RT in place of surgery (e.g. RT for Head & Neck Cancer). For radiotherapy this is often also called organ preserving therapy - treatment is given that can offer a similar control rate to surgery, but which preserves the organ within which the tumour formed.
- Neo-adjuvant : using Chemo or RT to shrink (downstage) a tumour prior to definitive surgery (e.g. Colorectal cancer)
- Adjuvant : using Chemo or RT after surgery to improve loco-regional control and survival (e.g. Breast cancer). Most of the oncology therapies we deliver are given in the adjuvant setting.
- Concomitant : Using chemotherapy in combination with radiotherapy (e.g. Glioblastoma)

Weighing up treatment options

With diagnosis, stage and co-factoring we are ready to discuss treatment options and prognosis with the patient. Before we do this we need to consider the evidence base for different therapy options. In doing so, it is important to think about the level of evidence of a treatment, and the level of efficacy.

When reviewing treatment options it is important to think about the level of evidence (see table). NICE and CEBM put a lot of sway by randomized clinical trials, and this level of evidence is preferable if it is available.

Evidence category	Source
Ia	Systematic review and meta-analysis of randomised controlled trials
Ib	At least one randomised controlled trial
IIa	At least one well-designed controlled study without randomisation
IIb	At least one other type of well-designed quasi-experimental study
III	Well-designed non-experimental descriptive studies, such as comparative studies, correlation studies or case studies
IV	Expert committee reports or opinions and/or clinical experience of respected authorities

Adapted from Eccles M, Mason J (2001) How to develop cost-conscious guidelines. Health Technology Assessment 5 (16).

As an aside, it is interesting to note that randomized clinical trials were developed to compare two treatment options where there was no prior knowledge to suggest one treatment would be superior to another, offering the clinician and the patient true equipoise. These days with targeted therapies that have been designed to target cancer mechanistically, this may not hold true, and more advanced study designs may be needed using a Bayesian approach.

Treatment efficacy is often presented as a Kaplan-Meier (K-M) survival curve. This is a useful way of evaluating the efficacy of a treatment in a group of patients who start and complete treatment at different points in time.

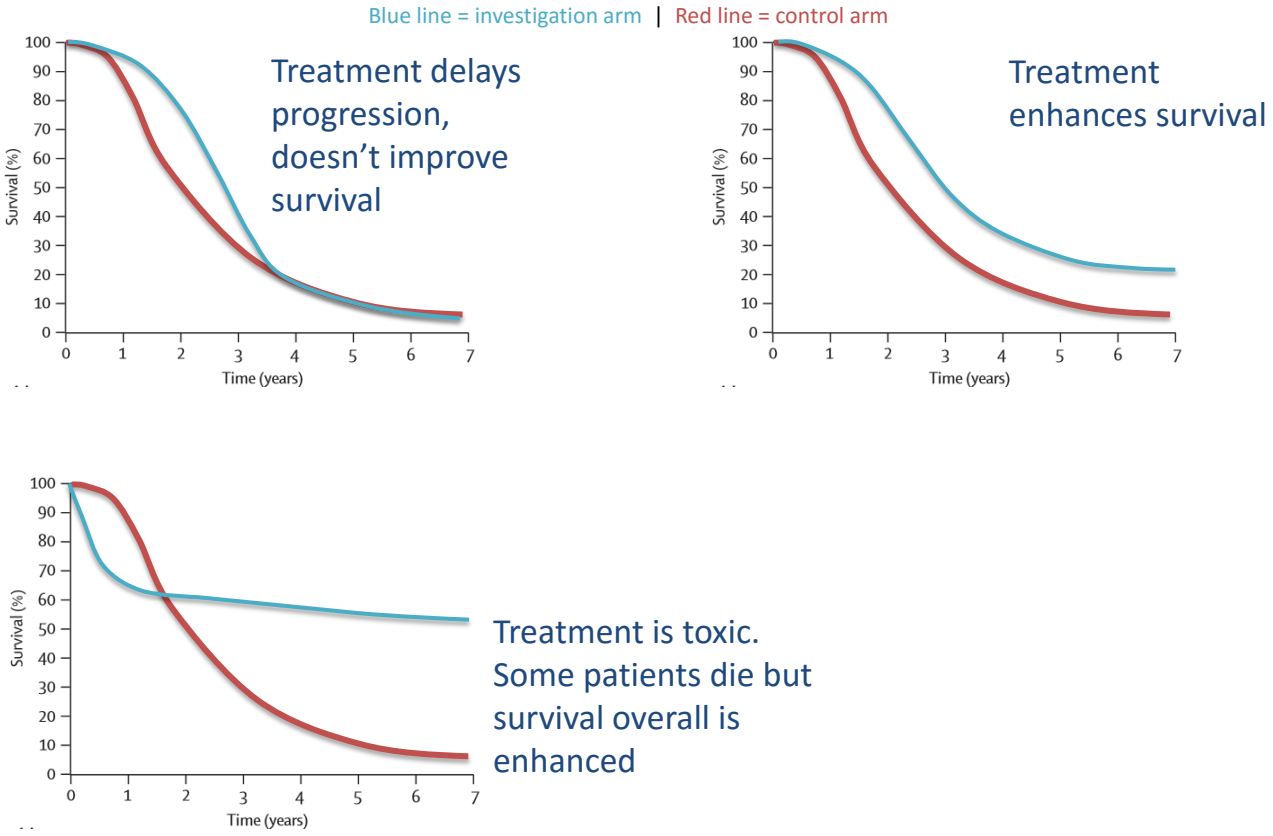
Click here for a YouTube explaining how K-M curves work [5'40"]

The cleaver thing about a Kaplan-Meier curve is that we can incorporate information from patients whose survival time is not known at the end of the study – this is known as censored data.

Examples of censored and uncensored data

- Patient 1 : Patient recruited in study and dies during follow up. Survival time is uncensored
- Patient 2 : Patient recruited in study and is still alive at end of follow-up. Survival time is censored, but we know it is at least the time of follow-up
- Patient 3 : Patient recruited into study and dies of an unrelated MI. Survival time is censored as patient did not die from event of interest

Many trials of adjuvant therapies will present survival curves as their outcome data. For a truly effective adjuvant treatment, we need to see a separation of the survival curves that is maintained over time. Some treatments simply increase the time to tumour progression, but ultimately patients will succumb to recurrent disease. In such situations the KM curves separate but then come together again:



Meta-analysis of trial data

It's an important skill being able to review evidence from trial data. Often individual trials will have bias introduced due to the design of the study, selection factors, or other factors that make the study

population to the patient you have in front of you. There is also publication bias, in that truly negative trials don't make for exciting reading and sometimes don't get published (New England Journal of Positive Results!).

Meta-analyses now tend to be performed by large organized groups such as the Oxford overviews or Cochrane. Ideally you should get individual patient outcome data from each study and pool the data for a meta-analysis, but it is not always possible to do this, and sometimes smart statistics can be used to combine estimates from different studies without individual level data being released.

It's important to understand Hazard Ratios in the context of clinical trials. Hazard ratios are commonly used when presenting results in clinical trials involving survival data, and allow hypothesis testing. They should not be considered the same as odds ratios. They reflect the analysis of time survived to some specific event (e.g. 5 year or 10 year survival). The event may or may not reflect tumour cure.

The statistical definition of hazard is the rate at which an event happens. Of course the hazard can vary over time, but the hazard ratio assumes that the hazard in one arm of a study is a constant proportion of the hazard in the other arm.

Summary

Oncologists use these key competencies in order to ensure that patients move from a suspected malignancy to a treated malignancy as soon as possible.

The commonest reason for a treatment recommendation at the MDT to be changed in the clinic is a lack of co-factoring information with the MDT referral. If you are making a referral to an MDT, good information on the functional status of the patient is absolutely vital – otherwise it is garbage in, garbage out.

Allocating patients to the best treatment, particularly in the palliative setting, requires a balance of the scholar and the physician.