Extension materials for lecture 1 : Key competencies

How did cancer pathways come about?

- 1990 Marked the start of the UK breast screening programme. Suddenly there was a need to review large amounts of imaging and pathology material to make decisions on treatment for women with screening detected lesions. The first clinic-pathological conferences (CPC's) were used to facilitate referrals for cancer treatment.
- For other cancers, increasing concern was being expressed in delays to diagnose cancer and start treatment. This was in part due to a lack of a clearly defined pathway by which suspected cancers should be referred.
- In 2000 the first NHS cancer plan was put into action, along with a significant investment in infrastructure for cancer services in Oncology, Surgery, Radiology and Pathology. It defined two targets:

14 day target for referrals for patients with suspected cancer, from decision for GP to refer

28 days target from referral to start of cancer treatment for childhood tumours, leukaemia, lymphoma, breast cancer

Significant infrastructure investment

- In 2007 the Cancer Reform Strategy document was released, aiming to consolidate on the original cancer plan

2 week wait from receipt of GP referral

Patient treated within 62 days of receipt of GP referral (31 days for children's cancer, germ cell, leukaemia)

- In July 2015 a new Cancer Plan document was published, outlining the government's strategy for the next five years. It is mostly operational, talking about which organisations have responsibilities for providing cancer services, and highlights the importance of removing inequalities in cancer care around the nation.

Red flag symptoms

These are an important list of symptoms, each of which has at least a 25% positive predictive value for a cancer diagnosis

- 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

Confirming a cancer diagnosis

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 used 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.

There are also several benign conditions (ductal carcinoma in situ of the breast, and a range of benign brain tumours including meningiomas) that are captured by the registration service, though patients may find some of the other benefits do not get activated for benign conditions. This is sometimes quite tough because an anaplastic meningioma growing near the base of the skull is a potentially life threatening condition.

There are some occasions where we make a diagnosis and start treatment without a biopsy. These are usually in benign conditions such as brain stem glioma and optic nerve sheath meningioma, where the risk of paralysis or blindness exceeds the benefit of a histological diagnosis.

Co-factoring and performance status

We use performance status a lot in oncology. Many treatment algorithms and patient selection criteria of clinical trials will make reference to the performance status of the patient. 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.

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. 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

Staging and stage boundaries

The mechanics of staging patients is postgraduate oncology, but it is helpful for you to understand how staging works. It is helpful for defininig a common dialogue between doctors in MDT's, selected appropriate treatment strategies, and in defining inclusion criteria for clinical trials.

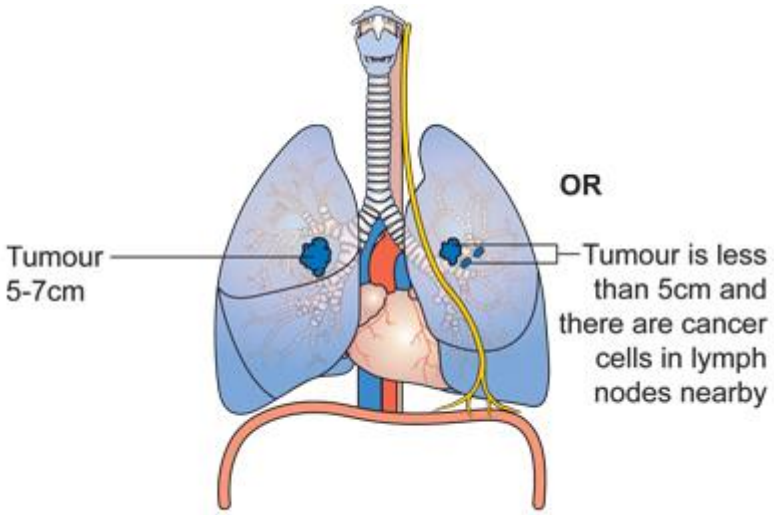
The International Union for Cancer Control (UICC) maintains the TNM classification system which is widely used in solid tumours. There are some exclusions:
-Gynaecological Malignancy is often staged according to the FIGO classification (International federation of gynaecology and obstetrics).
-Brain tumours tend to be staged by the WHO classification
- Sarcomas are poorly staged by TNM, so alternatives based on tumour grade tend to be used.

In some diseases, stage groups are often used. These are usually grouping of TNM stage that are treated in the same way. Consider Stage 2 lung cancer outlined below. The staging groups are really very complicated, but in essence what we are trying to establish is whether the tumour is amenable to complete surgical resection (stage 2A) or would leave a high risk of residual disease (Stage 2B)

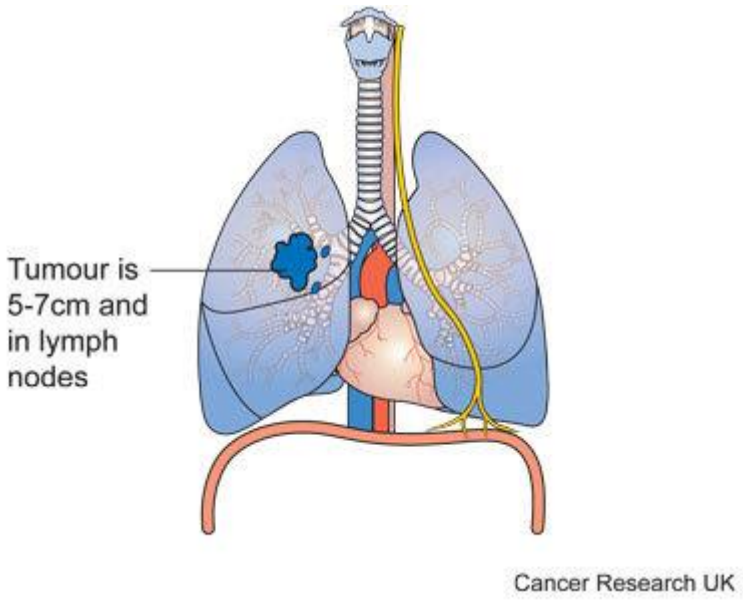
Stage 2

This is divided into 2A and 2B.

Stage 2A means that the cancer is between 5 and 7cm but there are no cancer cells in any lymph nodes. **Or** it is 5cm or less and there are cancer cells in the lymph nodes close to the affected lung. In either case it may have spread into nearby structures such as the main airway of the lung (bronchus) or the membrane covering the lung (pleura). Or the lung may have partly collapsed.

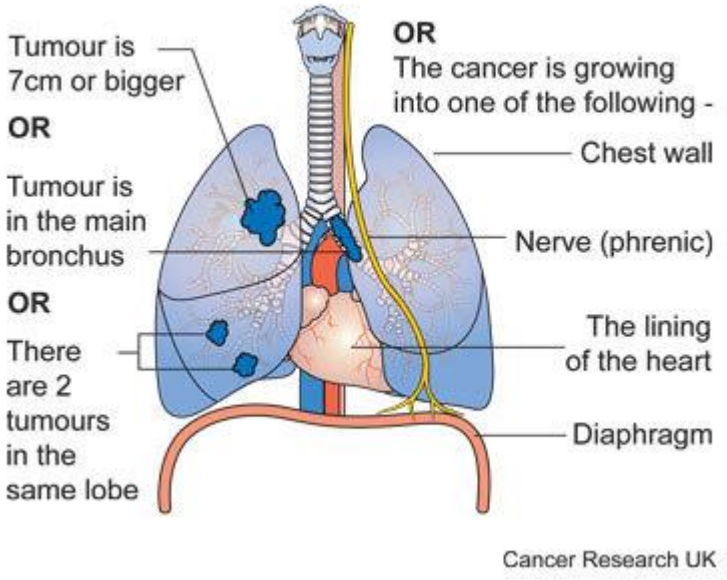


Stage 2B means that the cancer is between 5 and 7cm and there are cancer cells in the lymph nodes close to the affected lung



Or stage 2B is when the cancer is

- Larger than 7cm but there are no cancer cells in any lymph nodes **OR**
- Not in any lymph nodes but has spread into one or more of the following areas – the chest wall, the muscle under the lung (diaphragm), the phrenic nerve, or the layers that cover the heart (mediastinal pleura and parietal pericardium) **OR**
- In the main airway (bronchus) close to where it divides to go into each lung **OR**
- Making part of the lung collapse **OR**
- Any size but there is more than one tumour in the same lobe of the lung



Understanding survival curves

It is important to understand how a survival curve is calculated and what it means.

If statistics do not come naturally to you, there is a really concise explanataion of Kaplan-Meier curves here:
https://www.youtube.com/watch?v=1Fz6kBXmAt0

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 saurvived 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.

Screening programmes

The Wilson criteria outline what is required for a successful screen programme:

- The condition should present a significant health problem to the population
- The natural history of the disease must be understood
- Early and late stages of disease must be recognisable
- Available screening test is available which is sensitive and specific
- An accepted policy should be available for who needs treatment
- Accepted treatment options for the disease should be available
- Treatment in early stage must impact on survival

- Screening should be cost effective

The breast screening programme is an example of a programme that fulfills these criteria, and has had a positive impact on survival. It has generated something of a headache over ductal carcinoma in-situ, a disease that was rarely diagnosed prior to screening of asymptomatic women, and the impact of treating DCIS on breast cancer survival overall remains unclear.

The Cervical screening programme probably does not fulfill the criteria, on the basis of the size of the health problem and cost effectiveness. It is an example of a screening programme that was introduced because we had a technology developed (Papanicolau smears) that could detect it. It will be interesting to see the effect of HPV immunisation on cervix cancer incidence.

PSA screening for prostate cancer also does not fulfill the Wilson criteria, as most people diagnosed with prostate cancer will die with their disease rather than because of it.