UNIVERSITY OF BIRMINGHAM

Incidence of cerebral metastases in cancer: implications for vocational drivers

Aggressive Research Intelligence Facility

West Midlands Health Technology Assessment Collaboration

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For the Drivers Medical Group

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About ARIF and the West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service's Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG)

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

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1. Aims

1. Provide estimates of the incidence of cerebral matastases by TNM stage in six common cancers at annual intervals following successful primary treatment

2. Identify the commonest primary cancers associated with cerebral metastases

3. Provide estimates of the proportion of cerebral metastases

    a. presenting as seizures

    b. resulting in seizure at some point

    c. occurring as single or multiple lesions

2. Background and epidemiology

2.1 Cerebral metastases

2.1.1 Incidence of cerebral metastases

Metastatic brain tumours are the most common cause of brain cancer, with an incidence rate approximately ten times higher than primary brain cancer (Armstrong 2000; Klos 2004). The precise incidence and prevalence of cerebral metastases (CM) are unknown, but studies suggest that incidence is rising, in part due to the increasing incidence of cancer (Klos 2004). Other factors which may contribute to increased incidence include improved imaging techniques, routine staging tests to assess the central nervous system (CNS) and improved survival in cancer patients with metastatic lesions being protection from systemic chemotherapy from the blood-brain barrier (O'Neill 2003 cited in Langer 2005).

An estimated 20-40% of patients with cancer develop CM (Posner 1995, cited in Klos 2004), but many cases remain undiagnosed prior to death despite the presence of neurological symptoms and may not be found or reported post mortem (Klos 2004). In autopsy studies, typically around a quarter of cancer patients are found to have CM (Delattre 1988, cited in Armstrong 2000; Klos 2004; Lassman 2003), although figures as high as 85% have been reported (Armstrong 2000). Differences between studies may be due to patient selection, for example some investigators note that brains may have been

selected for study due to neurologic symptoms prior to death, the inclusion or exclusion of haematological primary cancers, differences in the classification of primary cancers and of the site of metastases, and differences in autopsy technique (Lassman 2003).

The most common primary tumours associated with CM are lung, breast, melanoma, renal and colon cancers (Sawaya 1997, cited in Armstrong 2000). Although melanoma has the highest rate of metastasis to the brain, estimated as 40-50% (Chidel 2000) more brain metastases overall result from lung and breast cancer as these cancers are more common (see Table 1).

Small cell lung cancer (SCLC) also has a much higher propensity to metastasise than most other cancers, with around 40% of SCLC patients found to have CM in autopsy studies compared to just 20% for other lung cancers. Non-small cell lung cancer (NSCLC) is nevertheless responsible for more cases of CM overall as it is responsible for around 80% of lung cancer cases. Sarcoma, ovarian, prostate and bladder cancer rarely metastasise to the brain although the high incidence of prostate cancer, predominantly in elderly men, means that it accounts for 7% of brain metastases overall.

Table 1 Frequency of primary cancers in patients with cerebral metastases

Primary cancer	Armstrong 2000 Freq (%)	Lassman & DeAngelis 2005 Freq (%)
Lung	34	18-64
Breast	21	2-21
Melanoma	12	4-16
Colorectal	-	2-11
Urinary tract / renal	8	1-8
Thyroid	-	<1-10
Leukaemia	-	12
Lymphoma	-	10
Prostate	7	-
Unknown	-	1-18
Other	18	

[1]*Adapted from Posner 1995*

[2]*Combined analysis of 9 studies; figures are the range of results*

Metastases may enter the brain via the blood supply or lymphatic system. This spread often occurs from either primary or metastatic disease in the lungs, with malignant cells being picked up by the blood supply and being carried on to other organs, such as the brain (Sze 1990, cited in Armstong 2000). The role of the lungs in transferring malignant cells to the blood supply and onto the brain is suggested by studies which have estimated that lung metastases are present in 79-99% of cases with CM (Lassman 2005).

Table 2 Primary tumour type in 729 patients with cerebral metastases

Primary cancer	Total number (%)[1]	Single lesions[1] (% of total)	Multiple lesions[1] (% of total)
NSCLC	178 (24)	89 (50)	89 (50)
Breast	121 (17)	59 (49)	62 (51)
SCLC	110 (15)	48 (43)	62 (57)
Melanoma	80 (11)	39 (49)	41 (51)
Renal cell	45 (6)	25 (56)	20 (44)
Gastrointestinal	45 (6)	30 (67)	14 (33)
Uterine/vulvar	38 (5)	20 (53)	18 (47)
Unknown	33 (5)	23 (70)	10 (30)
Ovarian	14 (2)	8 (57)	6 (43)
Bladder	14 (2)	9 (64)	5 (36)
Prostate	11 (2)	9 (82)	2 (18)
Testicular	11 (2)	6 (55)	5 (45)
Other	29 (4)	19 (65)	10 (35)
Total	729 (100)	384 (53)	345 (47)

[1] *From Klos et al 2004, based on Nussbaum et al 1996*

Approximately 85% of metastases to the brain occur in the cerebrum and 10-15% in the posterior fossa, with 1-3% in the brain stem (Arbit 1995, cited in Armstrong 2000); the most common area for metastases is the gray-white junction in the cerebrum. In general the distribution of CM in the brain follows the weight of blood flow to the different structures, although there is some variation in frequency at different sites according to primary tumour (Lassman 2005). In particular, the incidence of brain metastases in the posterior fossa (which includes the cerebellum and brain stem) may be higher with primary colorectal and genitourinary tumours whilst haematological malignancies metastasise disproportionately to the leptomeninges (Delattre 1988, cited in Lassman 2005).

A CT-based study of 729 patients with CM found that 53% had single and 47% multiple lesions (Delattre 1988, cited in Klos 2004). Single lesions were markedly more common than multiple lesions in gastrointestinal, bladder and particularly prostate cancer and slightly more common in renal cell, ovarian and testicular cancers. Single and multiple lesions were equally common in other cancers (see Table 2).

2.1.2 Detection and management of cerebral metastases

The presence of CM may be identified through CT or MRI scanning, with the latter being a more sensitive test; gadolinium-enhanced MRI can detect lesions as small as 1.9mm in diameter (Schaeffer 1996, cited in Klos 2004). In one study CT scanning identified lesions in 50% of patients compared to 70% identified with MRI (Akeson 1995, cited in Armstrong 2000). Although less sensitive, CT scanning is useful for acute evaluation to rule out haemorrhage, obstructive hydrocephalus and subdural effusion as causes of observed neurological deficit and may be useful when clinical deterioration is rapid (Klos 2004). Lesions identified through scanning may be due to metastases, an abscess, infarction (stroke), heamorrhage, multiple sclerosis or a primary brain tumour. Brain biopsy is often required for definitive diagnosis. A study of patients with a known history of cancer found that around 90% of patients with solitary lesions on MRI had brain metastases, with the remainder having infections or primary brain cancer (Patchell 1990, cited in Klos 2004).

The goal of treatment for CM is to alleviate neurologic symptoms and improve quality of life. For solitary lesions the goal of treatment may be resection with curative intent while treatment of multiple lesions is more often palliative in intent. Treatment may not be indicated if the patient's age, burden of disease and overall performance status suggest that aggressive treatment is unwarranted (Klos 2004). Only about half of patients with single lesions are surgical candidates due to comorbidity, systemic metastases or inaccessibility of the tumour (Buckner 1992, cited in Klos 2004). Treatment strategies include corticosteroids, cranial irradiation, surgery, radiosurgery, chemotherapy and biologic agents and emergency treatments to correct life-threatening complications such as obstructive hydrocephalus, elevated intracranial pressure or posterior fossa haemorrhage (Klos 2004).

2.1.3 Symptoms and prognosis associated with cerebral metastases

Cerebral metastases may present with focal or generalised symptoms. Some lesions present slowly with progressive headache or cognitive dysfunction, others present acutely with seizures (Lassman 2003). Presentation primarily depends on the location of the tumour in the brain. Lesion size, swelling (oedema), multiple lesions and the extent of other metastatic sites will also affect presentation (Armstrong 2000).

With the introduction of CT and MRI scanning metastases are discovered earlier than previously, with up to 10% of patients showing no presenting symptoms; cognitive disturbance is now the most common presenting symptom (Lassman 2003). The frequency of presenting symptoms are given in Table 3; common signs and symptoms are given in Table 4.

A recent study of 401 patients with CM (Meyers 2004, cited in Langer 2005) included careful neurocognitive testing of memory, verbal fluency, executive function and fine motor control; 90% of patients were impaired in at least one neurocognitive domain at the time of diagnosis of CM. Memory, executive function and fine motor control were particularly affected. The degree of impairment correlated with tumour volume but not with the number of lesions and was an independent predictor of survival.

Approximately 15% of cancer patients experience venous thromboembolic events (VTE); there is some evidence that the incidence of VTE is higher in those with primary or metastatic brain tumours. Prophylactic use of pneumatic compression boots and graduated compression stockings have been shown to reduce the risk of DVT in neurosurgical patients (Batchelor, 1996). The use of anti-coagulation treatment in patients with brain tumours is complicated by the possible enhanced risk of catastrophic CNS haemorrhage (Olin 1987, cited in Batchelor 1996). However, there is no evidence that the risk or severity of bleeding episodes is substantially greater in patients treated with anti-coagulation therapy (Coon 1974; Schiff 1994, both cited in Batchelor 1996). Patients with CM due to particular primary tumours, such as melanoma, renal cell carcimoma, thyroid carcinoma and choriocarcinoma may have a greater propensity to haemorrhage and consequently may be at greater risk from the use of anti-coagulants (Mandybur 1977, cited in Klos 2004).

The median survival of patients with untreated CM is estimated at 4 weeks (Markesbery 1978, cited in Klos 2004). Palliative treatment with corticosteroids may extend survival by a few weeks (Klos 2004). Whole brain radiotherapy (WBRT) is the standard of care for multiple lesions and may extend median survival up to 3-6 months (Sneed 1996, Zimm 1991; Lagerwaard 1999, all cited in Klos 2004). A surgical series of 583 patients with CM reported a median survival of 9.4 months (Arbit 1996, cited in Klos 2004). Brain metastases may reoccur in 30-50% of patients following treatment (Klos 2004).

Table 3 Presenting clinical features in 1013 patients with cerebral metastases

Signs & Symptoms	Freq (%)[1]
Cognitive or change in mental status	34
Headache	31
Weakness	24
Seizure	19
Ataxia	11
Visual change	5
Nausea or vomiting	4
Other (eg bulbar symptoms, dizziness, syncope)	4
Sensory change	2
Papilledema	<1
None	9

[1]*From Lassman & de Angelis 2003, based on Zimm et al 1981, Nussbaum et al 1996 and Posner 1995*

Table 4 Signs and symptoms of cerebral metastases

Signs & Symptoms	Armstrong 2000[1] Freq (%)	Klos 2004[2] Freq (%)
Hemiparesis	59	44
Impaired cognitive function	58	-
Headache	49	42
Mental disturbance/change	32	31, 35 [3]
Focal weakness	30	27
Hemisensory loss	21	9
Gait ataxia	19, 21 [3]	13, 17 [3]
Papilledema	20	9
Aphasia	18	-
Seizures	18	20
Speech difficulty	12	10
Sensory disturbance	-	6

[1] *Based on Posner 1995*

[2] *Using pooled data from Cairncross et al1980 and Hall et al 2000, 329 patients in total*

[3] *Reported as sign and symptom separately; the lower figure in each case refers to the symptom*

The type of primary cancer affects survival as death does not always result from the cerebral metastases themselves. In a study of 740 patients with brain metastases, the 2 year actuarial survival rate ranged from 1.7% for those with primary SCLC to 23.9% for those with ovarian cancer (Hall 2000, cited in Langer 2005). Important prognostic factors for survival include single vs multiple lesions, surgical resection and the use of WBRT and chemotherapy combined. Age, sex, histology, location of a single lesion, systemic chemotherapy and stereotactic radiosurgery do not appear to influence survival (Hall 2000, cited in Klos 2004). An analysis conducted by the Radiation Therapy Oncology Group (RTOG) identified three broad prognostic groups. Class 1 included those with Karnofsky performance status (KPS) of 70 or more, with a controlled primary tumour, under 65 years of age and no extracranial metastases, with a median survival of 7.1 months. Class 2 included all other patients with KPS of 70 or more, with a median survival of 4.2 months. Class 3 included all patients with KPS of less than 70, with a median survival of 2.3 months.

2.2 Seizures due to cerebral metastases

15-20% of patients with CM present with a seizure, while 30-40% will experience at least one seizure during the course of their illness (Cohen 1988 cited in Batchelor 1996). Patients with slowly growing chronic lesions are more likely to have a seizure of some sort and incidence may be as high as 75% in these patients (Morris 1993, cited in Liigant 2001). Cerebral metastases resulting from melanoma may have a higher propensity to cause seizures. This may be explained by the higher frequency of multiple cortical metastases, a relatively high propensity to invade gray matter over white matter and a greater tendency for the lesions to haemorrhage (Byrne 1983, cited in Klos 2004). The frequency of seizures by location of tumour, taken from a retrospective study of 721 patients with primary or metastatic brain cancer (Liigant 2001), is given in Table 5; the frequency of different types of seizure from the same study is given in Table 6. In this study, just over a quarter of patients experiencing seizures had no other neurological symptoms and around three quarters had presented with seizures as the first manifestation of a brain tumour.

Seizures due to CM are normally simple partial or complex partial type with a relatively high likelihood of Todd's paralysis (Jacobs 1990; Posner 1995; Weaver 1995, all cited in Batchelor 1996). Status epilepticus is rare in patients with CM, but where it does occur results in a mortality rate of 6-35% (Engel 1989; Posner 1995, both cited in Batchelor 1996).

2.2.1 Prophylaxis and treatment of seizures

Anti-epilepsy drugs (AEDs) are generally given after first seizure although there is limited data to suggest that they are effective (Batchelor 1996). There is no evidence that the routine use of

prophylactic AEDs (prior to first seizure) in patients with CM is of any benefit and current evidence suggests that such treatment is not indicated (Glantz 2000, cited in Klos 2004). A recent meta-analysis of prophylactic AEDs in brain cancer included 12 trials, 10 of which included patients with CM (Sirven 2004). None of the included trials supported the use of AEDs prior to first seizure and there was some suggestion that side effects were more frequent in patients with brain tumours, possibly due to interactions between AEDs and other treatments (Glantz 2000, cited in Lassman 2003). It has been argued that the very high risk of seizure associated with CM due to melanoma and in patients with both cerebral and leptomeningeal metastases (50% and 60% respectively) may justify prophylactic treatment in these groups (Batchelor 1996; Byrne 1983, cited in Klos 2004).

Table 5 Tumour location and incidence of seizures in 721 patients

Location	Total	With seizures (%)
Frontal lobe only	83	32 (39)
Frontal and parietal	38	22 (58)
Frontal and temporal	36	16 (44)
Frontal, temporal and parietal	11	5 (45)
Parietal lobe only	64	22 (43)
Temporal lobe only	52	21 (40)
Temporal and parietal	49	11 (23)
Occipital lobe only	9	1 (11)
Occipital and parietal or temporal	26	4 (15)
Central structures	30	6 (20)
Parasagittal region	29	12 (41)
Hypophyseal region	46	0 (-)
Other supratentorial	30	4 (13)
Multilocular	55	6 (11)
Infratentorial	148	3 (2)

Table 6 Type of seizure in 151 patients with primary or metastatic brain cancer

Seizure type	Freq (%)
Secondary generalised	77 (51)
Simple partial	
without secondary generalisation	41 (27)
with secondary generalisation	14 (9)
Complex partial	
without secondary generalisation	14 (9)
with secondary generalisation	1 (<1)
Both simple partial and complex partial	1 (<1)

2.3 Prognostic factors in cancer

Prognosis in cancer is influenced by a complex combination of factors, including stage of disease, size or extent of invasion of primary tumour, operability, residual mass following surgery, histopathological characteristics of the tumour and molecular biological factors. Some of these factors are routinely measured and recorded whilst others are less likely to be available. Prognosis may also be dramatically changed by treatment and response to treatment.

One of the most important – and most widely reported – prognostic factors in any cancer is stage, which not only describes the extent of disease but will also influence management, including the type and aggressiveness of any treatment attempted. The TNM staging system is based on systems developed separately by the UICC and AJCC but now united in a single classification adopted and published by both groups. The T, N and M components refer to the tumour, regional lymph nodes (locally advanced disease) and distant metastases respectively. The TNM system is the most widely used staging system worldwide, although it is not applicable to certain cancers such as lymphoma (where the Ann Arbor system has been adopted instead). The TNM publications provide a comparison, where relevant, with other widely used staging systems (such as Duke's for colorectal cancer).

3. Methods

In the first instance, it is proposed to address this question for the 6 commonest cancers (lung, breast, renal, malignant melanoma, colorectal, lymphoma). These cancers are amongst the most common primary cancers in patients with CM.

Vocational drivers who are able to return to work after a diagnosis of cancer are likely to be those with a reasonably good prognosis and in a relatively good state of health. It is therefore important to take individual prognosis into account as far as is practicably possible rather than to assume that the overall risk of metastasis in all patients with a given cancer will apply to all those wishing to return to work. Metastasis is frequently fatal (see section 2.1.3) and so patients with a lower risk of recurrence or death will also have a lower risk of developing cerebral metastases.

3.1 Data sources

In defining the prognostic groups for which risk estimates will be obtained it is important to maintain a practicable scheme, ie to use a classification which should be readily available to the DVLA via the applicant's doctor(s). It will also be important to use data which is of high quality and is as up-to-date as possible, given the limited resources available for this research. We therefore propose to use the empirical data underlying the most recent staging systems in use in the UK for each cancer as outlined in the UICC publication *Prognostic Factors in Cancer* (Gospodarowicz *et al* 2001) which accompanies the TNM staging system. The TNM publications provide a comparison with other staging systems which may be in use. There are a number of advantages to this approach:

1. The data will be of high quality and reasonably up-to-date; staging systems are updated, or new systems introduced, on the basis of new information about prognosis, usually based on large high quality empirical studies and meta-analyses.

2. The data will be reasonably comparable across different cancers, given the limitations of the research available, and the same approach may be adopted for any cancer (including those not considered in this initial report).

3. The need to update the data for any particular cancer is easily identified through the publication of an updated staging system for that cancer; important new prognostic studies will be included in the regularly updated editions of *Prognostic Factors in Cancer*.

3.2 Estimation of risk

Ideally we would require large studies including a broad range of patients which report the endpoint of time to development of CM for specific prognostic subgroups. It is unlikely that an ideal data set for our purposes has been reported for each cancer of interest given the quite specific nature of this endpoint. However, the more commonly reported endpoints of survival, recurrence-free survival, along with data on the incidence of metastases and specifically CM should enable us to obtain reasonable estimates of the incidence of CM over time in specific prognostic subgroups.

Recurrence-free survival (time to growth or reappearance of primary tumour or metastasis or death) would be a particularly useful item as we would anticipate that the majority of applicants for a vocational driving licence will be in remission with no sign of recurrence or metastatic disease. Median survival following recurrence is usually short (a few months up to 2 years for most cancers), with some exceptions such as certain types of breast cancer. One approach therefore, would be to use information on recurrence-free survival to predict the probability of relapse. The risk of CM following recurrence would be high for most patients.

Figure 1 illustrates a simple model for estimating the risk of developing metastases based on survival following recurrence or progression of disease. The hypothetical cancer illustrated has a median survival after recurrence of 12 months, modelled using a simple exponential distribution; similar curves for a range of median survivals following recurrence are shown in Figure 2. The proportion of patients with CM is estimated as 25% of the proportion who have died (the accepted figure for most primary cancers based on autopsy studies; see section 2.1.1), with an assumed average survival following the development of CM of 6 months (based on median survival following development of metastases of 1-9 months depending on treatment and type of primary cancer, and some time delay in diagnosing CM; see section 2.1.3). Note that this model assumes that a small proportion of patients will have developed CM prior to recurrence, despite development of CM being a condition which meets the definition for recurrence; this is not an unreasonable assumption given the clinical reality that the date of progression will be recorded as the date that progression has been diagnosed, rather than the date that it actually occurred.

Recurrence-free survival, however, is not commonly reported in large studies focusing on prognostic factors; overall survival is often the only survival endpoint reported. We will therefore adopt a similar approach using information on overall survival by prognostic group. The incidence of CM will be estimated by assuming that average survival from development of CM is 6 months, with the proportion of patients dying with CM calculated using estimates from autopsy studies (see section 2.1.1). This approach may slightly overestimate the risk of CM in the group of interest to the DVLA as the survival

data used will include a proportion of patients with recurrent disease who would be disqualified from holding a vocational driving licence due to medical evidence of recurrent disease.

Figure 1 Survival following progression/recurrence and development of metastases

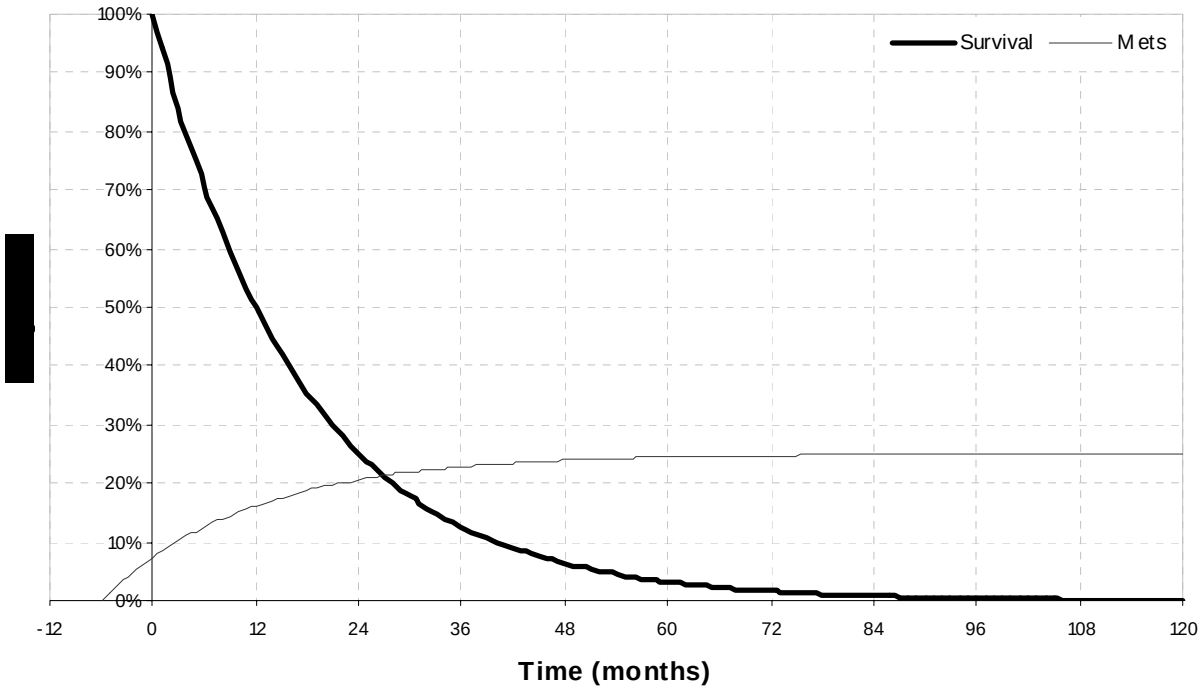
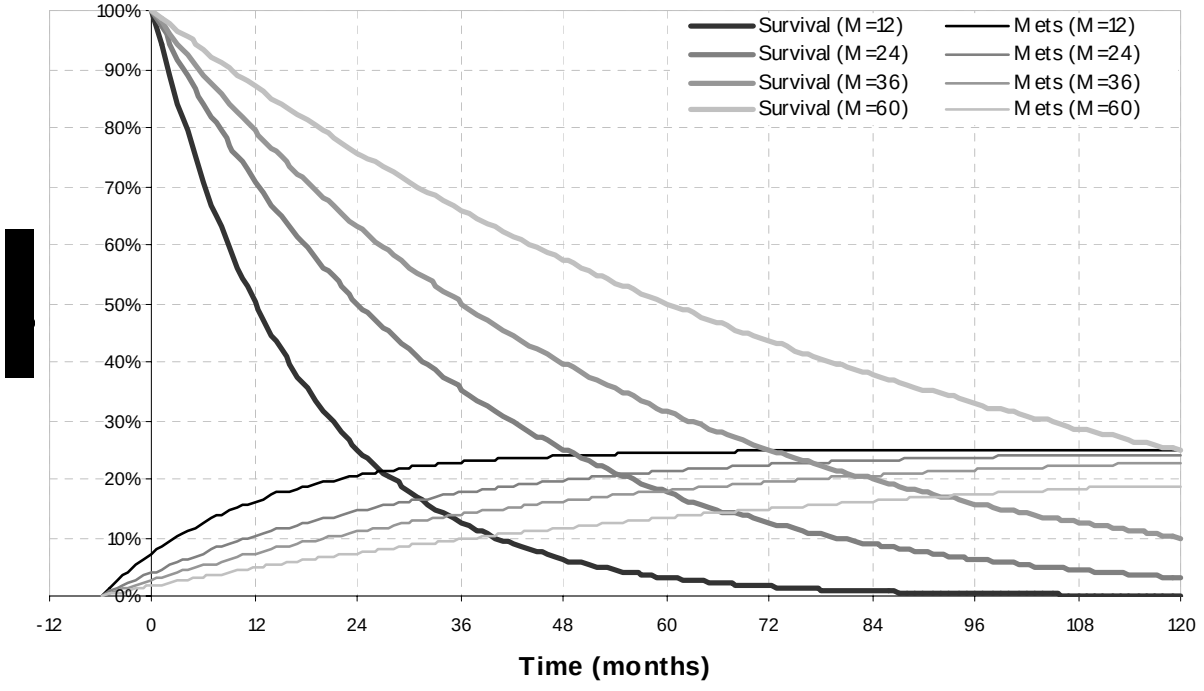


Figure 2 Survival following progression/recurrence and development of metastases for median survival after progression/recurrence of 12-60 months



For most primary cancers 30-40% of patients (and up to 50% for some cancers such as melanoma) will experience seizures due to CM (see section 2.1.3). A maximum risk of 2% per annum for sudden disabling events (ie seizure due to CM) suggests that the risk of developing CM should therefore be no greater than 10% per annum[1]. Given the high incidence of seizures and the high incidence (~90%) of other neurological complications in patients with CM (see section 2.1.3), we suggest that the risk of CM itself may be the issue of primary importance for the DVLA in assessing suitability for a vocational driving licence; this would suggest that a 10% risk of CM should be considered an absolute maximum and the threshold risk per annum should perhaps be somewhat less, of the order of 4-5%.

Published data on overall survival and the simple models presented above will be used to obtain estimates of the risk of developing CM in a given time period after diagnosis and treatment (eg 0-1, 1-2, 2-3, etc years) in each of the primary cancers considered in this report. For the majority of cancers, 5 years without recurrence of disease is considered indicative of cure, with some exceptions such as breast cancer which has a significant recurrence rate beyond 5 years; risk of recurrence will tend to reduce with time. Estimates will be presented as incidences (new cases in those free of cerebral metastasis immediately prior to that timepoint). Estimates will be presented for different prognostic subgroups of patients defined by routinely available prognostic factors, primarily stage of disease. Consideration will be given as to whether the risk of CM following local recurrence is sufficiently small for any particular subgroup to warrant further estimates of the risk of CM for applicants with locally recurrent disease.

[1] The figure of 10% per annum risk takes into account that applicants are free of CM at the start of the year. If 10% develop CM by the end of the year the average exposure to risk is only around 6 months. If 40% of patients with CM experience seizures as a result, this would give a 2% risk of seizures per annum.

4. Incidence of cerebral metastases in six common cancers

4.1 Lung cancer

4.1.1 Staging and TNM classification for lung cancer

The staging system for lung cancer is given in Table 7. The definitions for T, N and M categories are described below.

T – Primary Tumour

TX Primary tumour cannot be assessed *or* tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy

T0 No evidence of primary tumour

Tis Carcinoma in situ

T1 Tumour 3cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie not in the main bronchus)

T2 Tumour with any of the following features of size or extent: > 3 cm in greatest dimension, involves main bronchus 2 cm or more distal to the carina, invades the visceral pleura, is associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3 Tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphagm, mediastinal pleura, parietal pericardium; *or* tumour in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; *or* tumour associated with atelectasis or obstructive pneumonitis of the entire lung

T4 Tumour of any size with invasion of any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina; separate tumour nodule(s) in the same lobe; tumour with malignant pleural effusion

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis of ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension

N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M – Distant metastasis

MX Presence of distant metastasis cannot be assessed

M0 No distant metastasis
M1 Distant metastasis present

Table 7 Stage grouping for lung cancer

Stage	T status	N status	M status
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

4.1.2 Prognostic factors in lung cancer

The most important distinction between prognostic subgroups in lung cancer is by histological sub-type: small-cell (SCLC) and non-small-cell lung cancer (NSCLC). Although some early prognostic studies included both types of lung cancer, the two are now considered so dissimilar that they are generally treated as quite separate clinical entities (Brundage & MacKillop, 2001).

A second important prognostic factor is stage or extent of disease. For SCLC, stage of disease is usually classified as limited or extensive, following the Veterans Administration Lung Cancer Study Group (VALCSG), with limited disease being defined as disease confined to one hemithorax and those regional lymph nodes which can be encompassed within a tolerable radiotherapy port. This classification may also be useful in non-resectable NSCLC where management is predominantly non-surgical, but staging for NSCLC is usually done using the TNM system (Brundage & MacKillop, 2001). The TNM staging criteria were last revised in 1997, based on long-term follow-up from 5319 patients treated at the MD Anderson Center from 1975-1988 (Mountain 1997).

Stage in NSCLC will influence management and in particular will determine whether or not surgery is possible. The literature commonly splits patients with NSCLC into three broad groups: resectable, locally advanced and advanced disease (both of the latter being unsuitable for surgical management due to the extent of the tumour and/or fitness of the patient to undergo pulmonary resection).

Prognostic factors for surgically resected NSCLC, unresectable NSCLC and SCLC respectively are given in Table 8, Table 9 and Table 10 below.

Table 8 Prognostic factors in patients with surgically resected NSCLC

Prognostic factors[1]	Tumour related	Host related	Environment related
Essential	Stage	Weight loss	Resection margin
	N category	Performance status	
	Hypercalcaemia		
Additional	T category	Sex	
	Nodal level	Age	
	Intrapulmonary metastases		
	Grade		
	Cell type		
	Vessel invasion		

[1] *Adapted from Brundage & MacKillop in Gospodarowicz et al, 2001*

Table 9 Prognostic factors in patients with advanced NSCLC

Prognostic factors[1]	Tumour related	Host related	Environment related
Essential	Stage (III vs IV)	Weight loss	Chemoradiotherapy (selected stage III)
	Hypercalcaemia	Performance status	
	SVCO		Chemotherapy (selected stage IV)
Additional	T category	Sex	Physician opinion
	N category	Age	
	Stage IIA vs IIIB	Symptoms	
	Number of sites involved		
	Pleural effusion		
	Liver metastases		
	Haemoglobin, LDH and albumin		

[1] *Adapted from Brundage & MacKillop in Gospodarowicz et al, 2001*

Table 10 Prognostic factors in patients with SCLC

Prognostic factors[1]	Tumour related	Host related	Environment related
Essential	Stage (limited vs extensive)	Performance status	Chemotherapy Thoracic radiotherapy
Additional	Histologic subtype Serum LDH Serum alkaline phosphatase Cushing's syndrome Mediastinal involvement (limited disease) Number of sites involved, bone or brain involvement, WBC and platelet count (extensive disease)	Weight loss Sex	Completion of chemotherapy

[1] *Adapted from Brundage & MacKillop in Gospodarowicz et al, 2001*

4.1.3 Estimated incidence of cerebral metastases in lung cancer by prognostic group

4.1.3.1 Resectable NSCLC

The most recent TNM staging system was based on a large series of 5319 patients treated at the MD Anderson from 1975-1988; this series included 1524 consecutive previously untreated patients treated at MD Anderson between 1983 and 1988 combined with a previously published database (Mountain 1997). The estimates presented in this section are based on this data.

The reported survival rates at annual intervals from Mountain 1997 are reproduced in Table 11.

Table 11 Survival at 1-5 years in early stage NSCLC

Stage[1]	N	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)
pIA	511	94	86	80	73	67
pIB	549	87	76	67	62	57
pIIA	76	89	70	64	61	55
pIIB	375	73	56	46	42	39
pIIIA	399	64	40	32	26	23

[1] *the p indicates pathologically determined stage (as opposed to clinically determined), indicating that resection has been possible*

Autopsy studies suggest that around 20% of NSCLC patients have CM at death (see section 2.1.1). Figure 3 shows the survival data from Table 11 with estimated time to development of CM; the latter was estimated by fitting a Weibull distribution to each set of survival data, assuming that 20% of patients have developed CM at the time of death with an average survival with CM of 6 months. Estimates of the annual risk of developing CM by stage are given in Table 12.

Figure 3 Survival and estimated time to development of CM in resectable NSCLC

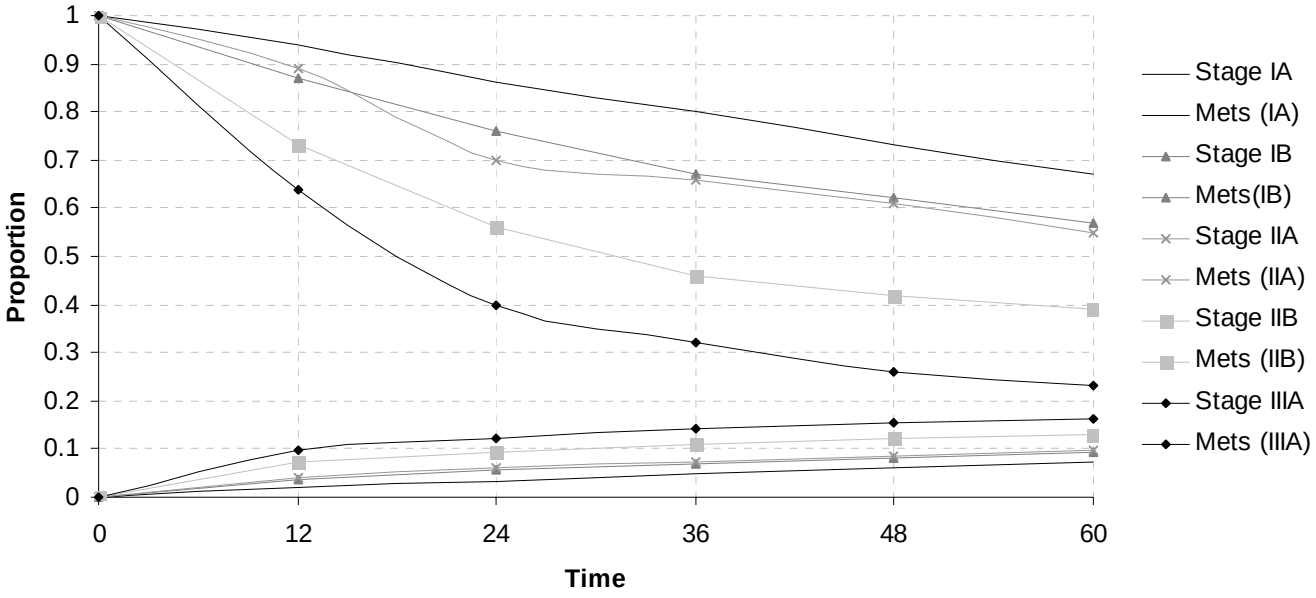


Table 12 Estimated annual risk of developing CM in early stage NSCLC

Time period (years)	Stage				
	pIA	pIB	pIIA	pIIB	pIIIA
0-1	2.0%	3.8%	4.1%	7.3%	9.7%
1-2	1.5%	2.2%	2.4%	3.6%	5.5%
2-3	1.6%	2.0%	2.2%	3.1%	4.9%
3-4	1.6%	1.9%	2.0%	2.8%	4.5%
4-5	1.7%	1.8%	1.9%	2.6%	4.2%

4.1.3.2 Unresectable NSCLC

Unresectable NSCLC includes all later stage NSCLC (cIIIB-cIV) and early stage (cIA-cIIIA) inoperable cancers. The prognosis for this group is considerably worse than for resectable NSCLC. One year survival for stage IIIB is around 34%, decreasing to 19% for stage IV (Mountain 1997). The annual risk of CM in these patients is high (of the order of 15% in the first year) and precludes the issue of a vocational driving licence at any point following diagnosis.

4.1.3.3 SCLC

SCLC, whether limited or extensive, has a much worse prognosis than NSCLC, with survival rates comparable to later stage unresectable NSCLC (Brundage & MacKillop 2001). According to autopsy studies, approximately 40% of patients with SCLC will develop CM prior to death (see section 2.1.1). The annual risk of CM in these patients is very high (of the order of 30% in the first year) and precludes the issue of a vocational driving licence at any point following diagnosis.

4.1.3.4 Recurrent disease

Survival following recurrence is poor. The annual risk of CM following recurrence, whether local or metastatic, is high and precludes the issue of a vocational driving licence.

4.2 Breast cancer

4.2.1 Staging for breast cancer

The staging system for breast cancer is given in Table 13. The definitions for T, N and M categories are described below.

4.2.1.1 TNM classification

T – Primary Tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ; intraductal carcinoma, or lobular carcinoma in situ, or Paget disease of the nipple with no tumour

T1 Tumour 2 cm or less in greatest dimension
- T1mic Microscopic invasion 0.1cm or less in greatest dimension
- T1a More than 0.1cm but no more than 0.5cm in greatest dimension
- T1b More than 0.5cm but no more than 1cm in greatest dimension
- T1c More than 1cm but no more than 2cm in greatest dimension

T2 Tumour more than 2 cm but not more than 5 cm in greatest dimension

T3 Tumour more than 5 cm in greatest dimension

T4 Tumour of any size with direct extension into the chest wall or skin only as described in T4a-d
- T4a Extension to chest wall
- T4b Edema (including peau d'orange), or ulceration of the skin or breast, or satellite skin nodules confined to the same breast
- T4c Both 4a and 4b above
- T4d Inflammatory carcinoma

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed (eg previously removed)

N0 No regional lymph node metastasiss

N1 Metastasis to movable ipsilateral axillary node(s)

N2 Metastasis to ipsilateral axillary node(s) fixed to one another or to other structures

N3 Metastasis to ipsilateral internal mammary lymph node(s)

M – Distant metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Table 13 Stage grouping for breast cancer

Stage	T status	N status	M status
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

4.2.2 Prognostic factors in breast cancer

Stage is the most important prognostic factor in breast cancer; other factors are listed in Table 14.

Table 14 Prognostic factors in patients with breast cancer

Prognostic factors	Tumour related	Host related	Environment related
Essential	Stage Grade and histologic type Mitotic figure count Hormone receptor status Tumour recurrence or metastasis after primary therapy	Age	Effect of local and systemic treatment
Additional	Genetic factors Peritumoral vascular invasion	Pregnancy, ethnicity, socioeconomic status, heredity, sex	Effect of screening

Adapted from Fitzgibbons in Gospodarowicz et al, 2001

4.2.3 Estimated incidence of cerebral metastases by prognostic group

The estimates in this section are taken from a series of 22616 patients from the SEER Program for the National Institute of Cancer (Henson 1991). Progression-free survival is not reported and so estimates are based on reported overall survival. 5-year survival rates were used to construct survival curves with a Weibull distribution and shape parameter of 1.1. The proportion with CM was estimated as 25% of the proportion who have died, in line with autopsy studies (see section 2.1.1) and CM were assumed to appear an average of 6 months prior to death (see section 2.1.3).

Figure 4 shows the estimated survival curves with estimated time to development of CM; the latter was estimated by assuming that 25% of patients have developed CM at the time of death with an average survival with CM of 6 months. Estimates of the annual risk of developing CM by stage are given in Table 15.

Figure 4 Survival and estimated time to development of CM in breast cancer

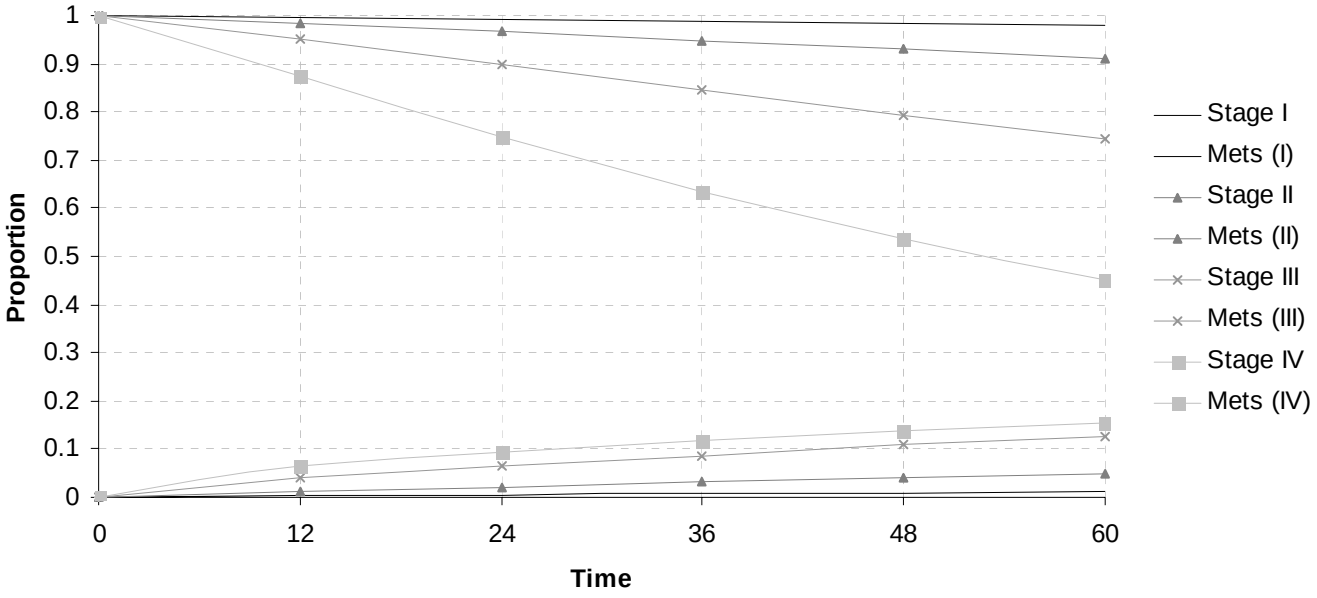


Table 15 Estimated annual risk of developing CM in breast cancer

Time period (years)	Stage			
	Stage I	Stage II	Stage III	Stage IV
0-1	0.3%	1.3%	3.9%	9.2%
1-2	0.2%	0.9%	2.9%	7.1%
2-3	0.2%	1.0%	3.1%	7.4%
3-4	0.2%	1.0%	3.2%	7.6%
4-5	0.2%	1.1%	3.2%	7.8%

4.2.3.1 Recurrent disease

Survival following early recurrence (within 5 years of first diagnosis) is poor. The annual risk of CM following recurrence, whether local or metastatic, is high in these patients and precludes the issue of a vocational driving licence.

Survival following a late local recurrence, 5 years or more from first diagnosis, is much better and some consideration might be given to whether the risk of CM is sufficiently low in these patients to allow the issue of a vocational driving licence if treatment for recurrent disease is successful.

4.3 Colorectal cancer

4.3.1 Staging for colorectal cancer

The TNM and Duke's staging systems for colorectal cancer are given in Table 16. The definitions for T, N and M categories are described below.

T– Primary Tumour

TX Tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ: intraepithelial or invasion of lamina propria

T1 Tumour invades submucosa

T2 Tumour invades muscularis propria

T3 Tumour invades through the muscularis propria into the subserosa or into nonperitonealised pericolic or perirectal tissue

T4 Tumour directly invades other organs or structures and/or perforates visceral peritoneum

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in 1 to 3 regional lymph nodes

N2 Metastasis in 4 or more regional lymph nodes

M – Distant Metastases

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis present

Table 16 Stage grouping for colorectal cancer

Stage	T status	N status	M status	Duke's Stage
Stage 0	Tis	N0	M0	
Stage I	T1	N0	M0	A
	T2	N0	M0	
Stage II	T3	N0	M0	B
	T4	N0	M0	
Stage III	Any T	N1	M0	C
	Any T	N2	M0	
Stage IV	Any T	Any N	M1	D

4.3.2 Prognostic factors in colorectal cancer

Pathologic stage of disease is the most powerful prognostic factor in colorectal cancer. The TNM system is advocated for use in clinical trials and clinical practice, although the Duke's system is also widely used. The key difference between the two systems is that the Duke's system does not account separately for tumour invasion and lymph node status. Other prognostic factors are given in Table 17.

Table 17 Prognostic factors in resectable colorectal cancer

Prognostic factors[1]	Tumour related	Host related	Environment related
Essential	TNM stage	Obstruction	Negative surgical margin
	Blood/lymphatic invasion	Perforation	Surgeon
	CEA >5		Adjuvant chemotherapy
			Adjuvant radiotherapy
Additional	Grade		
	Histologic type		
	Tumour border configuration		
	Perineal invasion		

[1] *Adapted from Hobday & Erlichman in Gospodarowicz et al, 2001*

Table 18 Prognostic factors in unresectable or metastatic colorectal cancer

Prognostic factors[1]	Tumour related	Host related	Environment related
Essential	Resectable metastatic disease Tumour burden Disease-free interval	Performance status	Surgeon
Additional	Grade CEA level		

[1] *Adapted from Brundage & MacKillop in Gospodarowicz et al, 2001*

4.3.3 Estimated incidence of cerebral metastases by prognostic group

4.3.3.1 Resectable colorectal cancer

The estimates in this section are taken from a series of 1050 patients with colorectal cancer undergoing surgery (Wolters 1996). Data were read from published survival curves. The proportion with CM was estimated as 25% of the propotion who have died, in line with autopsy studies (see section 2.1.1) and CM were assumed to appear an average of 6 months prior to death (see section 2.1.3).

Figure 5 shows the survival curves with estimated time to development of CM; the latter was estimated by fitting a Weibull distribution to each set of survival data, assuming that 25% of patients have developed CM at the time of death with an average survival with CM of 6 months. Estimates of the annual risk of developing CM by stage are given in Table 19.

Figure 5 Survival and estimated time to development of CM in colorectal cancer following surgery

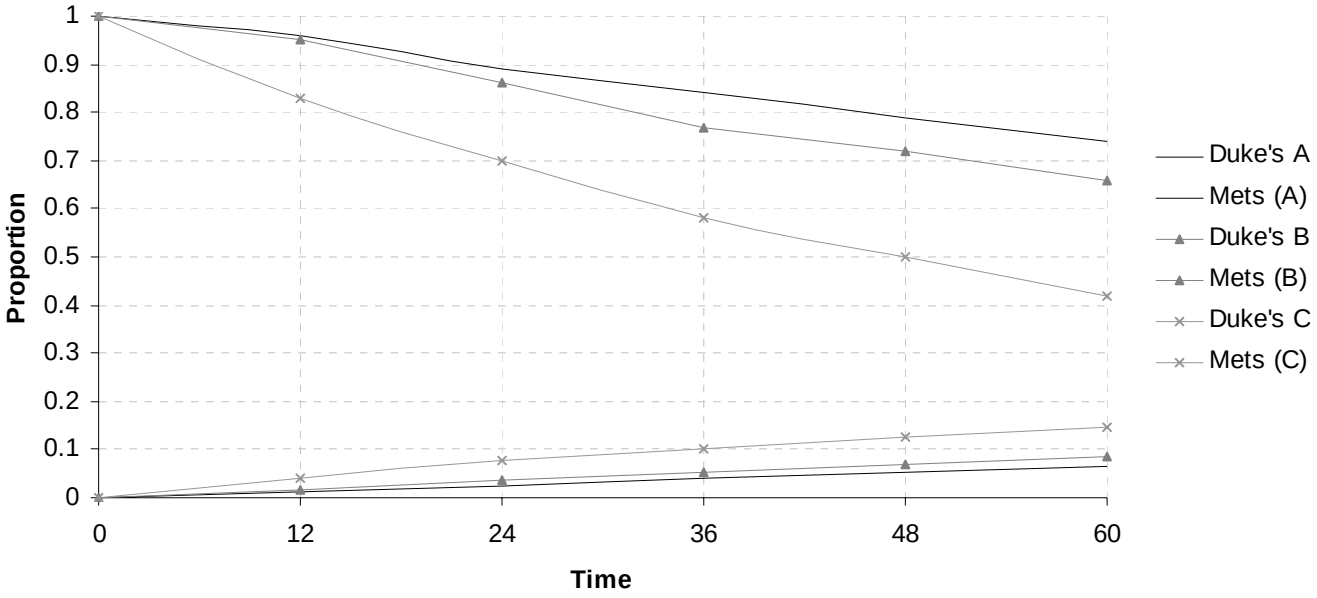


Table 19 Estimated annual risk of developing CM in resectable colorectal cancer

Time period (years)	Stage		
	Duke's A Stage I	Duke's B Stage II	Duke's C Stage III
0-1	1.2%	1.7%	4.3%
1-2	1.4%	2.0%	4.0%
2-3	1.5%	2.1%	3.9%
3-4	1.6%	2.2%	3.9%
4-5	1.6%	2.3%	3.8%

4.3.3.2 Unresectable colorectal cancer

Unresectable colorectal cancer and Duke's D (metastatic disease) has a poor prognosis. One year survival for Duke's D is around 35% (Wolters 1997). The annual risk of CM in these patients is high (of the order of 15% in the first year) and precludes the issue of a vocational driving licence at any point following diagnosis.

4.3.3.3 Recurrent disease

Survival following recurrence is poor. The annual risk of CM following recurrence, whether local or metastatic, is high and precludes the issue of a vocational driving licence.

4.4 Renal carcinoma

4.4.1 Staging for renal-cell carcinoma

The TNM staging system for renal-cell carcinoma is given in Table 20. The definitions for T, N and M categories are described below.

4.4.1.1 TNM classification

T – Primary Tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

T1 Tumour 7cm or less in greatest dimension, limited to the kidney

T2 Tumour more than 7cm in greatest dimension, limited to the kidney

T3 Tumour extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota fascia

- T3a Tumour directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota fascia
- T3b Tumour grossly extends into the renal vein or its segmental (i.e., muscle-containing) branches, or the vena cava below the diaphragm
- T3c Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava

T4 Tumour invades beyond Gerota fascia

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single regional lymph node

N2 Metastasis in more than one regional lymph node

M – Distant Metastases

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Table 20 Stage grouping for renal-cell carcinoma

Stage	T status	N status	M status
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0, N1	M0
Stage IV	T4	N0, N1	M0
	Any T	N2	M0
	Any T	Any N	M1

4.4.2 Prognostic factors in renal-cell carcinoma

The most important prognostic factor in renal cancer is stage of disease at diagnosis. The TNM system is currently considered standard. Other prognostic factors are listed in Table 21.

Table 21 Prognostic factors in renal-cell carcinoma

Prognostic factors[1]	Tumour related	Host related	Environment related
Essential	Stage Grade	Hereditary diseases	Radical or partial nephrectomy
Additional	Histologic type Vena cava invasion Nuclear morphometry Mitotic rate Sedimentation rate Symptoms	Performance status	Adrenalectomy Lymph node dissection

[1] *Adapted from van Poppel, Beckers & Baert in Gospodarowicz et al, 2001*

4.4.3 Estimated incidence of cerebral metastases by prognostic group

The estimates presented in this section are based on a small series of 155 patients undergoing nephrectomy for renal-cell carcinoma at Manchester Royal Infirmary between 1965 and 1985 (Sene 1992). One larger series of 328 patients was identified (Giberti 1997), but results in this paper were not presented by stage and so estimates could not be obtained in a useful form for this report.

Progression-free survival is not reported and so estimates are based on reported overall survival. Data were read from published survival curves. The proportion with CM was estimated as 25% of the proportion who have died, in line with autopsy studies (see section 2.1.1) and CM were assumed to appear an average of 6 months prior to death (see section 2.1.3).

Figure 6 shows the survival curves with estimated time to development of CM; the latter was estimated by fitting a Weibull distribution to each set of survival data, assuming that 25% of patients have developed CM at the time of death with an average survival with CM of 6 months. Estimates of the annual risk of developing CM by stage are given in Table 22.

Figure 6 Survival and estimated time to development of CM in renal-cell carcinoma following nephrectomy

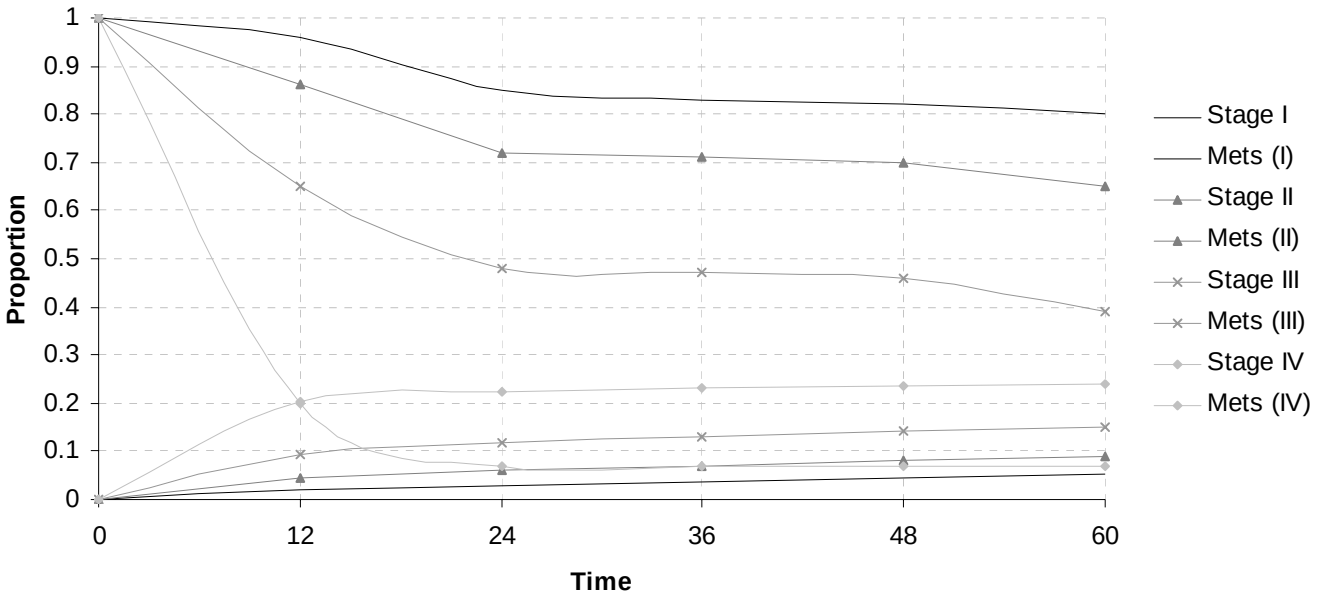


Table 22 Estimated annual risk of developing CM in renal-cell carcinoma following nephrectomy

Time period (years)	Stage			
	Stage I	**Stage II**	**Stage III**	**Stage IV**
0-1	1.9%	4.3%	9.5%	20.5%
1-2	1.2%	2.0%	3.6%	9.8%
2-3	1.0%	1.5%	2.7%	7.5%
3-4	0.9%	1.3%	2.2%	6.2%
4-5	0.8%	1.2%	1.9%	5.4%

4.4.3.1 Recurrent disease

Survival following recurrence is poor. The annual risk of CM following recurrence, whether local or metastatic, is high and precludes the issue of a vocational driving licence.

4.5 Malignant melanoma

4.5.1 Staging for melanoma

The TNM staging system for melanoma is given in Table 23. The definitions for T, N and M categories are given below.

T – Primary Tumour

T1 Tumour less than or equal to 1mm
- T1a Without ulceration
- T1b With ulceration or Clark level IV or V

T2 Tumour more than 1mm and less than or equal to 2mm
- T1a Without ulceration
- T1b With ulceration

T3 Tumour more than 2mm and less than or equal to 4mm
- T1a Without ulceration
- T1b With ulceration

T4 Tumour greater than 4mm
- T1a Without ulceration
- T1b With ulceration

N – Regional Lymph Nodes

N1 One lymph node
- N1a: micrometastasis
- N1b: macrometastasis

N2 2-3 lymph nodes
- N2a: micrometastasis
- N2b: macrometastasis
- N2c: in-transit met(s)/satellite(s) without metastatic lymph nodes

N3 Four or more metastatic lymph nodes, matted lymph nodes, or combinations of in-transit mets(s)/satellite(s) without metastatic lymph nodes

M – Distant Metastases

M1 Distant skin, SQ, or lymph node metastases with normal LDH

M2 Lung metastases with normal LDH

M3 All other visceral or any distant metastases with normal or elevated LDH

Table 23 Stage grouping for malignant melanoma

Stage	T status	N status	M status
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1, N2	M0
Stage IV	Any T	Any N	M1

4.5.2 Prognostic factors in malignant melanoma

The most important prognostic factor in malignant melanoma is stage of disease. Other prognostic factors are listed in Table 24.

Table 24 Prognostic factors in malignant melanoma

Prognostic factors[1]	Tumour related	Host related	Environment related
Essential	Tumour thickness (primary tumour) Site of metastases (cutaneous, lymph nodes, systemic)	Age Sex Anatomic site	Completeness of primary excision
Additional	Mitotic rate, ulceration, regression, level of invasion, TIL, growth phase, histologic type, cross-sectional profile		Lymph node dissection, excision of isolated metastases Treatment (chemotherapy, radiotherapy, immunotherapy)

[1] *Adapted from Heenan, Yu & English in Gospodarowicz et al, 2001*

4.5.3 Estimated incidence of cerebral metastases by prognostic group

The estimates for this section are taken from a report based on 8500 cases of malignant melanoma treated at The University of Alabama and the Sydney Melanoma Unit from 1955 to1986 (Balch et al).

Progression-free survival is not reported and so estimates are based on reported overall survival. Data were estimated from published survival curves. The proportion with CM was estimated as 45% of the proportion who have died, in line with autopsy studies (see section 2.1.1) and CM were assumed to appear an average of 6 months prior to death (see section 2.1.3).

Figure 7 shows the survival data from Balch *et al* with estimated time to development of CM; the latter was estimated by fitting a Weibull distribution to each set of survival data, assuming that 45% of patients have developed CM at the time of death with an average survival with CM of 6 months. Estimates of the annual risk of developing CM by stage are given in Table 25.

Figure 7 Survival and estimated time to development of CM in melanoma

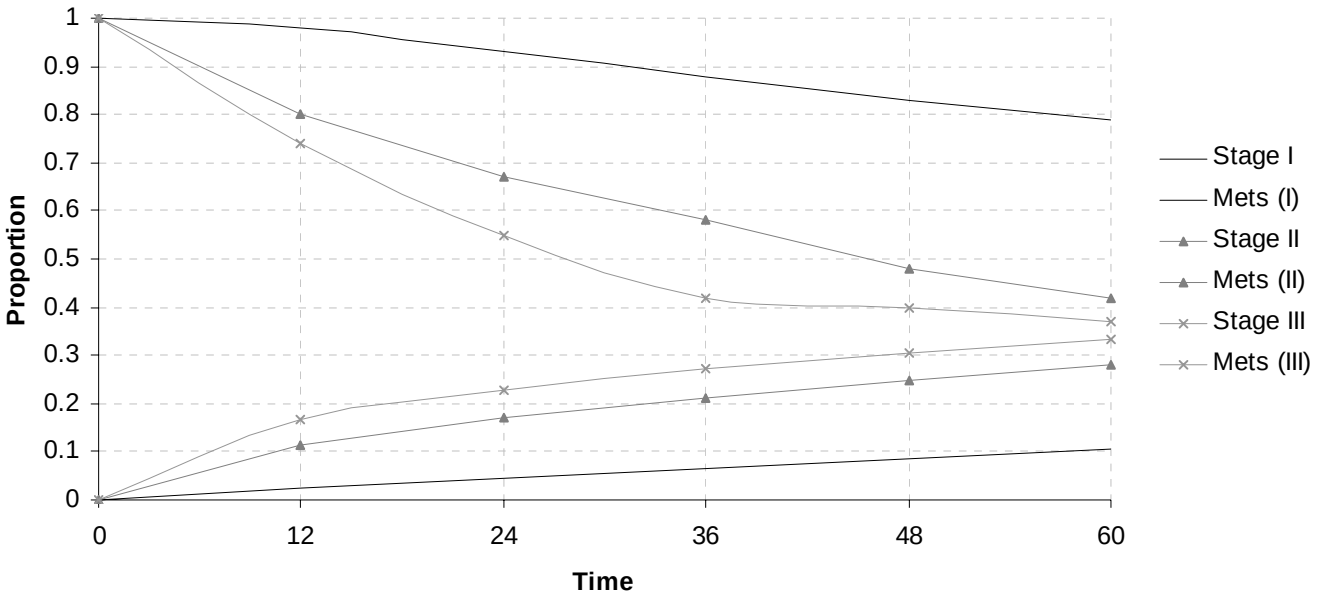


Table 25 Estimated annual risk of developing CM in melanoma

Time period (years)	Stage		
	Stage I	**Stage II**	**Stage III**
0-1	2.4%	11.5%	16.6%
1-2	2.0%	7.4%	10.1%
2-3	2.2%	7.2%	9.4%
3-4	2.3%	7.0%	8.9%
4-5	2.4%	6.9%	8.6%

The prognosis for Stage IV melanoma is considerably worse than for earlier stages. One year survival is around 10% (Balch et al). The annual risk of CM in these patients is high (of the order of 40% in the first year) and precludes the issue of a vocational driving licence at any point following diagnosis.

4.5.3.1 Recurrent disease

Survival following recurrence is poor. The annual risk of CM following recurrence, whether local or metastatic, is high and precludes the issue of a vocational driving licence.

4.6 Lymphoma

4.6.1 Staging for non-Hodgkin's lymphoma

The TNM staging system does not apply well to lymphoma and so the Ann-Arbor staging system (originally formulated for Hodgkin's disease) has been widely adopted instead, and is included in the TNM publications (see Table 26).

Table 26 Ann-Arbor staging classification for non-Hodgkin's lymphoma

Stage I	Involvement of a single lymph node region (I) or localised involvement of a single extra-lymphatic organ or site (I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of a single extra-lymphatic organ or site and its regional lymph node(s) with or without involvement of other lymph node regions on the same side of the diaphragm (II_E).
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localised involvement of an associated extralymphatic organ or site (III_E) or by involvement of the spleen (III_S) or both (III_{S+E})
Stage IV	Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement

4.6.2 Prognostic factors in non-Hodgkin's lymphoma

The Ann-Arbor staging system does not include some more recently discovered prognostic factors, such as LDH levels, and is not a particularly good predictor of outcome on it's own. A list of known prognostic factors in lymphoma is given in Table 27.

In 1993 The International Non-Hodgkin's Lymphoma Prognostic Factors Project published an international prognostic index (IPI) which was more successful in distinguishing prognostic groups. The simplified age-adjusted version of this index, for younger patients aged 60 years or less, is given in Table 28. This index has been chosen as it is both simpler and more likely to be applicable to applicants for a vocational driving licence. In the full IPI, when age (≤60 vs >60) is included as a risk factor, extra-nodal site involvement is also an important risk factor and is included in the full model; for patients aged 60 years or less extra-nodal site involvement is not an important predictor of outcome and can therefore be excluded from the index for younger patients.

Table 27 Prognostic factors in non-Hodgkin's lymphoma

Prognostic factors[1]	Tumour related	Host related	Environment related
Essential	Histologic type	Age	
	Stage	HIV status	
	Presenting extranodal site		
Additional	LDH	IPI score	Malnutrition
	Molecular/cytogenetics		
	BCL-2 protein		

[1] *Adapted from Crump & Gospodarowicz in Gospodarowicz et al, 2001*

Table 28 Age-adjusted International prognostic index (IPI) for non-Hodgkin's Lymphoma in patients aged 60 years or less

Risk factor	Low risk	High risk
Serum lactate dehydrogenase (LDH)	Normal	Elevated
Ann-Arbor Stage	I or II	III or IV
Performance status	0 or 1	2-4

Risk group	Definition
Low risk (L)	0 risk factors present
Low intermediate risk (LI)	1 risk factors present
High intermediate risk (HI)	2 risk factors present
High risk (H)	3 risk factors present

4.6.3 Estimated incidence of cerebral metastases by prognostic group

The estimates presented in this section are based on the original publication of the IPI by the International Non-Hodgkin's Lymphoma Prognostic Factors Project (IN-HLPFP 1993). The age adjusted index (see Table 28) is based on data from 885 patients with aggressive non-Hodgkins lymphoma aged 60 years or less.

Data were estimated from published survival curves. The proportion with CM was estimated as 25% of the proportion who have died, in line with autopsy studies (see section 2.1.1) and CM were assumed to appear an average of 6 months prior to death (see section 2.1.3).

Figure 8 shows the survival data from the IN-HLPFP IPI, along with estimated time to development of CM; the latter was estimated by fitting a Weibull distribution to each set of survival data, assuming that 25% of patients have developed CM at the time of death with an average survival with CM of 6 months. Estimates of the annual risk of developing CM by stage are given in Table 29.

Figure 8 Survival and estimated time to development of CM in lymphoma

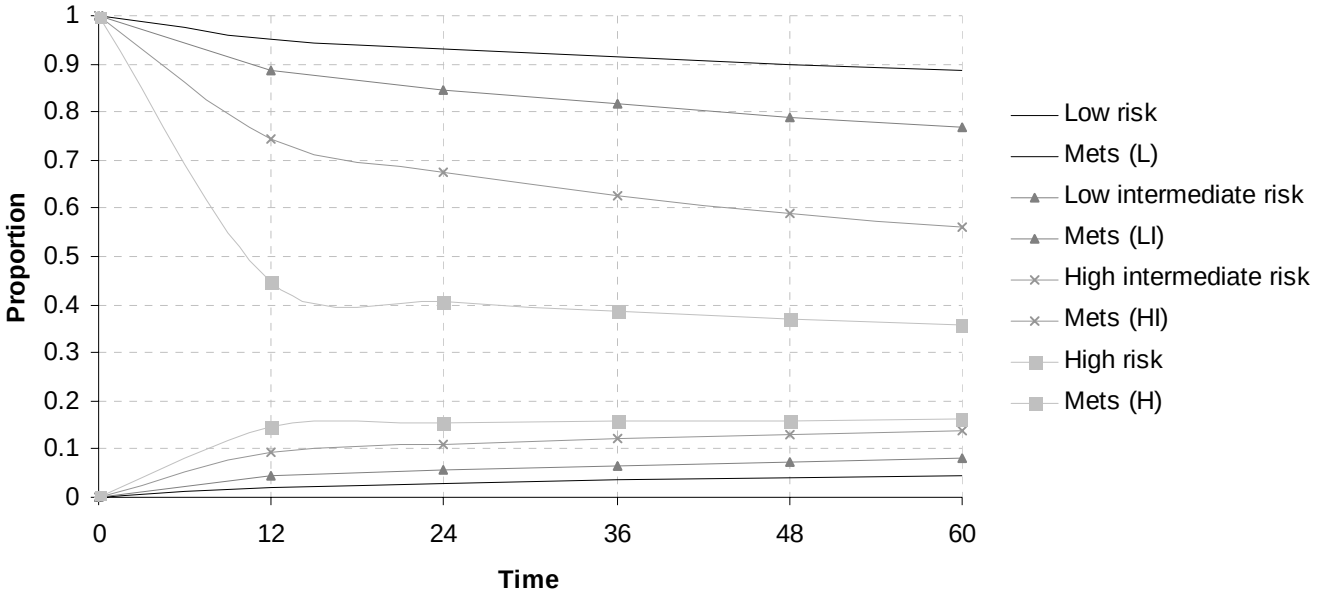


Table 29 Estimated annual risk of developing CM in lymphoma

Time period (years)	IPI risk			
	Low	Low intermediate	High intermediate	High
0-1	2.2%	4.6%	9.3%	15.4%
1-2	0.9%	1.7%	3.1%	2.3%
2-3	0.7%	1.3%	2.3%	1.5%
3-4	0.6%	1.1%	1.9%	1.1%
4-5	0.6%	1.0%	1.7%	0.9%

4.6.3.1 Recurrent disease

Survival following recurrence is poor. The annual risk of CM following recurrence, whether local or metastatic, is high and precludes the issue of a vocational driving licence.

5. Discussion

5.1 Limitations of the report

A very simple model has been used to estimate the risk of CM. In all cases overall survival has been used to estimate risk, working backwards from the proportion dying with CM and utilising data on median survival following development of CM. A somewhat more complex model based on recurrence-free survival would be preferable as the populations used to estimate these curves more closely match those likely to be applying and potentially eligible for a vocational driving licence.

All of the estimates are based on single reports. Methods for meta-analysing prognostic factor analyses are not well developed, and such an undertaking is well beyond the scope of this project. In most cases large series were obtainable through the literature, although data from some of the larger series available were not always reported in an appropriate form for the purposes of this report.

In all cases apart from lymphoma (and to a limited extent, lung cancer), estimates are provided for subgroups defined by a single prognostic factor – stage of disease. Whilst this is the most important, and most easily obtainable, factor for most cancers, further refinements could be made by taking into account other important factors (such as differentiation of tumour, ulceration in melanoma, multifocal vs bilateral renal-cell carcinoma, hormone receptor status in breast cancer, and so on). However, this would require a very substantial extension to the research as much more complex modelling work would be required to obtain multi-variate estimates from the existing literature. It might be possible to identify well-researched, widely accepted and simple to apply prognostic indices similar to the IPI for lymphoma in order to extend the work for some of these cancers.

5.2 Recommendations for further research

This report has focused on the six most common cancers, which are also amongst the most common primary cancers associated with CM. Further work on other cancers should prioritise by propensity to metastasise and incidence. Amongst the other most common primary cancers resulting in CM but not considered in this report are thyroid, leukaemia and prostate cancer. Prostate cancer, however, has a relatively low propensity to metastasise to the brain and appears on this list primarily because it is so common; as prostate cancer affects predominantly elderly men well beyond the age of retirement, it should probably not be a priority for further investigation for the DVLA with regards to vocational driving licences. Sarcoma, ovarian and bladder cancer also metastasise to the brain relatively infrequently.

Breast cancer is unusual in that late (occurring more than 5 years after initial diagnosis) local (non-metastatic) recurrences have a relatively good prognosis compared to other cancers. Whereas for most cancers any recurrence confers an unacceptably high risk of CM, there may be a subset of applicants with locally recurrent breast cancer for whom issue of a vocational driving licence might be appropriate.

Survival data has been used for most of this report due to lack of availability of progression-free survival data for many cancers. This work could be extended to employ an alternative model using recurrence-free survival data, where obtainable, at least as a check on the accuracy of the approach using survival data alone. This endpoint is frequently not considered in large population-based prognostic studies – often due to difficulties in obtaining accurate data – and so it may be difficult to obtain suitable estimates from large population-based series.

6. References

Akeson P, Larsson EM, Kristofferson DT, Jonsson E & Holtas S. Brain metastases: comparison of gadodiamide injection-enhanced MRI imaging at standard and high dose, contrast-enhanced CT, and non-contrast-enhanced MR imaging. *Acta Radiologica*, 1995; **36**: 300-306

Arbit E & Wronski M. the treatment of brain metastases. *Neurosurgical Quarterly*, 1995; **5**; 1

Armstrong TS & Gilbert MR. Metastatic brain tumours: diagnosis, treatment and nursing interventions. *Clinical Journal of Oncology Nursing*, 2000; **4**: 217-225

Balch C, Soong SJ, Shaw H *et al*. An analysis of prognostic factors in 8500 patients with cutaneous melanoma. In: Balch C, Houghton A, Sober AJ *et al* (Eds): *Cutaneous Melanoma* (pp 165-187, 2nd edition). Philadelphia: Lippincott; 1992

Batchelor T & DeAngelis LM. Medical management of cerebral metastases. *Neurosurgery clinics of North America*, 1996; **7**: 435-446

Brundage MD & MacKillop WJ. Lung Cancer. In: Gospodarowicz MK, Henson DE, Hunter RVP, O'Sullivan B, Sobin LH, Wittekind Ch (Eds). *Prognostic Factors in Cancer*. New York: Wiley; 2001

Byrne TN, Cascino TL & posner JB. Brain metastases from melanoma. *Journal of Neurooncology*, 1983; **1**: 313

Buckner J. Surgery, radiation therapy and chemotherapy for metastatic tumors to the brain. *Current Opinion in Oncology*, 1992; **4**: 518-524

Chidel MA, Suh JH & Barnett G. Brain metastases: presentation, evaluation, and management. *Cleveland Clinic Journal of Medicine*, 2000; **67**: 120-127

Cohen N, Strauss G, Lew R *et al*. Should prophylactic anticonvulsants be administered to patients with newly diagnosed cerebral metastases? A retrospective analysis. *Journal of Clinical Oncology*, 1988; **6**: 1621-1624

Coon WW & willis PW. Hemorrhagic complications of anticoagulant therapy. *Archives of Internal Medicine*, 1974; **133**: 386-392

Crump M & Gospodarowicz M. Non-Hodgkin's malignat lymphoma. In: Gospodarowicz MK, Henson DE, Hunter RVP, O'Sullivan B, Sobin LH, Wittekind Ch (Eds). *Prognostic Factors in Cancer*, 2001. New York: Wiley

Delattre JY, Krol G, Thaler HT *et al*. Distribution of brain metastases. *Archives of Neurology*, 1988; **45**: 741-744

Engel J. *Seizures and Epilepsy*. Philadephia: Davis; 1989

Fitzgibbons ML. Breast cancer. In: Gospodarowicz MK, Henson DE, Hunter RVP, O'Sullivan B, Sobin LH, Wittekind Ch (Eds). *Prognostic Factors in Cancer*. New York: Wiley; 2001

Giberti C, Oneto F, Martorana G, Rovida S & Carmignani G. Radical nephrectomy for renal-cell carcinoma: long-term results and prognostic factors on a series of 328 cases. *European Urology*, 1997; **31**: 40-48

Glantz MJ, Cole BF, Forsyth PA *et al*. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 2000; **54**: 1886-1893

Gospodarowicz MK, Henson DE, Hunter RVP, O'Sullivan B, Sobin LH, Wittekind Ch (Eds). *Prognostic Factors in Cancer*. New York: Wiley; 2001

Hall WA, Djalilian HR, Nussbaum ES *et al*. Long-term survival with metastatic cancer to the brain. *Medical Oncology*, 2000; **17**: 279-286

Heenan PJ, Yu L & English DR. Cutaneous malignant melanoma. In: Gospodarowicz MK, Henson DE, Hunter RVP, O'Sullivan B, Sobin LH, Wittekind Ch (Eds). *Prognostic Factors in Cancer*. New York: Wiley; 2001.

Henson DE, Ries MS, Freedman LS & Carriaga M. Relationship among outcome, stage of disease and histologic grade for 22,616 cases of breast cancer: a basis for a prognostic index. *Cancer*, 1991; **68**: 2142-2149

Hobday TJ & Erlichman C. Colorectal cancer. In: Gospodarowicz MK, Henson DE, Hunter RVP, O'Sullivan B, Sobin LH, Wittekind Ch (Eds). *Prognostic Factors in Cancer*. New York: Wiley; 2001

International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *New England Journal of Medicine*, 1993; **329**: 987-994

Jacobs M & Phuphanich S. Seizures in brain metastasis and meningeal carcinamatosis. *Proceedings of the American Society of Clinical Oncology*, 1990; Abstract 373

Klos KJ & O'Neill BP. Brain metastases. *The Neurologist*, 2004; **10**: 31-46

Lagerward FJ, Levendag PC, Nowak PJ *et al*. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *International Journal of Radiation Oncology Biology Physics*, 1999; **43**: 795

Langer CJ & Mehta MP. Current management of brain metastases, with a focus on systemic options. *Journal of Clinical Oncology*, 2005; **23**: 6207-6219

Lassman AB & DeAngelis LM. Brain Metastases. Brain metastases. *Neurologic Clinics of North America*, 2003; **21**: 1-23

Liigant A, Haldre S, Oun A, Linnamagi U, Saar A, Asser T, Kaasik A-E. Seizure disorders in patients with brain tumours. *European Neurology*, 2001; **45**: 46-51

Mandybur TI. Intracranial hemorrhage caused by metastatic tumours. *Neurology*, 1977; **27**: 650

Markesbery WR, Brooks WH, Gupta GD *et al*. Treatment for patients with cerebral metastases. *Archives of Neurology*, 1978; **35**: 754-756

Meyers CA, Smith JA, Bezjak A *et al*. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *Journal of Clinical Oncology*, 2004; **22**: 157-165

Morris HH & Estes ML. Brain tumors and chronic epilepsy. In Wyllie (Ed), *The treatment of epilepsy: principles and practice* (pp 659-666). Philadephia: Lea & Febiger; 1993

Mountain CF. Revisions in the international system for staging lung cancer. *Chest*, 1997; **111**: 1710-1717

Olin JW, Young JR, Graor RA *et al*. treatment of deep venous thrombosis and pulmonary emboli in patients with primary and metastatic brain tumors. *Archives of Internal Medicine*, 1987; **147**: 2177-2179

O'Neill BP, Iturria NJ, Link MJ *et al*. A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastases. *International Journal of Radiation Oncology Biology Physics*, 2003; **55**: 1169-1176

Patchell R, Tibbs P, Walsh J *et al*. A randomized trial of surgery in the treatment of single brain metastases. *New England Journal of Medicine*, 1990; **322**: 494-545

Posner JB. *Neurologic complications of cancer*. Philadephia: F A Davies, 1995

Sawaya R & Bindal RJ. Metastatic brain tumours. In AH Kaye & ER Laws (Eds), *Brain tumors* (pp 923-926). New York: Churchill Livingstone

Schaeffer PW, Budzik RF & Gonzalez RG. Imaging of cerebral metastases. *Neurosurgical Clinics of North America*, 1996; **7**: 404

Schiff D, DeAngelis LN. Therapy of venous thromboelbolism in patients with brain metastases. *Cancer*, 1994; **73**: 493-498

Sene AP, Hunt L, McMahon RFT & Carroll NP. Renal carcinoma in patients undergoing nephrectomy: analysis of survival and prognostic factors. *British Journal of Urology*, 1992; **70**: 125-134

Sirven JL, Wingerchuk DM, Drazkowski JF *et al*. Seizure prophylaxis in patients with brain tumors: a meta-analysis. *Mayo Clinic Proceedings*, 2004; **79**: 1489-1494

Sneed PK, Larson DA & Wara WM. Radiotherapy for cerebral metastases. *Neurosurgical Clinics of North America*, 1996; **7**: 505-515

Sze G, Milano E, Johnson C & Heier L. Detection of brain metastases: comparison of contrast-enhanced MRI with unenhanced MRI and enhanced CT. *American Journal of Neuroradiology*, 1990; **11**; 785-791

van Poppel H, Beckers G & Baert L. Renal-cell carcinoma. In: Gospodarowicz MK, Henson DE, Hunter RVP, O'Sullivan B, Sobin LH, Wittekind Ch (Eds). *Prognostic Factors in Cancer*. New York: Wiley; 2001.

Weaver S, Forsyth P, Fulton D *et al*. A prospective randomised study of prophylactic anticonvulsants in patients with primary brain tumours or metastatic brain tumors and without prior seizures. A preliminary analysis of 67 patients. *Neurology*, 1995; **45** (suppl 4): A263, abstract 371P

Wolters U, Stutzer H, Keller HW, Schroder U & Pichlmaier H. Colorectal cancer: a multivariate analysis of prognostic factors. *European Journal of Surgical Oncology*, 1996; **22**: 592-597

Zimm S, Wampler GL, Stablein D *et al*. Intracerebral metastases in solid tumour patients: natural history and results of treatment. *Cancer*, 1981; **48**: 384