William Hamilton, Jacqueline Barrett, Sally Stapley, Debbie Sharp and Peter Rose

Clinical features of metastatic cancer in primary care:

a case–control study using medical records

Abstract

Background
How metastatic cancer initially presents is largely unknown.

Aim
To identify clinical features of metastatic cancer in primary care.

Design and setting
Case–control study in 11 general practices in Devon, UK.

Method
Cases of patients who had died with metastatic breast, colorectal, or prostate cancer were selected. In addition, two control groups were formed of patients with the same primary cancer but without metastases ('cancer controls') and patients without cancer ('healthy controls'), matched for age, sex, and practice. All symptoms, signs, and laboratory test abnormalities in the year before metastasis were identified. The primary analysis used conditional logistic regression.

Results
In total, 162 cases, 152 cancer controls, and 145 healthy controls were studied. Common symptoms associated with cancer were: vomiting, 40 (25%) cases and 13 (9%) cancer controls (multivariable odds ratio [OR] 3.5, 95% confidence interval [CI] = 1.3 to 9.4, *P* = 0.011); low back pain, 38 (24%) cases and 17 (11%) cancer controls (OR 2.5, 95% CI = 1.1 to 5.6, *P* = 0.032); loss of appetite, 32 (20%) cases and nine (6%) cancer controls (OR 4.0, 95% CI = 1.2 to 13.2, *P* = 0.021); and shoulder pain, 27 (17%) cases and eight (5%) cancer controls (OR 5.3, 95% CI = 1.6 to 18, *P* = 0.007). Groin pain was uncommon, but strongly associated (16 [10%] cases and one [1%] cancer control [OR 10, 95% CI = 1.2 to 82, *P* = 0.032]), as was pleural disease (nine [6%] cases and one [1%] cancer control [OR 10, 95% CI = 1.1 to 92, *P* = 0.038]).

Conclusion
These features of disseminated cancer have been reported before in studies from secondary care, but the scarcity of specific symptoms (such as local pain) and the fairly common occurrence of non-specific symptoms (vomiting and loss of appetite) is important and may explain delays in the diagnosis of metastases.

Keywords
cancer; diagnosis; metastasis; primary health care.

INTRODUCTION

There are approximately 2.5 million survivors of cancer in the UK, and this population is increasing by 3% annually.[1] This population is at risk of recurrence, either locally, regionally, or as distant metastases. Cancer recurrence is the main cause of mortality in this group,[2] so when a survivor of cancer develops a new symptom, one of the key clinical questions is whether the symptom represents a recurrence.

Although cancer can spread to many different organs, there are recognisable patterns for specific primary sites and the site, or sites, of metastases.[3] The most common sites of spread are lymph nodes, bones, brain, lung, and liver, although multiple sites are common. The most common metastatic sites for the three types of cancer in this study are:

- breast cancer — bone, liver, lung, and brain;
- prostate cancer — bone, liver, and lung; or
- colorectal cancer — liver, lung, peritoneum.[4,5]

Symptoms of metastases may be site specific, as in a pathological fracture causing pain, or systemic, such as fatigue, nausea, or anorexia. Abnormal laboratory tests suggesting possible metastatic spread include anaemia, abnormal liver function, and hypercalcaemia.[6]

In the UK, guidelines from the National Institute for Health and Care Excellence (NICE) suggest post-treatment follow-up of patients with cancer for:

- up to 5 years for breast cancer;
- 3 years for colorectal cancer; and
- a minimum of 2 years of prostate-specific antigen (PSA) monitoring for prostate cancer.[7–9]

Hospital follow-up is the norm, although primary care follow-up may be offered as an option.

Local, regional, or metastatic spread may be identified at routine follow-up. However, many patients present with new symptoms between outpatient follow-ups, or after follow-up has ceased; these symptoms are usually reported to primary care. In one trial of breast cancer follow-up, 69% of recurrences were detected by the patients themselves and presented as interval events, and 44% of the women presented first to their GP.[10] In a more recent study of patients with early-stage breast cancer, 22% of recurrences presented outside routine follow-up; overall, 33.5% of relapses were symptomatic, with routine follow-up mammography being the main alternative mode of identification.[11]

W Hamilton, MD, professor of primary care diagnostics; **J Barrett**, BSc, associate research fellow; **S Stapley**, PhD, research fellow, University of Exeter Medical School, Exeter. **D Sharp**, MA, PhD, FRCGP, professor of primary health care, Centre for Academic Primary Care, University of Bristol, Bristol. **P Rose**, FRCGP, clinical lecturer, Department of Primary Care Health Sciences, University of Oxford, Oxford.

Address for correspondence
William Hamilton, University of Exeter Medical School, College House, St Luke's Campus, Magdalen Road, Exeter EX1 2LU, UK.
E-mail: W.Hamilton@exeter.ac.uk

Submitted: 5 January 2015; **Editor's response:** 18 February 2015; **final acceptance:** 18 March 2015.

This is the full-length article (published online 27 Jul 2015) of an abridged version published in print. Cite this article as: **Br J Gen Pract 2015; DOI: 10.3399/bjgp15X686077**

How this fits in

There are approximately 2.5 million survivors of cancer in the UK, with many at risk of disease recurrence in the form of metastases. The clinical presentation of metastases occurs almost wholly in specialist clinics rather than primary care, although most patients with metastases present initially to primary care. The clinical features of the patients and cases in this study were dominated by common, non-specific symptoms, such as vomiting, low back pain, and loss of appetite; more specific symptoms, such as groin pain or signs of pleural disease, were much less frequent. Metastatic cancer presents with systemic symptoms primarily, rather than local symptoms from the metastatic deposit. This makes identification of metastases in primary care more difficult and may lead to delays.

Early identification of progressive disease in patients with cancer may not lead to an improvement in survival but symptom relief can be made more effective. Prompt diagnosis of bone metastases, followed by active management of pain, fractures, or spinal cord compression, can considerably influence functional outcome and quality of life.[12,13] Early detection of liver and lung metastases can allow palliative therapy and — in rare instances —curative resection of metastases from colorectal cancer.[14]

Clinical features of the presentation of metastatic cancer are poorly described. Almost all previous studies have originated in secondary care, yet the clinical problem of diagnosis resides, in part at least, in primary care. There are no studies that reflect all aspects of recurrence — timing, site, and symptoms — in a single cohort. Although there is evidence of delay in presentation and diagnosis of primary cancer, there is no evidence about the presence or absence of delay in the diagnosis of metastatic cancer in primary care. There is also no national guidance for primary care in the detection of recurrent disease.

This study sought to fill this gap by identifying and quantifying the risk of cancer recurrence in primary care patients who were symptomatic and had received treatment with a curative intent for an earlier cancer.

METHOD

Design

This was a case–control study, using data from medical records; the data, although analysed retrospectively, were collected prospectively between 2002 and 2009 from the primary care records of patients in 11 general practices in Devon, UK. The combined population was 172 000 people aged ≥40 years (mid-2006). The study was undertaken in tandem with a case–control study of ovarian cancer using similar methods.[15]

Cases

Cases were identified from computerised searches at each of the participating practices for deceased patients with a prior record of breast, colorectal, or prostate cancer. Being deceased was a requirement of the ethical approval. For retention in the study, cases had to detail patients who had had radiologically or histologically proven metastatic cancer. Patients with recurrences only at the primary site were excluded, although patients with spread to local lymph nodes were included (in practice, most had widely disseminated disease). Exclusion criteria were as follows:

- The primary cancer was considered incurable at the time of initial diagnosis (this included cases of prostate cancer in which there was a PSA value of >100ng/ml at diagnosis, as metastatic disease at diagnosis was considered to be likely), or metastatic spread had occurred within 6 months of diagnosis of the primary cancer;

Administrative cases, comprising:

- cases in which the primary cancer was diagnosed before the patient had reached 40 years of age;
- patients whose metastases occurred before registration at the current practice; or
- cases, the full record for which had been archived off site after death.

The date that metastatic disease was first diagnosed in the cases was labelled as the index date, and the same date was used for controls. This was defined as the date of specialist confirmation of metastatic disease, and was usually based on imaging or biopsy. Ambiguities relating to the index date were resolved by consensus, including one of the clinical members of the research team.

The original study design included lung cancer; however no cases of lung cancer met the above criteria.

Controls

For each case, two controls — alive at the

time of the diagnosis of metastatic cancer in the case — were selected from the practices' databases and matched on sex, age and GP practice. Two types of controls were used:

- 'healthy controls' — without cancer, matched to the year of birth of the relevant case; and
- 'cancer controls' — diagnosed with the same cancer as the relevant case, but without relapse at the index date.

Cancer controls had to have at least as long an interval from their primary diagnosis to the index date as the interval from primary diagnosis to the index date (metastatic spread) in the case. If there was more than one available cancer control, the control with their cancer diagnosis closest to the age at primary diagnosis of the case was selected. All controls had to have had at least one GP consultation in the year before the index date.

Controls who were still alive were invited by letter, explaining the purpose of the study, and consent to access their medical records was sought. When a patient declined participation, a replacement control was invited (to a maximum of two replacement invitations). Written consent was given by all participating controls. The ethical approval granted for this study permitted use of controls' records if they were deceased.

Data collection

Anonymised copies of the GP notes, including investigations, referral letters, specialist consultations, and histology results were taken for the year before the index date. All symptoms, investigations and clinical findings, and metastatic sites (collectively termed 'features' from here on) were coded on a customised database by three researchers and blinded to case–control status using an adapted form of the International Classification of Primary Care-2.

The inter-rater reliability of coding was not assessed as this was the same as that used in previous studies and had previously shown very high reliability.[15] Some abnormal tests were grouped: for instance, abnormal liver function was defined as the presence of any liver enzyme above the normal range.

Analysis

The main method of analysis was conditional logistic regression. Univariable analyses were performed initially, retaining variables with a *P*-value of <0.1 to enter into multivariable analyses. The multivariable analysis used a *P*-value of 0.05 for retention. Only variables that were present in >2% of the cases were studied.

The cancer controls and healthy controls were used in separate analyses, and the cancer sites were also analysed separately. Finally, all three cancer sites (breast, colorectal, and prostate) were merged and a unified analysis performed. Clinically plausible interaction terms were added to each model, and likelihood ratio testing was applied to test whether they improved the models. Secondary analyses examined the clinical features by metastatic site (bone, liver, or lung) using only the cancer controls; these studied the features that were present a minimum of 90 days before diagnosis. Stata (version 12) was used to undertake the analyses.

The sample size calculation was based on the sub-analysis by metastatic site, in that the researchers expected the symptom profiles to reflect the site of the deposit more than that of the primary tumour. The calculation was based on specific features being present in 20% of cases and 2% of cancer controls; this would require 61 cancers in each metastatic site, using a one-sided α of 0.05. With the likelihood of patients having multiple metastatic sites, the researchers aimed for 150 cases. In practice, all cases from the recruited practices were accepted, so this number was slightly exceeded.

RESULTS

A total of 523 potential cases were identified from the practice searches; these included patients who were deceased and whose record contained a code for either breast, colorectal, or prostate cancer. Of those, 130 showed no record of metastatic disease, 189 showed incurable disease at initial diagnosis or metastases within 6 months, and 42 constituted administrative exclusions; this left 162 cases eligible for inclusion in the study.

A total of 208 cancer controls and 177 healthy controls were also identified from the practice searches and were invited to participate. Of these, 56 cancer controls and 32 healthy controls declined participation or constituted administrative exclusions, leaving 152 matched cancer controls and 145 matched healthy controls. The demographic data for the patients in the study are shown in Table 1. The number of years between diagnosis of the primary cancer and metastasis was 1.7 (interquartile range [IQR] 1.2–2.6) in colorectal cancer, 4.3 (IQR 2.1–8.3) in breast cancer, and 4.5 (IQR 2.8–6.3) in prostate cancer.

Table 1. Patients' demographic data

Characteristic	Cases	Cancer controls	Healthy controls
Primary site, *n* (%)			
Breast	80 (49)	76 (50)	71 (49)
Colorectal	46 (28)	42 (28)	40 (28)
Prostate	36 (22)	34 (22)	34 (23)
Sex,[a] *n* (%)			
Male	31 (67)	29 (69)	27 (67)
Female	15 (33)	13 (31)	13 (33)
Years between primary diagnosis and index date, median (IQR)	3.2 (1.6–6.1)	5.1 (2.2–9.3)	n/a
Age in years at diagnosis of metastatic cancer, median (IQR)	75 (65–82)	n/a	n/a
Age in years at diagnosis of primary cancer, median (IQR)	70 (60–78)	68 (58–74)	n/a

[a]Colorectal cancer only. IQR = interquartile range.

Table 2. Features of metastatic cancer and the final models, compared with controls

				Cancer controls		Healthy controls	
				Multivariable analysis		Multivariable analysis	
Feature	**Cases, *n* (%)**	**Cancer controls, *n* (%)**	**Healthy controls, *n* (%)**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Groin pain	16 (10)	1 (1)	5 (4)	10.2 (1.2 to 8.2)	0.032	NS	
Pleurisy/pleural effusion	9 (6)	1 (1)	1 (1)	10.2 (1.1 to 9.2)	0.038	NS	
Shoulder pain	27 (17)	8 (5)	21 (15)	5.3 (1.6 to 1.8)	0.007	NS	
Loss of appetite	32 (20)	9 (6)	8 (6)	4.0 (1.2 to 1.3)	0.021	NS	
Vomiting	40 (25)	13 (9)	9 (6)	3.5 (1.3 to 9.4)	0.011	3.6 (1.3 to 1.0)	0.016
Low back pain	38 (24)	17 (11)	10 (7)	2.5 (1.1 to 5.6)	0.032	4.2 (1.5 to 1.2)	0.006
Flank/loin pain	17 (11)	7 (5)	1 (1)	NS		19.4 (1.8 to 2.10)	0.016
Chest pain: musculoskeletal	37 (23)	12 (8)	8 (6)	NS		5.3 (1.7 to1.6)	0.004
Oedema	35 (22)	16 (11)	11 (8)	NS		3.4 (1.1 to 10)	0.029
Investigation							
Abnormal liver function	61 (38)	21 (14)	14 (10)	3.5 (1.6 to 7.5)	0.002	5.1 (1.9 to 1.4)	0.002

NS = not significant in the final multivariable model. OR = odds ratio.

Table 3. Clinical features of metastatic cancer by metastatic site

	Metastatic site[a]					
	Bone metastases		Liver metastases		Lung metastases	
Feature	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Low back pain	2.6 (1.0 to 6.7)	0.045	–	–	–	–
Vomiting	–	–	4.7 (1.3 to 17.5)	0.021	–	-
Pleurisy/effusion	–	–	–	–	10.5 (1.0 to 118.7)	0.050
Abnormal liver function test	4.6 (1.6 to 11.7)	0.004	2.9 (1.1 to 7.9)	0.041	5.1 (1.1 to 24.2)	0.043

[a]For these analyses, patients with metastases in multiple sites were studied in each relevant group (bone metastases, n = 75; liver metastases, n = 55; lung metastases, n = 45). OR = odds ratio.

Clinical features

Overall, 207 separate features were recorded in at least 2% of cases. Of these, 50 (43 symptoms and seven abnormal investigations) were associated with metastatic cancer, with a *P*-value of ≤0.1 in the univariable analysis in the cancer controls; 53 features (46 symptoms and seven abnormal investigations) were associated in the healthy controls. These features were entered for multivariable analyses, with the final models shown in Table 2. A total of 80% of the cases presented with at least one of the seven features in the final model (data not shown).

Only one variable/primary site interaction term was conventionally significant. Low back pain was more strongly associated with metastases in colorectal cancer using cancer controls (interaction odds ratio [OR] 75 (95% CI = 1.8 to 3000)], *P* = 0.02).

The results of the sub-analyses by metastatic site, using the seven significant variables from the cancer control analysis, are shown in Table 3. Results for brain metastases and/or 'other' sites (for example, intra-abdominal) are not shown as the numbers were too small for reliable analysis. Thirty-five (22%) of the cases detailed presentation with disease at multiple metastatic sites.

Again, using only the seven variables significantly associated with metastases in the cancer control analysis, the multivariable analysis (Table 2) was repeated after removing the final 90 days of consultations. Only vomiting (OR 3.0, 95% CI = 1.3 to 6.8, *P* = 0.08) and an abnormal liver function test (OR 2.1, 95% CI =1.0 to 4.3, *P* = 0.044) were associated with future metastases. The time from first presentation to primary care with a relevant feature of possible metastatic cancer to confirmation of the disease was longest in the patients with colorectal cancer, with a median of 178 (IQR 31–269) days. For the prostate and breast cancer cases the median interval was 176 days (IQR 84–311) and 120 days (IQR 28–270) respectively.

DISCUSSION

Summary

To the authors' knowledge, this is the first article to describe the clinical features of metastatic cancer in primary care. The main findings were that vomiting, shoulder pain, low back pain, and loss of appetite were fairly common markers of metastatic spread, but that these features were also experienced by patients with a previous cancer and no metastases. As a result, for these features the strength of the association — as measured by the multivariable OR — was only moderate, ranging from 2.5 to 5.3.

Two other less-common features had

stronger associations: groin pain and pleural disease. Abnormalities of liver function were also associated with metastatic cancer; furthermore, this laboratory abnormality and vomiting were still associated with metastases, even when data were used a minimum of 3 months before diagnosis.

The time to diagnosis of metastases was surprisingly long, with a median interval between the first putative symptom and diagnosis exceeding 3 months.

Strengths and limitations

The study methods employed were driven by pragmatism but may have introduced bias at a number of points. First, all the cases were deceased. This was a requirement of the ethical approval but, because those currently alive with metastatic cancer were excluded, the cases used may have had disproportionately severe disease. In addition, only three cancers were studied; however, it should be noted that these were three of the four most common and study of the fourth — lung cancer — was impossible.

A small number of potential controls declined to participate, although it is likely that this was too few to have introduced severe bias. It was also not always clear precisely when metastatic disease was diagnosed; again, however, uncertainty surrounding the index date was usually restricted to a few days and is unlikely to have greatly affected the findings.

The methods used relied on primary care note keeping; if symptoms were either unvoiced by the patient, or voiced but unrecorded, they could not have been included in this study. This would be of concern if under-recording were greater in one of the groups — presumably controls — but, based on the companion studies,[16] there is no reason to think that this is the case. This study also examined the notes directly, avoiding any possible concerns arising from data hidden in an inaccessible field, as can happen with studies based on electronic research databases.[17]

The researchers chose to study a 1-year period before the metastases; this was a semi-arbitrary choice, but based on several similar studies they had performed. Some of the symptoms reported may have been part of chronic illness rather than 'new' symptoms, particularly in controls. As such, the clinical situation in an individual patient may be simpler than the results suggest; however, there is always the danger of ascribing a symptom of malignant origin to a prior benign diagnosis. Furthermore, some patients may have been under investigation of possible metastases while reporting their symptoms to primary care; again this would make the primary care clinical decision making simpler. Some features of possible metastases were not identified in this study. Few patients had brain metastases, and headache was not found to be associated with metastatic disease in the main analysis. This may be a type II error due to the small size of the study, but does provide some reassurance for clinicians and their patients.

On the positive side, the overall sample size was achieved, although fewer patients had lung metastases than expected. The estimates in the sample size calculation were slightly inaccurate: most features were, indeed, present in at least 20% of cases, but symptom reporting was higher in controls than expected. Healthy controls also had a surprisingly high number of symptoms, and these were similar in frequency to those of the controls who had cancer. As a result, the site-specific analysis was slightly underpowered, although the main analysis had ample power. As the main clinical question in a patient with a previous cancer is the possibility of cancer recurrence rather than the specific site of the recurrence, the main analysis is the more important one.

Data were also collected on comorbidities; however few were common enough to enter analysis and none survived multivariable analysis. For an individual patient, comorbidities may explain symptoms such as back pain. Overall, the results still clearly point towards metastases as being worthy of consideration.

Comparison with existing literature

As stated earlier, primary care research on this subject is sparse. The trial of primary care versus secondary care follow-up of breast cancer reported 10 women who reported recurrences in primary care: three had skeletal pain, three a nodule or mass, two respiratory symptoms, with one having vaginal bleeding; two were apparently asymptomatic and had their disease identified on mammography.[10]

Secondary care reports largely concentrate on the frequency and site of metastases, rather than the symptoms prompting discovery of the cancer spread. In line with this, there are no previous reports on the time to diagnosis of metastatic disease. In a study of 13 cancer types, diagnosis of primary cancer took a median of 77 days (IQR 35–195) in 2007–2008, approximately the same date as this study.[18] In the current study, diagnosis of metastatic disease was slower: this could reflect the

non-specific nature of the symptoms or the absence of a clear pathway for investigation, such as the 2-week clinics for suspected primary cancer. The axial skeleton is the most common site for bone metastases,[19] which is supported by the results presented here

Implications for research and practice

Two broad groups of symptoms — generic and specific — were associated with metastatic spread in the three cancer sites studied. The generic symptoms were common in those with metastases, but were more common in the control groups; be they healthy controls or those with cancer. Nonetheless, vomiting, low back pain, and loss of appetite appear to warrant investigation in patients with a previous cancer; how the investigation should proceed will depend on local arrangements.

Abnormal liver function test results — the only feature associated with cancer for all three metastatic sites — also mandate investigation. Primary care X-ray or ultrasound may uncover metastases, although more sophisticated imaging, such as computerised tomography or magnetic resonance imaging, may be required; this will usually mean re-referral to the relevant specialist.

The rarer, but higher-risk, presentation of pleural disease would usually be investigated as a matter of course. This may be a primary care chest X-ray in the first instance, although if a pleural effusion is detectable clinically, this would generally lead to prompt re-referral, perhaps simultaneously with ordering the chest X-ray.

Groin pain and shoulder pain were strongly associated with metastatic disease, and presumably represented particular sites of metastasis, although neither variable was significant in the specific bone metastasis sub-analysis. The three anatomical sites associated with metastases were low back pain, shoulder pain (probably from breast cancer), and groin pain (perhaps representing pelvic deposits from prostate cancer). In the continuum from sclerotic to lytic bone metastases, breast and prostate cancer bone metastases are the most sclerotic, so will usually be easily visualised on plain radiology.[19] As this study only investigated prostate, breast, and colorectal cancer, it is impossible to know whether the same clinical features would be present across all cancers, as it is possible that lytic bone metastases present differently; even so, it is clear that a new, persistent skeletal pain in a survivor of cancer should be investigated. It was surprising that weight loss was also not associated with metastases, although loss of appetite was; this finding suggests that the initial metastasis occurs when the patient is not obviously unwell, making early diagnosis of metastases more difficult. Patients with metastatic cancer present to primary care with common, non-specific features of ill health, sometimes supplemented by specific features that are likely to represent the anatomical site of the deposit. These non-specific features make diagnosis more complicated, although the features described in this study should help clinicians to identify cancer spread more rapidly than is done so at present.

All the features of disseminated cancer have been reported before in secondary care studies, but the scarcity of specific symptoms, such as local pain, and the fairly common occurrence of non-specific symptoms, such as vomiting and loss of appetite is an important finding. This may explain, in part at least, the long time to diagnosis of metastases.

Funding

The study authors received funding from the National Institute for Health Research (NIHR) School for Primary Care Research funding scheme. Additionally, William Hamilton was funded through a National Coordinating Centre for Research Capacity Development (NCCRCD) post-doctoral fellowship. Jacqueline Barrett was funded by an unrestricted grant from Macmillan to William Hamilton. This research was also supported by the NIHR Collaboration for Leadership in Applied Health Research and Care South West Peninsula at Royal Devon and Exeter NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily of the NHS, NIHR, or the Department of Health. The study sponsor was the University of Bristol. The authors were independent from the funder and sponsor, who had no role in conduct, analysis, or the decision to publish.

Ethical approval

Ethical approval was obtained from Devon and Torbay Research Ethics Committee (reference: 07/H0202/136).

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

Acknowledgements

The authors thank all participating general practices (Heavitree, Honiton, Ide Lane, Mount Pleasant (×2 practices), Okehampton, Pinhoe, St Leonard's, St Thomas', Topsham, Westbank, and Whipton), along with the two research assistants, Cath Stabb and Rachel Pearce.

Discuss this article

Contribute and read comments about this article: **bjgp.org/letters**

REFERENCES

1. Maddams J, Utley M, Møller H. Projections of cancer prevalence in the United Kingdom, 2010–2040. *Br J Cancer* 2012; **107(7):** 1195–1202.
2. DeSantis CE, Lin CC, Mariotto AB. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin* 2014; **64(4):** 252–271.
3. Kemp C. Metastatic spread and common symptoms. Part one: Introduction, bladder cancer, and brain cancer. *Am J Hosp Palliat Care* 1998; **15(6):** 355–360.
4. Kemp C. Breast cancer, colorectal cancer, and esophageal cancer. *Am J Hosp Palliat Care* 1999; **16(1):** 403–411.
5. Kemp C. Metastatic spread and common symptoms. Part six: Advanced cancer of the pancreas, prostate, stomach, and uterus. *Am J Hosp Palliat Care* 1999; **16(5):** 673–681.
6. Banks J, Hollinghurst S, Bigwood L, *et al.* Preferences for cancer investigation: a vignette-based study of primary-care attendees. *Lancet Oncol* 2014; **15(2):** 232–240.
7. National Institute for Health and Care Excellence. *Colorectal cancer: the diagnosis and management of colorectal cancer. NICE guidelines [CG131].*http://www.nice.org.uk/guidance/cg131/resources/guidance-colorectal-cancer-pdf (accessed 18 Jun 2015).
8. National Institute for Health and Care Excellence. *Early and locally advanced breast cancer: diagnosis and treatment. NICE guidelines. [CG80].* https://www.nice.org.uk/guidance/cg131 (accessed 18 Jun 2015).
9. National Institute for Health and Care Excellence. *Prostate cancer: diagnosis and treatment (CG175).* https://www.nice.org.uk/guidance/cg175 (accessed 18 Jun 2015).
10. Grunfeld E, Mant D, Yudkin P, *et al.* Routine follow up of breast cancer in primary care: randomised trial. *BMJ* 1996; **313(7058):** 665–669.
11. Montgomery DA, Krupa K, Jack WJ, *et al.* Changing pattern of the detection of locoregional relapse in breast cancer: the Edinburgh experience. *Br J Cancer* 2007; **96(12):** 1802–1807.
12. Paterson AH, Powles TJ, Kanis JA, *et al.* Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* 1993; **11(1):** 59–65.
13. Crnalic S, Hildingsson C, Bergh A, *et al.* Early diagnosis and treatment is crucial for neurological recovery after surgery for metastatic spinal cord compression in prostate cancer. *Acta Oncol* 2013; **52(4):** 809–815.
14. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995; **19(1):** 59–71.
15. Hamilton W, Peters TJ, Bankhead C, Sharp D. Risk of ovarian cancer in women with symptoms in primary care: population based case-control study. *BMJ* 2009; **339:** b2998.
16. Hamilton W. The CAPER studies: five case-control studies aimed at identifying and quantifying the risk of cancer in symptomatic primary care patients. *Br J Cancer* 2009; **101(Suppl 2):** S80–86.
17. Price SJ, Shephard EA, Stapley SA, *et al.* Non-visible versus visible haematuria and bladder cancer risk: a study of electronic records in primary care. *Br J Gen Pract* 2014; DOI: 10.3399/bjgp14X681409.
18. Neal RD, Din NU, Hamilton W, *et al.* Comparison of cancer diagnostic intervals before and after implementation of NICE guidelines: analysis of data from the UK General Practice Research Database. *Br J Cancer* 2014; **110(3):** 584–592.
19. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001; **27(3):** 165–176.