Article:
Brooks, D., Hughes, P., Farrington, C. et al. (2018) Implementation of a metastatic malignancy of unknown primary origin service led by a palliative physician. Hospital Practice, 46 (1). pp. 37-42. ISSN: 2154-8331

https://doi.org/10.1080/21548331.2018.1418140

Hospital Practice

ISSN: 2154-8331 (Print) 2377-1003 (Online) Journal homepage: http://www.tandfonline.com/loi/ihop20

Implementation of a metastatic malignancy of unknown primary origin service led by a palliative physician

David Brooks, Philippa Hughes, Clare Farrington, Peter A. Bath, Mary McGregor, Wasim Ahmed & Bill Noble

To cite this article: David Brooks, Philippa Hughes, Clare Farrington, Peter A. Bath, Mary McGregor, Wasim Ahmed & Bill Noble (2017): Implementation of a metastatic malignancy of unknown primary origin service led by a palliative physician, Hospital Practice, DOI: 10.1080/21548331.2018.1418140

To link to this article: https://doi.org/10.1080/21548331.2018.1418140

Accepted author version posted online: 29 Dec 2017.

Publisher: Taylor & Francis

Journal: *Hospital Practice*

DOI: 10.1080/21548331.2018.1418140

Implementation of a metastatic malignancy of unknown primary origin service led by a palliative physician

Implementation of a metastatic malignancy of unknown primary origin service led by a palliative physician

David Brooks[3], Philippa Hughes[1], Clare Farrington[1], Peter A. Bath[2], Mary McGregor[1], Wasim Ahmed[2] and Bill Noble[4]

[1]*Academic Unit of Supportive Care, School of Medicine and Biomedical Sciences, University of Sheffield*

[2]*Information School, University of Sheffield*

[3]*Chesterfield Royal Hospital NHS Foundation Trust, Chesterfield*

[4] *Faculty of Health and Wellbeing, Sheffield Hallam University*

Corresponding author: David Brooks, Consultant in Palliative Medicine, Chesterfield Royal Hospital, Calow, Derbyshire, S44 5BL, davidbrooks@nhs.net, 07789935724

Implementation of a metastatic malignancy of unknown primary origin service led by a palliative physician

Abstract

Background: Cancer of unknown primary is the fourth most common cause of cancer death in the United Kingdom. National guidance in 2010 recommended the establishment of a dedicated unknown primary team to facilitate targeted investigation and symptom control. A service development project was undertaken to identify those affected by malignancy of unknown origin and institute a pathway for coordinating their care led by a palliative physician.

Aim: To describe the patient population and illness trajectory and to assess the effect of the new pathway on the clinical outcomes.

Design: A retrospective and prospective comparative case notes survey to identify the pre- and post-pathway population.

Setting/participants: This took place in secondary care. Inclusion criteria were patients with metastatic disease with no known primary; exclusion criteria were where the site of metastasis was so suggestive of a primary that it would be managed as per that disease process. 88 patients were included.

Results: Mean age was 72.5 years. The mean survival time from presentation was 81.8 days. There was no difference pre or during pathway implementation in age, performance status or survival time. There was no reduction in the numbers referred for tumour directed therapy. There was a non-statistically significant reduction in the number who died in hospital during the pathway implementation.

Conclusions: This study suggests having a metastatic malignancy of unknown primary origin service led by a palliative physician does not reduce the number referred for tumour directed therapy. It also adds evidence of the poor prognosis and thus the need for early palliative care input.

Keywords: Neoplasms, Unknown Primary; Neoplasms; Neoplasms, metastasis; Decision Making; Malignancy of Undefined primary origin; Palliative care

1.Introduction

Carcinoma of Unknown Primary is the fourth most common cause of cancer death,with an incidence stated to be from 3% to 5% of all malignancies [1,2,3]. Up to eighty per cent have unfavourable prognostic features[4] and, in this subset, a meta-analysis has not shown chemotherapy to lengthen survival[5]. While some studies have described the management of those who end up with a diagnosis of Cancer of Unknown Primary Origin [7-9] there have been no studies that describe the early management of the larger group that who present with Metastatic Malignancy of Undefined Primary origin[10].

Until recently this patient group had not had care and management overseen by any one specific team. National Institute for Health and care excellence (NICE) guidance on diagnosis and management of metastatic malignant disease of unknown primary origin[1] recommended the establishment of a dedicated unknown primary team (including oncologist, palliative care physician and specialist nurse) in hospitals with a cancer unit to provide equity with site-specific cancers. The aim of a specialist team is to ensure early symptom control, individualised support and information which is to be delivered alongside targeted investigations and appropriate treatment. The importance

of supportive and palliative care within this process suggests the palliative physician as a suitable person to be the lead clinician.

1.1 Rationale for service development

A small scale audit of patients with cancer of unknown primary was conducted at a district general hospital. This indicated a similar situation to that reported in the wider literature. No system existed to identify these patients as a distinct group, but retrospective audit showed that 11 of 14 patients reviewed had died in the hospital, with an average length of stay of 21.5 days. Repeating of tests was common, suggesting an important burden at the end of life. Specialist palliative care involvement conferred benefit, but was sometimes a late consideration[6].

Contemporary with the devising of the NICE Guidance a service development was planned at the district general hospital. This initiative aimed to identify patients presenting with metastatic malignancy of undefined primary origin, and institute a new pathway for co-ordinating their care, with the palliative physician as lead clinician. This development would provide more data about patients who present in this way, assess whether a palliative care led service would work, and document the definitive treatments and outcomes for patients.

1.2 Designing the Intervention: a new pathway approach

A multidisciplinary Unknown Primary team was set up consisting of a palliative

physician (lead clinician), an oncologist with interest in cancer of unknown primary origin, a histo-pathologist, a radiologist and specialist palliative care nurses. In-patients referred to the Unknown Primary team were to be reviewed within one working day on the ward. Patients were discussed at a weekly Unknown Primary MDT meeting which included an upper GI surgeon and physician in addition to the core team. Additional discussions took place between core team members to expedite decisions and facilitate patient flow. The intervention aimed to provide individualised patient care; assessment of history, family history and risk factors; and review of fitness for potential future Tumour Directed Treatment (TDT) with assessment of patients' wishes. Alongside this, the intervention ensured attention to early symptom control, maximising quality of life and ensuring on-going support and information.

The main barrier to developing the service was that this was not seen by commissioners or managers as "new business" for the hospital. These patients were being managed in various parts of the hospital already so implementing a service which co-ordinated their care more effectively and provided additional support was not going to generate extra income for the hospital. It was therefore difficult to identify additional resource to develop the service. The funding that was initially identified was partial and non recurrent out of charitable funds but much of the service was developed through goodwill. Only when the service was established and shown to be beneficial was recurrent funding identified.

2. Evaluation study

An evaluation study was set up with the aim of assessing the clinical and service quality outcomes, and patient experiences before and following the implementation of the pathway. This was granted ethical approval from the East Midlands- Leicester Research Ethics Committee (reference number 08/H0406/178).

The main objective was to describe this patient population, service need and subsequent illness trajectory using a pragmatic clinical approach based on mode of presentation, rather than criteria based on final confirmed diagnosis.

2.1 Inclusion criteria

All patients who had presumed or probable metastatic disease with no known (or highly suspected) primary disease were included. In addition, we included patients for whom the suspected primary disease had been excluded, who would no longer be appropriately managed by the site-specific pathway multi-disciplinary team.

2.2 Exclusion criteria

Where the site and histology of lymph node disease is so indicative of a primary site that it would be managed as per that disease process even when the primary is not discovered, then direct referral to the site specific MDT is the norm.

3. Method

The study was a multi method research study located in a district general hospital, Chesterfield Royal Hospital NHS Foundation Trust, with a catchment population of 375,000) over two six-month periods (November 2008-April 2009 and April 2010-October 2010). This paper reports on a retrospective and prospective comparative cross-sectional survey of data from patients' clinical records before and during the intervention. This was one element of a larger study.

A method of identifying patients with metastatic malignancy of undefined primary origin(MUO) was devised. Pre-intervention this was conducted retrospectively and made use of site-specific MDT meetings, radiological reports marked serious or unexpected findings, palliative care patient database, and in-patient admission coding. During the intervention phase patients with metastatic malignancy of undefined primary origin were identified prospectively: referred by other clinicians to the pathway (as in-patients or out-patients), or for discussion at the Unknown Primary MDT, or identified by the team as suitable for the pathway from their palliative care referrals. To ensure comparability and to evaluate the referral rate, patients were also identified retrospectively using the pre-intervention process and included in the intervention group for the purpose of analysis.

3.1 Outcome Measures

The primary outcome measure was the time from referral to instigation of definitive treatment.

The date of referral was the point where a secondary care physician was first alerted to the presumed or probable presence of metastatic disease that required investigation. Instigation of definitive treatment was defined as the date the patient received their definitive treatment, or the date when this decision was made, whichever was the latest.

Secondary outcome measures included: the number of patients referred to, offered and subsequently accepting oncological treatment, survival time and place of death.

3.2 Data analysis

Kaplan Meier survival analyses were undertaken to compare the mean survival times of groups of patients. The mean time and 95% confidence intervals (CI) were calculated between date of referral and the institution of definitive treatment for the two groups of patients, pre and post implementation of the intervention. Comparison was made of secondary outcome measures in the two groups of patients. Analyses were undertaken using IBM Statistical Package for the Social Sciences (SPSS, also know as PASW) versions 19 and 22.

4. Results

4.1 The process of instituting the intervention

The initiation of the pathway was more staggered than anticipated; initially the service consisted solely of an Unknown Primary MDT meeting and then in-patient reviews followed. A 'primary investigation' out-patient clinic was established, with a maximum two-week wait, accepting referrals from both primary care and hospital. Hospital procedures and systems led to delays in establishing this clinic until after the end of the second data collection phase. The service was advertised through cascade, word of mouth and through education meetings.

A total of 88 patients were identified in the two study periods, pre interventions and during pathway implementation. The mean age of participants was 72.51 years old (range 44-98; SD = 11.21; median = 75). Forty-eight patients were female (54.5%) and 40 were male (45.5%).

4.2 Performance status

The ECOG (Eastern Cooperative Oncology Group)performance status scale was used [11]. Twenty patients (22.7%) had a performance status of 0-1, 15 patients (17.0%) had a performance status of 2 and 52 patients (59.1%) had a performance status of 3-4.

4.3 Survival times

By 2nd April 2015 85 of the 88 patients had died. The mean survival time was 81.79 days (95% CI = 60.33, 103.25). Overall, the mean time from referral to death/censorship was 180.45 days (95% CI = 106.34, 272.75; median = 44; n = 88). Figure 1 shows survival curves for those who had the primary site of the malignancy identified versus those who remained as 'Unknown Primary'. The mean survival of those with an identified primary site was 152.8 days (95% CI =87.7, 217.97; median=65), whereas those who were unknown it was 85.3 days (95% CI=50.9, 119.7; median=28).

Figure 2 compares those who were referred for tumour directed therapy versus those who were not. The mean survival for those in the treatment group was 363 days (95% CI=172.34, 553.98; median = 130) versus 52 days (CI=29.17, 75.43; median = 26) in the supportive care only group. It should be noted that not all those who were referred received treatment.

4.4 Referrals to specialist palliative care

Forty-three patients (48.9%) had a final diagnosis of cancer of unknown primary (or MUO). Referral to specialist palliative care could come about either because specialist palliative care needs were already recognised in a patient's care, or because the newly introduced system prompted review by the palliative care physician.

4.4 Tumour-directed treatment (TDT)

Forty patients (46%) were not considered suitable for referral for TDT and eight (9%) died before a decision on referral could be made. One person declined any further investigation or treatment. Thirty-nine people (44%) were referred for consideration of TDT. Of these 39, twenty-three patients had TDT as planned or with modifications, seven patients had tumour-directed treatment planned but were too ill for it to begin, and six patients commenced TDT, but then was stopped because they became too ill. Of the remaining three: one was offered treatment, but declined; one had treatment held in readiness but not given; and one, it was decided not to attempt treatment.

Of the 23 patients who had treatment as planned or with modifications; 8 had radiotherapy; 7 chemotherapy; 3 a combination of radiotherapy and chemotherapy; 2 had surgery; 1 endocrine treatment; one a combination of surgery and radiotherapy; and one a combination of surgery and chemotherapy. Of the six who began treatment, but had to stop because they were too ill, 5 had chemotherapy and 1 had radiotherapy.

4.5 Site or sites of final diagnosis

Forty-three patients (48.9%) had a final diagnosis of cancer of unknown primary, and 45 patients (51.1%) had a final diagnosis of site-specific cancer or haematological malignancy. Table 1 shows the distribution of final diagnosis of the patients in the sample.

4.6 Place of death

44.3% of patients died in the district general hospital (n=39), 19.3% died at the local hospice (n=17) and 22.3% died at home (n=20). Of the remainder, 3.4% (n=3) were still living at the time of review. Three died in a community hospital, and three in Cancer Centres and three were unknown.

5. Comparison of the pre intervention and pathway implementation group.

Data was collected on two cohorts of patients. The first related to the pre-pathway phase, and numbered 50. The second was from the pathway implementation phase, and numbered 38.

In the implementation group, patients had experienced varying degrees of application of the new pathway approach. Of the 38 patients in this group: 8 (21%) were initiated on the pathway early in the diagnostic process; 8 (21%) were referred for discussion at the Unknown Primary MDT; 5 (13%) were referred to the Unknown Primary team late in the diagnostic process; 5 (13%) were picked up due to specialist palliative care referral; and 12 (32%) had no input from the Unknown Primary team.

5.1 Age, gender and Performance status

There was no statistically significant difference in the mean rank of the ages, gender or performance status of the pre-pathway patients compared with the pathway patients.

5.2 Patient survival

There was no significant difference in terms of time from instigation of definitive treatment to death, and time from MUO referral to death between pre and pathway patients

5.3 Primary outcome measure

This had been designated as the time from referral to instigation of definitive treatment. There was no difference between pre pathway and pathwayimplementation patients in the mean rank of time from referral to instigation of definitive treatment.

The range in the pre-pathway group was from 0 to 115 days, and the range in the pathway implementation group was from 0 to 74 days. This indicates that it is possible that the intervention shortens the pathway of those who wait the longest for definitive treatment. [Figure 3]

5.4 Secondary outcome measures

Twenty two of the pre-pathway patients (44%) were referred for TDT compared with 18 of the pathway patients (47.4%). For 23 (46%) patients in the pre-pathway group referral was not considered suitable; and for 17 (44.8%) patients in the pathway group referral was not considered suitable. Five patients in the pre-pathway group (10%), and 3 (7.9%) in the pathway implementation group died before a decision on referral could be made.

Fourteen of the pre-pathway patients (28.0%) and nine of the pathway patients (23.7%) had TDT as planned or with modifications. One of the pre-pathway patients (2.0%), and six of the pathway patients (15.8%) had TDT planned but it was not begun because they were too ill. Four of the pre-pathway patients (8.0%) and two of the pathway patients (5.3%) commenced TDT but it was stopped because they were too ill.

It appears from this that using a pathway approach with the palliative care physician as lead clinician has not resulted in fewer referrals for tumour-directed treatment. The small proportions in both groups who actually complete such treatment, and the numbers who die before a decision on referral can be made, underline the extent of illness, and the poor prognosis for the majority of patients who present in this way.

5.5 Final diagnosis

There was no significant difference between the pre-pathway patients and the pathway patients in terms of the final diagnosis (χ^2 =0.00; df = 1; p=1.00). Of the 50 pre-pathway patients, 26 patients (52.0%) had a primary site identified and 24 patients (48.0%) had a final diagnosis of unknown primary. Of the 38 pre-pathway patients, 19 patients (50%) had the primary site identified and 19 patients (50%) had a final diagnosis of unknown primary.

5.6 Place of death

We speculated that a death in the district general hospital might be a proxy for an incomplete resolution to the investigatory period. The grounds for this are that in those cases where care reached a point of resolution, patients would be discharged home, or referred to tertiary care. There was a difference between patients who died in the pre-pathway group and the pathway group in whether they died in the district general hospital or elsewhere, although this did not reach statistical significance (χ^2=3.255; df=1; p=0.071). Of the 48 pre-pathway patients who died, 27 died in the district general hospital (56.3%), whereas only 12 of the 37 pathway patients who had died (32.4%) died in the district general hospital.

More people died at home in the pathway group: 7 (14.6%) people in the pre-pathway group and 13 (35.1%) people in the pathway group. Numbers are small however, and could have arisen due to chance. Of the pre-pathway group, 30 died in hospital (60%), and of the pathway group, 14 died in hospital (37%). Of the 50 pre-pathway patients, 10 died in a hospice (20%), and of the 38 pathway patients, a similar proportion, 7 (18%), died in a hospice.

6. Discussion

Patients who presented to the hospital with MUO tended to be older (median age 75) with the majority having a poor performance status. They mostly have a poor prognosis,

as indicated by the median time from presentation to death which was 40 days. This cross-sectional study found approximately twice as many patients required palliative medicine referral (86.3%) compared to oncological or tumour-directed treatment referral (44.3%). Only around a quarter of patients (26.1%) completed planned tumour-directed treatment. Additionally, our data illuminated a number of issues concerning the current systems of recording, notably inconsistencies in coding, an issue also highlighted in NICE guidance.

The development of the Unknown Primary team and pathway, led by a palliative medicine clinician did not appear to reduce the mean rank time from presentation with MUO to definitive treatment but there is some indication it may curtail the longest investigatory periods. No significant difference was seen following the intervention in the proportion of patients who had a primary site identified (50%), nor in survival time. There is some indication that instituting a pathway for managing MUO in a district general hospital has the potential to contain the length of time taken for investigation and increase the proportion of those patients who are discharged or transferred before death.

This study describes a population of patients presenting with MUO and a potential method of implementing NICE guidance on referral pathways and management of these complex patients. The findings need to be interpreted with caution because this small

study was limited to one district general hospital. We were not able to realise fully the intended pre and post design, as the intervention cohort had variable exposure to the planned intervention, which took time to be fully embedded. This may have blunted some of the effect. Furthermore, the pre-intervention group may have been subject to the Hawthorn effect, as the rationale for the development of the Unknown Primary service, its approach and working methods were being discussed within the hospital during this period.

This study demonstrates the practicality and acceptability of introducing a pathway approach, establishing a team, and developing working practices, including a dedicated out-patient clinic within a district general hospital, for the management of care of patients presenting with MUO.

The study supports the case for timely assessment of what, if any, tumour-directed therapy the patient could tolerate, in conjunction with the patient's wishes regarding further investigations and treatment. Most of these patients have a poor prognosis and will be referred for specialist palliative care. Having a lead physician with a palliative medicine background could potentially improve continuity of care and symptom control for this complex group of patients. Importantly, this research does not support fears that early specialist palliative care involvement might decrease oncology referral, or reduce the likelihood of a final diagnosis being made.

The time necessary to fully establish the intervention, particularly the clinic should be noted, as should the need to ensure smooth processes for ensuring referral from primary care, and opportunities for early discharge with out-patient follow-up. Another important lesson was the need for discussions outside of the formal MDT meetings to expedite the process, and the invaluable nature of an interested radiologist and pathologist.

We will review our findings in a further study with over a longer period to include a larger population now that the pathway approach has been fully implemented into the clinical service. The difference in deaths at home shown in our data would also bear fuller investigation to test if the intervention had some impact here.

Conclusions

This evaluation adds support to NICE's recommendation of the development of multidisciplinary teams to investigate and support people presenting with metastatic malignancy of unknown primary origin and makes the case for Palliative Medicine Physicians to be Lead Clinicians in these teams.

Funding

This work was supported by a grant from Macmillan Cancer Support

Declaration of Interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

1. *NICE Guideline:* Diagnosis and management of metastatic malignant disease of unknown primary origin; *National Collaborating Centre for Cancer, Velindre NHS Trust Cardiff*, July 2010

2. Briasoulis, E; Pavlidis, N; Felip, E; On behalf of the ESMO Guidelines Working Group Cancer of unknown primary site: ESMO Clinical Recommendations for diagnosis, treatment and follow up. *Annals of Oncology* 2009;20 (Supplement 4) iv154-iv155

3. Pentheroudakis, George; Briasoulis, Evangelos; Pavlidis, Nicholas; Cancer of Unknown Primary Site: Missing Primary or Missing Biology; *Oncologist,* 2007; 12: 418-425

4. Shaw, P H S; Adams, R; Jordan, C; Crosby, T D L; A Clinical Review of the Investigation and Management of Carcinoma of Unknown Primary in a Single Cancer Network; *Clinical Oncology,* 2007; 19: 87-95

5. Pavlidis, Nicholas; Pentheroudakis, George, Cancer of unknown primary site. *The Lancet,* 2012; 379: 1428-35

6. James, Nicola, (2007); Managing cancer of unknown primary: Are we getting it wrong? *Cancer Nursing Practice,* 2007;6 (7): 25-28

7. Seve P1, Sawyer M, Hanson J, Broussolle C, Dumontet C, Mackey JR
The influence of comorbidities, age, and performance status on the prognosis and treatment of patients with metastatic carcinomas of unknown primary site: a population-based study. *Cancer.* 2006 May 1;106(9):2058-66.

8. Shaw PH1, Adams R, Jordan C, Crosby TD.
A clinical review of the investigation and management of carcinoma of unknown primary in a single cancer network. *Clin Oncol (R Coll Radiol)*. 2007 Feb;19(1):87-95.

9. Uzunoglu S1, Erdogan B, Kodaz H, Cinkaya A, Turkmen E, Hacibekiroglu I, Sari A, Ozen A, Usta U, Cicin I. Unknown primary adenocarcinomas: a single-center experience.
Bosn J Basic Med Sci. 2016 Nov 10;16(4):292-297.

10. Diagnosis and management of metastatic malignant disease of unknown primary origin Evidence Review July 2010 updated Feb 2012 Developed for NICE by the National Collaborating Centre for Cancer

11. Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J ClinOncol*1982; 5:649-655

Table 1: Site of final diagnosis

Final Diagnosis	**Frequency**	**%**
Carcinoma of Unknown Primary	43	48.9
Lung	14	15.9
Colorectal	9	10.2
Upper GI	4	4.5
Pancreatic	2	2.3
Hepatobiliary	1	1.1
Lymphoma	2	2.3
Brain	2	2.3
Breast	1	1.1
Gynae/Ovarian/Peritoneal	4	4.5
Prostate	1	1.1
Urological (excluding prostate)	2	2.3
Neuro-endocrine/carcinoid	2	2.3
Mesothelioma	1	1.1
Total	**88**	**100.0**

Table 2 Demographics:

	Pre-Pathway	Post Pathway
Age - mean	**73.0**	**71.8**
-median	**76**	**72**
-mode	**66**	**68**
Gender female %	**54.0**	**55.3**
ECOG Performance status %		
0	**18.0**	**13.6**
1	**66.0**	**71.6**
2	**14.0**	**12.5**
3	**0**	**1.1**
4	**2.0**	**1.1**

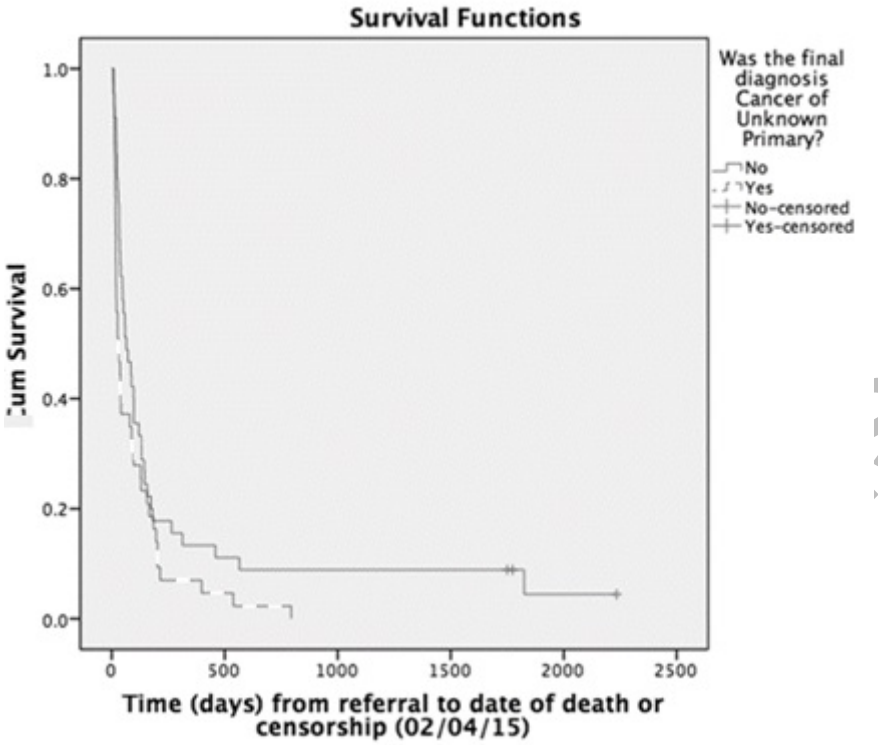

Figure 1: Time from referral to death (days) according to whether final diagnosis was unknown primary or not

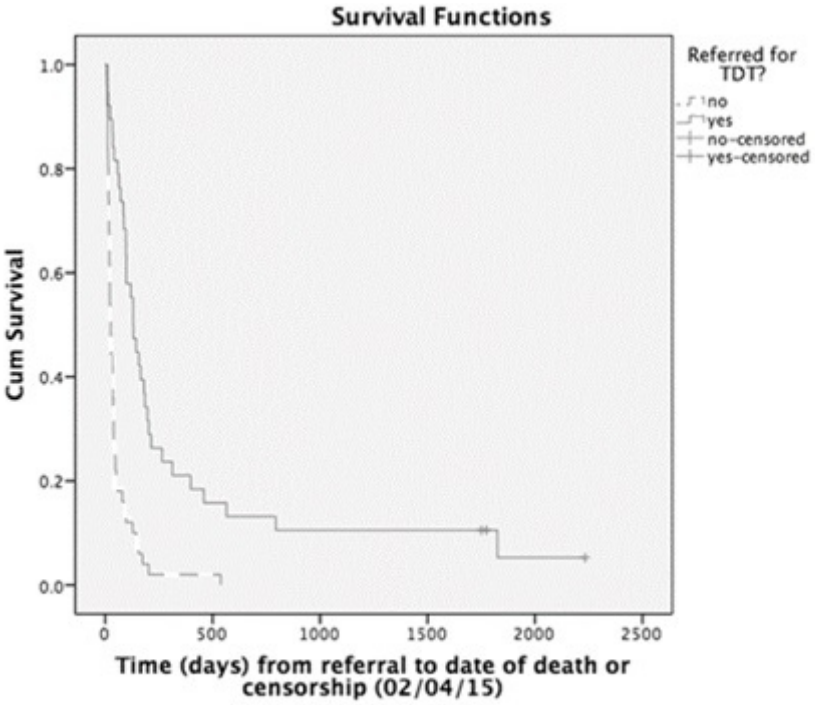

Figure 2: Time from referral to death according to whether Tumour directed therapy was considered

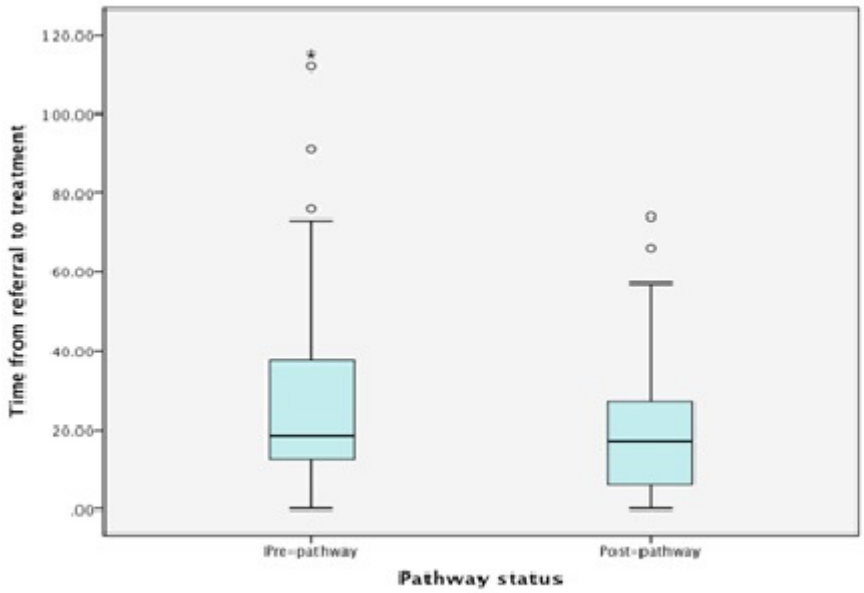

Figure 3: Range in Primary outcome measure pre and during pathway implementation