National Cancer Registry Ireland **Cancer Trends**

Cancer of unknown primary

Cancers of unknown primary: summary statistics

Between 2012 and 2016, over 450 patients per year were diagnosed with a malignant cancer where the primary site of their cancer was unspecified. These cancers were identified by the presence of metastatic disease where the cancer has spread to other organs in the body but the site of the original tumour was not identified.

While 15% of these tumours were broadly known to be located in particular regions of the body (e.g. 'thorax'), most - 390 cases per year or 2-3% of all invasive cancers (excluding non-melanoma skin cancer) - were of unknown site (Table 1). These are defined as "cancers of unknown primary" (CUP) for this report, which summarises the incidence, mortality, treatment and survival for these cancers in Ireland.

Table 1: Annual average number of cancer of unknown primary (CUP) 2012-2016

	Annual average	% of all
cancers of all unspecified sites	458	
C26 (digestive system)	41	9%
C39 (respiratory/intrathoracic)	>1	<1%
C76 (other ill-defined sites)	27	6%
C80 (unspecified site) CUP*	390	85%

** these cancers are the focus of this report*

Cases presented here are based on ICD-10 category C80, which is derived by NCRI using standard IARC translations from ICD-O-3 topography (site) and morphology. Cancers whose morphology is sufficiently specific to infer a primary site are translated to the ICD-10 code for that site. (For example, melanomas of unspecified site are as translated or defaulted to melanomas of skin for international comparability purposes, thus are excluded from NCRI figures on CUP.) Inclusion of such cases would increase the annual number of CUP cases only slightly, from 390 to 412 per year.

Typically, cancers of unknown primary have an aggressive clinical course associated with short survival times, and this feature may contribute to a lower likelihood of the primary site being reliably diagnosed. It has also been theorised that such cancers could have features leading to more rapid formation of metastases, compared with more typical cancers arising from the same primary sites, or that they may involve cancers where growth of the primary tumour is suppressed by or regresses as a result of the body's immune response[2]

Table 2 outlines summary incidence and mortality statistics for CUP for the period 2012-2016. Although the number of cases and deaths per year was similar between the sexes (with slightly higher counts in females), incidence and mortality rates were somewhat higher in males. An average of 286 deaths from CUP occurred each year with approximately 7 deaths for every 10 incident cases in both sexes. CUP represented approximately 2% of all cancers diagnosed and 3% of all cancer deaths, slightly higher in both cases for females. Of all patients diagnosed since 1994, 332 females and 415 males were known to be still alive at the end of 2016.

Table 2: Incidence and mortality statistics for CUP for the period 2012-2016

	females	males	total
INCIDENCE			
Total cases per year	200	190	390
Incidence rate (easr*[3])	6.7	7.9	-
Lifetime risk of diagnosis	1 in 239	1 in 197	-
% all invasive cancers	2.0%	1.7%	1.8%
Rank of all cancer cases	13th	15th	15th
MORTALITY			
Total deaths per year	148	138	286
Mortality rate (easr*[3])	4.7	5.8	-
Lifetime risk of death	1 in 378	1 in 287	-
% of all cancer deaths	3.5%	2.9%	3.2%
Rank of all cancer deaths	6th	13th	10th
Prevalence (23 year#)	332	415	747
Number alive per 100,000	14	18	16

**European Age Standardised Rate (cases/deaths per 100,000 per year)[3]. #vital status as per end 2016*

Currently almost two-thirds of all CUP are microscopically diagnosed, an increase from just 50% of patients in 1994-99 (Table 3a). Over time, there has been a corresponding decline in the proportion of patients that were diagnosed clinically only. Approximately one third of all cases are diagnosed radiologically each year.

Table 3a. Trends in method of diagnosis for CUP, 1994-2016

	1994-1999	2000-2005	2006-2011	2012-2016
histology/cytology	50%	51%	59%	64%
radiology	36%	38%	33%	31%
clinical	7%	4%	3%	1%
other/unknown	7%	7%	5%	4%

Reflecting the increase over time in the proportion of cases having a microscopic diagnosis, there was a comparable decrease in the percentage of cases that were of unknown cell type since 1994 (Table 3b). The majority of known subtypes were adenocarcinoma.

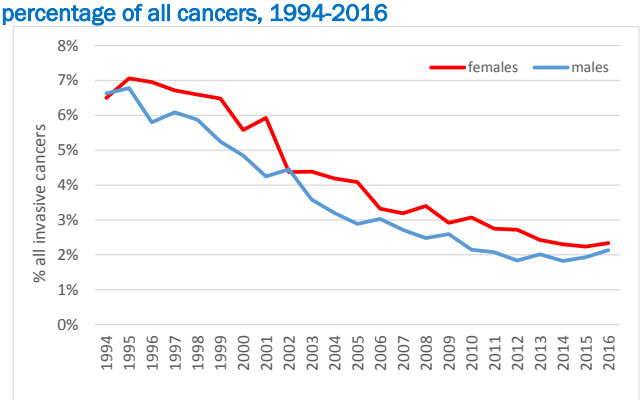
Table 3b. Trends in histological subtypes for CUP, 1994-2016

	1994-1999	2000-2005	2006-2011	2012-2016
adenocarcinoma	30%	30%	35%	36%
squamous cell	5%	5%	8%	12%
other specified	<1%	<1%	1%	1%
unspecified	65%	65%	57%	52%

Improvements in diagnostic investigations have also resulted in a reduction in the proportion of CUP as a percentage of all cancers over time (Figure 2) from over 6% in 1994 to under 3% in 2016.

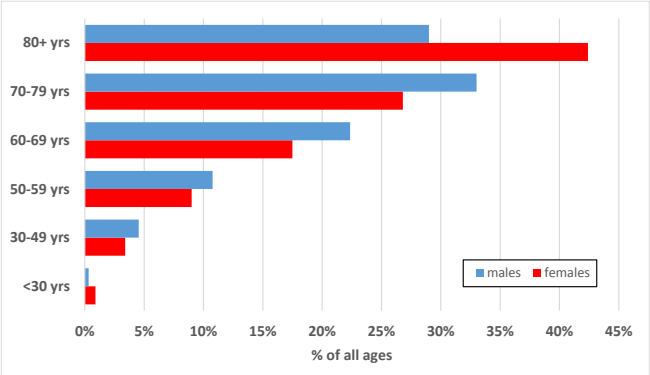
These figures are broadly in line with those from other developed countries, typically reported as in the range 3-5% of all invasive cancers (e.g. [2]) although definitions and inclusions can vary between studies.

Figure 2. Variation in the relative proportion of CUP as a percentage of all cancers, 1994-2016



The median age at diagnosis for CUP was 77 years for females and 73 years for males. Less than 5% of all cases were aged under 50 with 69% of females and 62% of males aged 70 or older. (Figure 3). There was little change in the age profile of patients over time.

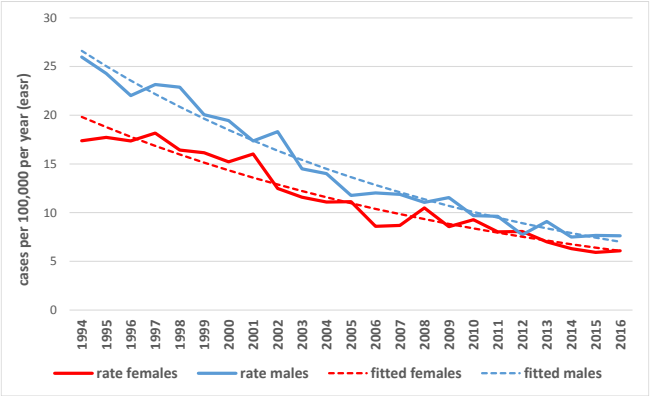
Figure 3. Percentage distribution of CUP by age in males and females, 2012-2016



Trends in incidence and mortality

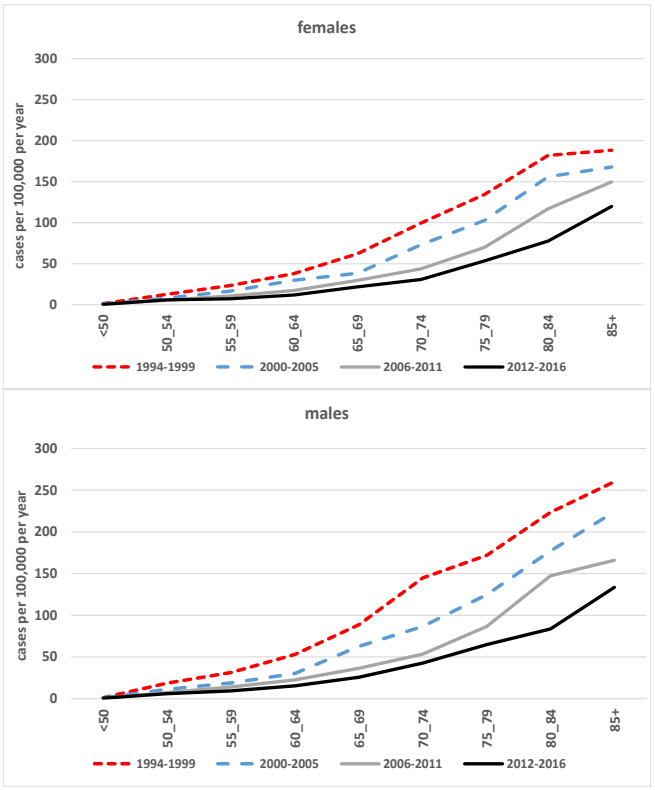
Incidence rates for CUP have fallen considerably since the mid-1990s and current rates are approximately one-third of those rates recorded in 1994 (Figure 4). This most likely reflects improvements in the quality and specificity of cancer diagnoses over time, as rate trends for cancer as a whole have been more stable.[4] Statistically significant decreases in incidence rates were observed for both sexes with an annual percentage decline of -5.2% (95%CI: -5.8%, -4.7%) for females and -5.9% (95%CI: -6.3%, -5.5%) for males since 1994. The greater rate of decline in males has narrowed the difference in rates between the sexes in recent years.

Figure 4. Incidence rates for CUP, 1994-2016



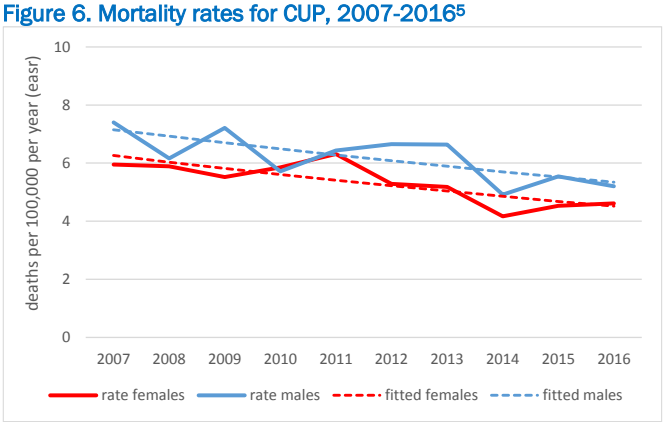
The reduction in incidence rate was observed across all age groups (Figure 5) with a maximum annual percentage decline of -6.7% in females aged 60-64 and -7.0% in males aged 65-74 years over the 22 year period.

Figure 5. Change in age specific incidence rates for CUP over time



Annual mortality rates between 2007 and 2016[5] show a significant decrease in mortality rates in both sexes (Figure 6). An annual percentage decline of -3.6% (95%CI: -5.6%, -1.5%) in females and -3.2% (95%CI: -5.6%, -0.7%) in males was observed over this 9 year period. Rates in 2016 were 22% lower than those in 2007 for females and male rates were 30% lower. As a comparison, incidence over the same period fell by 30% for females and 36% for males.

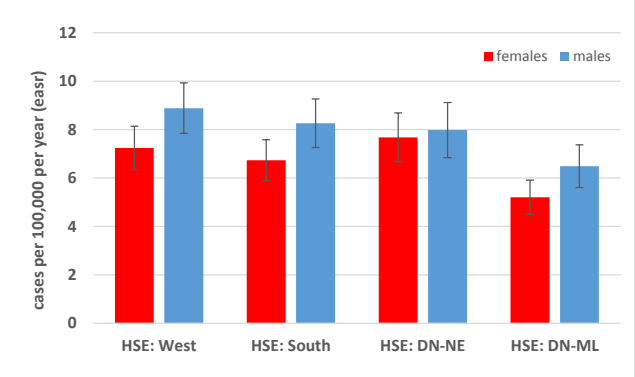
Figure 6. Mortality rates for CUP, 2007-2016[5]



Geographic variation in incidence

During 2012-2016, incidence rates were lowest in the HSE Dublin-Mid Leinster region compared to other HSE regions (Figure 7). Rates for females in this area were statistically significantly lower than those in both HSE Dublin-North East and HSE West. Male rates in Dublin-Mid Leinster were significantly lower than in HSE West.

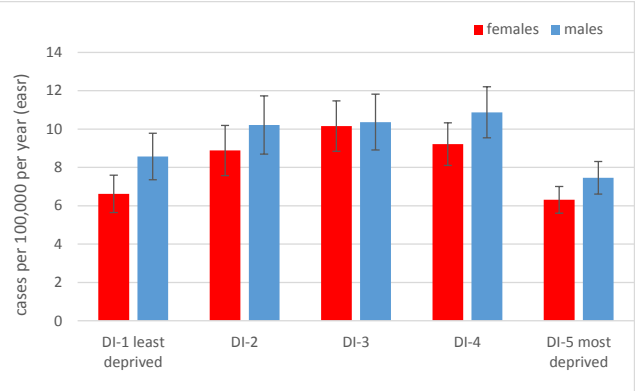
Figure 7. Incidence rates for CUP by HSE region, 2012-2016



DN-NE: Dublin & North East, DN-ML: Dublin & Mid Leinster

No obvious trend was observed between CUP incidence and deprivation (Figure 8). Lowest incidence rates were found for both sexes in the most and least deprived areas with fairly similar rates recorded in the 3 central quintiles.

Figure 8. Incidence rates for CUP by deprivation index[6], 2012-2016



Treatment[7]

The majority of all patients diagnosed with cancer of unknown primary do not receive cancer directed treatment (i.e. therapy targeted at reducing or removing the tumour) with over two-thirds of all patients having no treatment in 2011-2015 (Table 4). While many of these patients may have had palliative therapy or treatment for symptom relief, they did not have treatment targeted directly at reducing or removing their cancer. The percentage of these untreated patients has declined somewhat over time from a maximum of 78% in 1994-1999. This corresponds to an increase in the proportion of patients having chemotherapy which has doubled since 1994-99 (from 9% to 19%) together with a modest increase in the proportion of patients having radiotherapy (from 13% to 18%). The numbers of patients undergoing surgical resection is small with fewer than 25 patients (or 6% of all diagnosed cases) treated surgically per year.

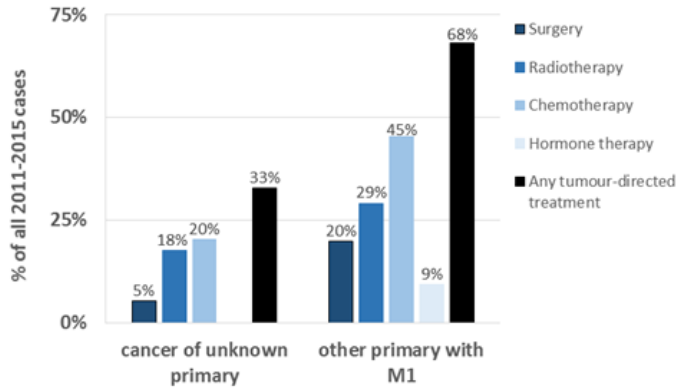
Males were twice as likely to receive radiotherapy compared to females. It is possible that differences between the sexes in the location of metastatic tumours may contribute to this difference. Slightly more females than males had no tumour directed treatment. Patients over the age of 70 were more likely not to have any treatment and the proportion of patients having chemotherapy and radiotherapy was greatest in under 60 year olds.

Table 4. Treatments received by CUP patients over time, by sex and age group, 1994-2015[7]

	surgery	radio-therapy	chemo-therapy	no treatment
1994-1999	4%	13%	9%	78%
2000-2005	4%	15%	14%	73%
2006-2010	6%	15%	17%	69%
2011-2015*	5%	18%	19%	67%
** for cases diagnosed 2011-2015 specifically:*				
females	5%	12%	19%	71%
males	5%	24%	20%	63%
<50 years	12%	25%	54%	39%
50-59 years	12%	34%	51%	36%
60-69 years	8%	27%	37%	45%
70-79 years	5%	17%	14%	70%
80+ years	2%	8%	3%	88%

In contrast, for 2011-2015, for solid cancers of other primary sites with distant metastatic involvement at diagnosis, a much higher percentage of cases received some tumour-directed treatment (68%), chemotherapy (45%), radiotherapy (29%) or surgery (20%) (Figure 9).

Figure 9. Percentage of CUP receiving tumour-directed treatment 2011-2015: comparison with treatment of distant metastatic (M1) cases of other primary cancers (solid cancers only)



These figures emphasise that treatment options for cancers of unknown primary (probably largely involving distant metastasis) tend to be even more limited than for distant metastatic cases involving more specific primary sites. However, some of the differences in treatment percentages between these categories may be associated with the older age at diagnosis (median 76 years) for patients with cancer of unknown primary compared with the other group (69 years). A comparison of the most frequent combinations of treatment modalities is tabulated below (Table 5).

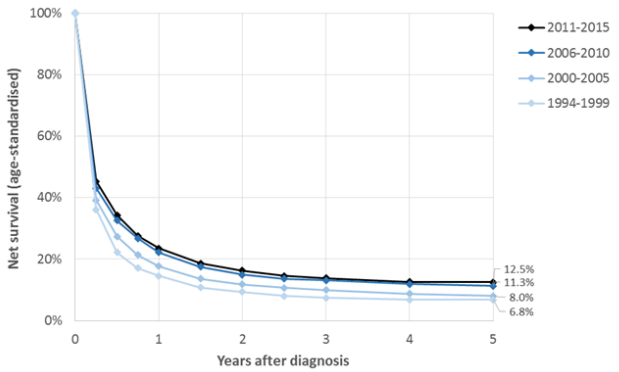
Table 5. Tumour-directed treatment combinations of CUP, 2011-2015: comparison with treatment of distant metastatic (M1) cases of other primary cancers (solid cancers only)

	CUP	other primary with M1
no treatment	67.2%	31.9%
chemotherapy only	12.3%	19.6%
radiotherapy only	9.2%	9.5%
radio & chemotherapy	6.0%	11.6%
surgery only	1.9%	4.8%
surgery & radiotherapy	1.4%	1.4%
surgery & chemotherapy	1.0%	8.8%
surgery, radio & chemotherapy	0.8%	3.2%
hormone therapy only	0.0%	4.2%
radio & hormone therapy	0.0%	1.9%
chemo & hormone therapy	0.0%	1.0%
radio, chemo & hormone therapy	0.0%	0.6%
surgery & hormone therapy	0.0%	0.6%
surgery, radio, chemo & hormone	0.0%	0.4%
surgery, radio & hormone therapy	0.0%	0.4%
surgery, chemo & hormone	0.0%	0.2%

Survival[8]

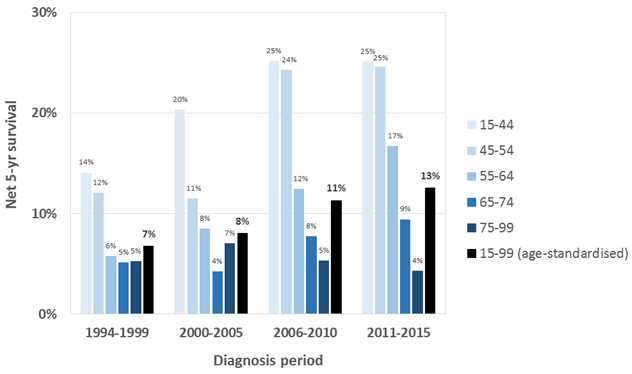
Survival is very poor for patients diagnosed with cancer of unknown primary, with a median survival time (whether expressed in terms of overall survival or net survival) of less than three months. Five-year net survival of patients diagnosed during 2011-2015 averaged only 13%. This does represent some improvement since the period 1994-1999, when five-year survival averaged just 7% (Figure 10).

Figure 10. Net survival of patients diagnosed with cancer of unknown primary, by period of diagnosis



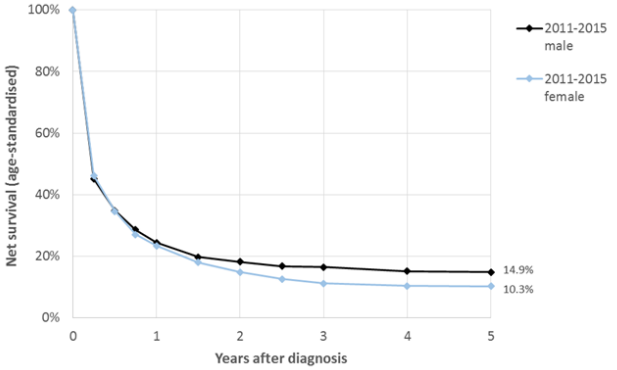
The greatest improvements in survival over time have been observed in the youngest patients, and no improvement has been seen among patients aged 75 or over (Figure 11).

Figure 11. Net survival of patients diagnosed with cancer of unknown by age group and period of diagnosis.



Looking at survival rates during this most recent diagnosis year period, males showed a slightly better overall five-year net survival (14.9%) compared to females (10.3%) (Figure 12).

Figure 12. Net survival of patients diagnosed with cancer of unknown primary: male/female comparison for diagnosis period 2011-2015



Conclusion

Despite poor survival from CUP, the significant reduction in incidence rates observed since 1994 along with declining mortality rates are indications that improvements in diagnostic methods and treatments are having a positive impact. Continued monitoring of this cancer may be a valuable indicator of future improvements in cancer services.

References and notes

1. National Cancer Institute, USA Carcinoma of Unknown Primary Treatment (PDQ®) https://www.cancer.gov/types/unknown-primary/patient/unknown-primary-treatment-pdq.
2. Kaaks R, Sookthai D. Hemminki K et al. Risk factors for cancers of unknown primary site: Results from the prospective EPIC cohort. Int J Cancer. 2014; 135: 2475-2481
3. All rates standardised to the European (1976) standard population
4. NCRI 2019. Cancer incidence projections for Ireland 2015-2045 https://www.ncri.ie/publications/cancer-trends-and-projections/cancer-incidence-projections-ireland-2020-2045
5. Central Statistics Office. Deaths by cause and year of occurrence https://www.cso.ie/px/pxeirestat/Statire/SelectVarVal/Define.asp?maintable=VSA08&PLanguage=0
6. Quintiles of deprivation score applied to the 2006 national census, SAHRU. http://www.sahru.tcd.ie/
7. Treatment data not complete for 2016 cases so treatment data for this year is not included. Only treatments administered within 1 year of diagnosis are included.
8. Follow-up is complete to end 2016.

