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Epidemiology of unknown primary tumours; incidence and population-based survival of 1285 patients in Southeast Netherlands, 1984–1992

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Abstract

Patients with an unknown primary tumour (UPT) represent 5–10% of all new cancer patients. Data on survival and prognostic factors of UPTs are based on selected patient series from specialised institutions. Population-based data on incidence, histology and determinants of survival for patients with UPT are not available. All patients diagnosed with UPT between 1984 and 1992 and entered in the population-based Eindhoven Cancer Registry for Southeast Netherlands were included. Follow-up of vital status is complete up to 1999. 1285 patients were registered. In 1024 patients, the diagnosis was confirmed histopathologically: 479 (47%) had adenocarcinoma, 453 (44%) poorly differentiated carcinoma (PDC) or adenocarcinoma (PDA), 76 (7%) squamous cell carcinoma and 16 patients (2%) had an undifferentiated malignant neoplasm. In 26% of these patients with UPT, the tumour was already widely disseminated at presentation. The majority of patients (67%) received only supportive treatment. The median survival was 11 weeks and only 15% were still alive 1 year after diagnosis. Favourable subgroups comprised young patients and patients with metastases localised in lymph nodes. In 261 cases, the diagnosis was made clinically. These patients were evaluated separately. They were older than the biopsy-confirmed patients, received less cancer therapy and their prognosis was even worse (median survival of 7 weeks). In a comparison with data from a tertiary referral centre in the United States of America (USA), our patients were older, received less therapy and had a poorer prognosis. Demographics of our favourable subgroup resembled the patients from the American study. The differences were most likely caused by the differences in the patient populations. In conclusion, we have demonstrated in a population-based study that the prognosis for patients with UPT is more unfavourable than suggested in most clinical studies.

Keywords: Unknown primary tumour; Epidemiology; Prognosis

1. Introduction

Unknown primary tumour (UPT) is defined as biopsy-proven metastasis of a malignancy in the absence of an identifiable primary site after complete history and physical examination, basic laboratory studies, chest X-ray and additional directed studies indicated by positive findings during the initial work-up [1]. Modern cancer management relies heavily on recognition of the primary tumour; thus the absence of a primary site poses major diagnostic and therapeutic problems.

Patients with an unknown primary tumour represent 5–10% of all new cancer patients [2,3]. The diagnosis was ranked as the eighth most frequent site of cancer in one large series [4]. Approximately 2500 new patients are diagnosed annually in The Netherlands giving an age-standardised incidence rate of 6.7 per 10^5 for males and 5.3 per 10^5 for females [5]. It is more common than non-Hodgkin's lymphoma.

In most clinical studies, the prognosis for patients with UPT was generally poor. Median survival from the time of diagnosis ranged from 5 to 11 months, and less than 25% of patients survived beyond 1 year [6,7].

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Treatable subgroups comprising approximately 30% of the total group can be recognised [3]. However, for the majority of patients with UPT, effective therapy does not exist. Since data on prognostic factors of UPT and most survival figures are usually obtained from specialised institutions, they may be only of limited relevance. We therefore report on incidence, histological findings, survival and prognostic factors for an unselected group of patients with UPT, treated in general hospitals and entered in the Eindhoven Cancer Registry for Southeast Netherlands between 1984 and 1992. We compared these data with results reported for a specialised institute in the USA [6].

2. Patients and methods

The Eindhoven Cancer Registry was started in 1955 as part of a programme for nationwide cancer registration. It served an area of approximately 2500 km^2 with almost one million inhabitants (almost 7% of the Dutch population). Access to specialised care was easy as a result of the relatively short distances to the eight hospitals, ample supply of health services and a sickness insurance system without major financial obstacles. The Eindhoven Cancer Registry provides full documentation on all forms of cancer in this region [8]. The data are retrieved via four different routes. Routine reports on all patients submitted by the Departments of Pathology and Radiotherapy are checked. Periodic active and direct collection of data from patient records in all hospitals is achieved in cooperation with the medical records offices, as well as direct contact with the secretarial offices of surgical departments. Finally cross-checks with specialised departments of the University Hospital in Nijmegen are carried out. Active follow-up was accomplished in cooperation with municipal population administrations in four rounds in 1987, 1991, 1994 and 1999. Death certificates cannot be tracked in The Netherlands.

From the database in question, 1285 new UPT patients were diagnosed during the period 1984–1992. All patients were coded according to the *International Classification of Diseases of Oncology*, 9th edition, codes 196–199 (ICD-O). These codes refer to different localisations of metastasis of an unknown primary malignancy. They are used when at the time of diagnosis and initial treatment, the tumour origin remains unknown to the physician. The series includes 1024 patients with microscopically-confirmed metastatic malignancies, as well as 261 patients with only a clinical diagnosis. The latter group was evaluated separately because it did not fulfil today's accepted definition of UPT. We did not exclude these patients because the high percentage (20%) of clinical diagnosis demonstrated that it was common practice, especially among the elderly, not to perform a biopsy, but to diagnose UPT only on the basis of clinical signs and symptoms.

The pathological reports came from three regional laboratories. Patients were divided into four subgroups: adenocarcinoma, poorly differentiated carcinoma (PDC) and poorly differentiated adenocarcinoma (PDA), squamous cell carcinoma and undifferentiated malignant neoplasm. Incidence was calculated per 100 000 person-years and age-adjustment occurred according to the European Standardized Population. Survival was calculated from the date of diagnosis, which is the date on which the biopsy was performed or the patient was hospitalised. Estimates of the survival distribution of patients were constructed using the method of Kaplan–Meier [9]. Differences between the survival curves for the various patient subgroups were evaluated for statistical significance with the log-rank test.

As a reference, we used data from the largest series of UPT patients in literature, reported by Abbruzzese and colleagues [6]. In this series, clinical data on 657 consecutive patients with unknown primary carcinoma referred to the M.D. Anderson Cancer Center between 1987 and 1992 were evaluated.

3. Results

In the period from 1984 to 1992, UPT was diagnosed in 1285 patients (1024 by biopsy; 261 clinically) and registered with the Eindhoven Cancer Registry, approximately 4% of all cancer patients in this period. Most patients were seen by an internist or pneumologist (63 and 15%, respectively).

The demographical and histological characteristics of the biopsy-proven 1024 patients are listed in Table 1. The mean age was 66 years and there was a slight male predominance. Adenocarcinoma and PDC/PDA were the most common histological diagnoses. The presenting sites of metastasis identified pathologically, radiographically or by physical examination are listed in Table 2. Metastases were found most frequently in the liver, followed by the lung or pleura and lymph nodes. In 26% of patients the tumour had already metastasised to three or more sites at the time of diagnosis. In the majority of cases (67%), only supportive treatment was given. Chemotherapy, radiotherapy or surgery was provided in 5, 14 and 5% of cases, respectively; 4% received combination therapy. Only 1% of the patients received hormonal therapy (Table 3).

In January 1999, 979 patients had died, 20 were lost to follow-up and 25 patients were still alive. The median survival for the biopsy-proven group was 11 weeks, with only 152 patients (15%) alive 1 year after diagnosis (Fig. 1).

Favourable subgroups comprised young patients (<50 years) and patients with lymph node metastases

Table 1
Characteristics of patients with unknown primary tumour; distribution according to age, gender and histology[a]

Characteristics	Present series						M.D. Anderson	
	I		Ia		II		III	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
	1024	(100)	131	(100)	261	(100)	657	(100)
Age (years)								
<40	32	(3)	3	(2)	2	(1)	65	(10)
40–49	70	(7)	16	(12)	5	(2)	98	(15)
50–59	191	(19)	31	(24)	22	(8)	175	(27)
60–69	303	(30)	47	(36)	63	(24)	208	(32)
⩾70	428	(42)	34	(26)	169	(65)	111	(17)
Gender								
Male	546	(53)	57	(44)	148	(57)	353	(54)
Female	478	(47)	74	(56)	113	(43)	304	(46)
Histological diagnosis								
Adenocarcinoma	479	(47)	44	(34)			255	(39)
PDC/PDA[b]	453	(44)	70	(53)			320	(49)
Squamous cell carcinoma	76	(7)	14	(11)			38	(6)
Undifferentiated malignant neoplasm	16	(2)	3	(2)			44	(7)

UPT, unknown primary tumour.
[a] I = 1024 patients with biopsy-confirmed UPT (this study); Ia = 131 patients who survived more than 1 year; (this study); II = 261 patients with clinical diagnosis UPT (this study); III = 657 patients with UPT [6].
[b] Poorly differentiated carcinoma/poorly differentiated adenocarcinoma.

(Table 4). Patients with brain metastases, as well as patients with an undifferentiated malignant neoplasm appeared to live longer, but random variation ($n = 18$ and $n = 16$) could have played a role.

The 261 patients with only a clinical diagnosis differed from the biopsy-confirmed patients in being older, receiving less cancer therapy and having a shorter median survival of 7 weeks (Fig. 1).

Table 2
Sites of metastasis in patients with unknown primary tumour[a]

Site of involvement	Present series						M.D. Anderson[b]	
	I		Ia		II		III	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
	1024	(100)	131	(100)	261	(100)	657	(100)
Liver	244	(24)	10	(8)	84	(32)	202	(31)
Lung/pleura	127	(12)	12	(9)	16	(6)	258	(39)
Lymph nodes	114	(11)	40	(31)	3	(1)	244	(37)
Bones	82	(8)	9	(7)	51	(20)	184	(28)
Peritoneum	92	(9)	11	(8)	3	(1)	39	(6)
Brain	18	(2)	7	(5)	55	(21)	50	(8)
Elsewhere	81	(8)	22	(17)	4	(2)		[c]
Disseminated	266	(26)	20	(15)	45	(17)		[c]

UPT, unknown primary tumour.
[a] I = 1024 patients with biopsy-confirmed UPT (this study); Ia = 131 patients who survived more than 1 year (this study); II = 261 patients with clinical diagnosis UPT (this study); III = 657 patients with UPT [6].
[b] 60% of patients presented with more than one metastatic site.
[c] Not mentioned separately.

Patients treated at the M.D. Anderson were younger, received in almost all cases some sort of therapy and lived longer. Approximately 40% had lymph node localisation, but it is unknown whether this was the only site of presentation.

4. Discussion

In a population-based study, we found that 4% of all new cancer patients were diagnosed as having UPT. In our registry this is the sixth most common malignant presentation among men and women [8]. Overall survival was very poor in the biopsy-proven group, with a median survival of 11 weeks and a 1-year survival rate of 15% and was even worse in the clinical diagnosed group (7 weeks).

Comparison with a large clinical study of patients with UPT in a tertiary referral hospital revealed similarities with respect to histopathological findings, male–female ratio, favourable prognostic factors (young age, squamous cell carcinoma and lymph node metastases) [6]. However, our patients were older: 42% versus 17% were 70 years of age and over and 10% versus 25% were under 50 years of age. Approximately 30% of the patients in our study received anticancer therapy. In most clinical studies, 50–90% of patients received some sort of treatment [6,7]. Median survival was 11 weeks which was far worse than the 11 months mentioned by Abbruzzese and also worse than the 5 months reported by others [2,3,6,7]. According to age and lymph node

Table 3
Primary therapy for patients with unknown primary tumour[a]

Therapy	Present series						M.D. Anderson	
	I		Ia		II		III[b]	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
	1024	(100)	131	(100)	261	(100)	657	(100)
Supportive care	688	(67)	50	(38)	202	(77)	67	(10)
Radiotherapy	147	(14)	32	(24)	46	(18)	189	(29)
Surgery	51	(5)	13	(10)	2	(1)	77	(12)
Chemotherapy	53	(5)	3	(2)	1	(<1)	324	(49)
Hormonal therapy	11	(1)	2	(2)	2	(1)		
Combination	45	(4)	25	(19)	1	(<1)		
Unknown	29	(3)	6	(5)	7	(3)		

UPT, unknown primary cancer.
[a] I = 1024 patients with biopsy-confirmed UPT (this study); Ia = 131 patients who survived more than 1 year (this study); II = 261 patients with clinical diagnosis UPT (this study); III = 657 patients with UPT [6].
[b] Only the primary treatment modality.

involvement these patients were similar to the favourable subgroup from our series who survived for more than 1 year.

The shorter survival could be caused by less treatment of mainly older patients in our study. Studies performed in the south of The Netherlands and in the state of Arizona (USA) have shown that the chance of not being treated for cancer or receiving less intensive treatment was higher among the elderly than in younger patients [10,11].

The high percentage (20%) of clinical diagnosis demonstrates that it was common practice, especially among the elderly, not to perform a biopsy but to diagnose UPT only on the basis of clinical signs and symptoms. The short survival probably supports this diagnosis for this particular group of patients.

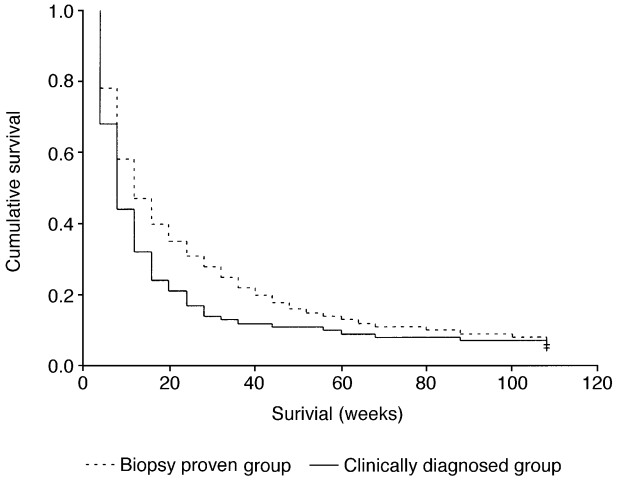

Fig. 1. Survival functions.

In order to treat and advise patients with UPT properly, it is important to be aware of the common behaviour of the disease. We have demonstrated in a population-based study that the prognosis of patients with UPT is more unfavourable than most clinical studies have suggested.

Table 4
Median duration of survival of 1024 new patients with biopsy-confirmed UPT, according to age, histology and site of metastases

Variable	Patients		Median survival (weeks)
	n	(%)	
Age (years)			
<40	32	(3.1)	20
40–49	70	(6.8)	24
50–59	191	(19)	12
60–69	303	(30)	9
⩾70	428	(42)	5
Histological diagnosis			
Adenocarcinoma	479	(47)	10
PDC/PDA[a]	453	(44)	11
Squamous cell carcinoma	76	>(7)	14
Undifferentiated malignant neoplasm	16	(2)	20
Site of involvement			
Liver	244	(24)	4
Lung/pleura	127	(12)	6
Lymph nodes	114	(11)	34
Bones	82	(8)	12
Peritoneum	92	(9)	5
Brain	18	(2)	2
Elsewhere	81	(8)	20
Disseminated	266	(26)	9

UPT, unknown primary tumour.
[a] Poorly differentiated carcinoma/poorly differentiated adenocarcinoma.

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