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Original Paper

Survival of Patients with Primary Liver Cancer, Pancreatic Cancer and Biliary Tract Cancer in Europe

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The EUROCARE Study is a European Union project to assemble survival data from population-based cancer registries and analyse them according to standard procedures. We investigated and compared liver, pancreatic and biliary tract cancer survival in 17 countries from 1985 to 1989. Time trends in survival over the 1978-1989 period were also investigated in 12 countries. The overall European mean 1 year relative survival was 16% for primary liver cancer, 26% for biliary tract cancer and 15% for pancreatic cancer. The corresponding 5-year relative survival was 5, 12 and 4%, respectively. Taking the European average as the reference, the relative risk (RR) of death was at least 20% higher for the three cancers in Denmark and Estonia. Survival tended to be higher in Spain for primary liver cancer and biliary tract cancer. Gender had little influence on survival whilst age at diagnosis was inversely related to prognosis. There was an improvement in 1-year relative survival rate for primary liver cancer: relative risk (RR) of 0.68 (95% confidence interval (CI) of 0.60-0.77) for 1987-1989 versus 1978-1980 and biliary tract cancer (RR 0.77, 95% CI 0.68-0.87). There was less variation in 5-year relative survival rate over time. Some intercountry survival differences for primary liver, biliary tract and pancreatic cancers exist over Europe. Differences in quality of care, in particular treatment aggressiveness, may explain some of these differences in survival. New approaches to the management of these cancers need to be found. © 1998 Elsevier Science Ltd. All rights reserved.

Key words: primary liver cancer, biliary tract cancer, pancreatic cancer, survival, time trends in survival, cancer registry, Europe

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INTRODUCTION

THE PROGNOSIS of primary liver cancer, pancreatic cancer and biliary tract cancer is known to be extremely poor because they are all generally diagnosed at a very advanced stage. Thus, these cancers represent an important cancer problem for clinicians. Community-based studies of survival, recording all cases diagnosed in a well-defined population, have the advantage of not being affected by selection biases that can affect the composition of clinical trials or hospital popula-

tions. International comparison of survival estimates after cancer diagnosis are now possible with the data collected by cancer registries over the past few years. This allows a consideration of whether survival rates differ between countries and whether they are improving with time. The first EURO-CARE study, based on combined data collected by 30 population-based registries from 11 countries, provided survival rates for cancer patients diagnosed during the 1978–1985 period [1]. The collaboration across Europe has now been extended to 45 registries in 17 countries. The aim of this study was to report on variation in relative survival of liver, pancreatic and biliary tract cancers diagnosed between 1985 and 1989 in 17 European countries and to determine changes in time trends in prognosis over the 1978–1989 period.

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^{*}The EUROCARE II Working Group for this study is listed in the Appendix.

PATIENTS AND METHODS

This study included primary liver cancer (ICD-9 155), biliary tract cancers (ICD-9 156) and pancreas cancers (ICD-9 157) registered between 1978 and 1989 in areas covered by cancer registries in 17 European countries. Only primary newly diagnosed malignant invasive tumours were considered. Cases registered from death certificates only (DCOs) or discovered incidentally at autopsy were excluded from the survival analysis. Description of the cancer registries, their gathering methods and the standardised procedures for insuring data comparability were published in the first EUROCARE monograph [1].

Table 1 provides a breakdown of the total 10 997 primary liver cancers, 11589 biliary tract cancers and 31312 pancreatic cancers by country. The registries of Finland, Denmark, Iceland, Estonia, Slovenia and Slovakia cover the entire population of these countries. U.K. registries cover approximately 50% of the whole population. Other countries are represented by one or more regional registries. In general there was a male predominance for primary liver cancer (particularly marked in France, Switzerland, Spain and Italy), a female predominance for biliary tract cancer (ranging between 60 and 78%) and a male/female ratio near 1 for pancreatic cancer. The proportion of patients ≥ 75 years of age was generally lower in Eastern European countries than in other European countries. The percentage of histologically verified cases varied considerably between countries: generally a higher percentage was reported in Northern countries and Switzerland and a lower proportion in England and Poland. The proportion of patients lost to follow-up was generally low. The proportion of DCOs was over 10% in

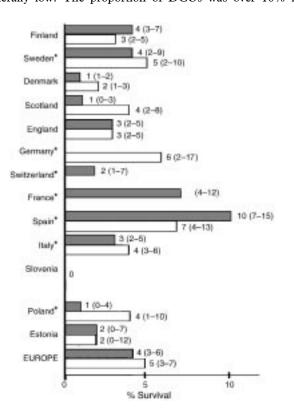


Figure 1. Age-standardised relative 5-year survival (95% confidence interval) for primary liver cancer patients according to sex for each country (1985–1989) (EUROCARE II). *<20% of the national population covered. Data not shown when there were only a small number of cases.

men,
women.

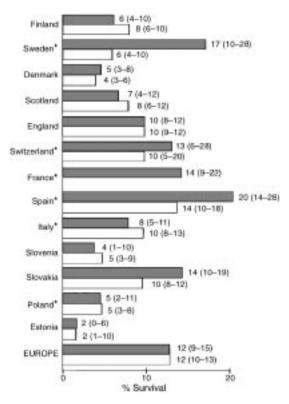


Figure 2. Age-standardised relative 5-year survival (95% confidence interval) for biliary tract cancer patients according to sex for each country (1985–1989) (EUROCARE II). *<20% of the national population covered. Data not shown for countries which had a small number of cases. ■ men, □ women.

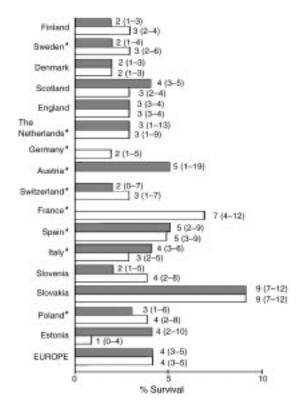


Figure 3. Age-standardised relative 5-year survival (95% confidence interval) for pancreatic cancer patients according to sex for each country (1985–1989) (EUROCARE II). *<20% of the national population covered. Data not shown for countries which had a small number of cases. ■ men, □ women.

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England, Germany, Austria, Spain, Slovakia and Poland for liver and pancreatic cancer.

Survival rates were calculated for the most recent 5-year period i.e. 1985–1989 by gender, age group and country including all participating registries. They are not shown for primary liver cancer and biliary tract cancer in Austria and Iceland, as well as for primary liver cancer in The Netherlands

because of the small number of cases. Variation in survival according to the period of diagnosis are also provided, including data from only 20 registries from 13 countries represented during the whole study period. The following 3-year periods were used: 1978–1980, 1981–1983, 1984–1986 and 1987–1989. Relative survival rates were computed using the Hakulinen program [2], defined as the ratio of

Table 1. Primary liver cancer, biliary tract cancer and pancreatic cancer cases by country (EUROCARE II)

Primary liver cancer								
Country	n of cases % Males		$\% \ge 75$ years of age	% DCO	% HV	% Lost to follow-up		
Northern Europe								
Iceland	32	53	66	0	66 0			
Finland	1127	52	38	2	87	0		
Sweden*	319	56	42	0	96	0		
Denmark	2033	55	40	0	74	0		
U.K.								
Scotland	734	63	35	7	64	0		
England	2036	62	31	17	60	0.1		
Western and Central Europe								
The Netherlands*	39	79	81	0	80	0		
Germany*	168	60		81 0 80 26 28 76 34 52 81				
Austria*	32	69	34	52	81	0 0		
Switzerland*								
	205	77	38	2	92	0.4		
France*	512	81	22	0	80	0.1		
Southern Europe	=		~.		- <u>-</u>	2.4		
Spain*	594	73	24	33	67	0.1		
Italy*	1948	66	32	11	44	0.1		
Eastern Europe								
Slovenia	148	61	14	0	93	1		
Slovakia	681	60	23	20	64	0		
Poland*	290	52	29	18	33	0.3		
Estonia	202	55	19	1 69		0		
Europe†	10 997	62	32	11	65	0.1		
		Bilia	ry tract cancer					
Country	n of cases	% Males	$\% \ge 75$ years of age	% DCO	% HV	% Lost to follow-up		
N. d. E								
Northern Europe Iceland	28	39	39	0	90	0		
				0 89		0		
Finland	1210	27	43	1	88	0		
Sweden*	475	31	40	0 96		0		
Denmark	1110	34	43	0 84		0		
U.K.								
Scotland	646	37	47	3 71		0		
England	2600	40	43	9 59		0		
Western and Central Europe								
The Netherlands*	182	34	38	0	86	0		
Germany*	464	25	44	12	82	0		
Austria*	99	35	40	91	78	0		
Switzerland*	132	32	55	2	91	0.7		
France*	315	36	47	0	85	0.6		
Southern Europe		- -	• •	-				
Spain*	580	33	42	11	74	0.2		
Spain^ Italy*	1281	33 34	42 42	11 4	74 64	0.2		
	1201	94	42	4	04	0.0		
Eastern Europe	444	0.0	25	•	7.4	0.0		
Slovenia	441	26	37	8	74	0.2		
Slovakia	1441	28	30	7	77	0		
Poland*	559 153	22	42	8	51	0.7		
Estonia	153	29	30	0	85	0		
Europe†	11 589	32	41	4	60	0.2		

(continued)

Table 1 (continued).

Pancreas cancer							
Country	n of cases	% Males	$\% \ge 75$ years of age	% DCO	% HV	%Lost to follow-up	
Northern Europe							
Iceland	118	54	41	0.1	65	0	
Finland	2850	47	37	1	77	0	
Sweden*	903	51	41	0	91	0	
Denmark	3257	50	38	0	76	0	
U.K.							
Scotland	2777	48	37	7	45	0	
England	12547	49	41	15	39	0.1	
Western and Central Europe							
The Netherlands*	294	52	26	0	65	0.3	
Germany*	456	50	38	24	68	0	
Austria*	100	41	54	25	79	0	
Switzerland*	375	48	44	2	81	0.5	
France*	629	56	35	0	72	0	
Southern Europe							
Spain*	716	56	31	23	52	0.4	
Italy*	2354	51	38	6	41	0.2	
Eastern Europe							
Slovenia	681	50	35	6	57	0.3	
Slovakia	1891	57	28	10	51	0	
Poland*	636	51	29	9	32	0.3	
Estonia	728	51	27			0.1	
Europe†	31 312	51	35	3	62	0.1	

^{*&}lt;20% of the national population covered. †The figures for Europe include cases not shown in the table because of small numbers.

the observed to the expected survival rate calculated from regional mortality tables. Age-standardised survival rates were computed from age-specific rates directly, taking the age distribution of the whole European sample as the standard. A weighted estimate of overall European survival was computed from age- and registry-specific relative survival rates. These were extended to all the cases in each country by applying a weighting which, for countries with national coverage, was the average of cases observed annually and, for countries represented by local registries, the estimated

Table 2. One and 5-year relative survival rates (% and 95% confidence interval) for primary liver cancer patients by country (EUROCARE II)

	1-year	RR	5-year	RR
Northern Europe				
Finland	17 (15–20)	0.97 (0.88-1.06)	4 (2-6)	1.07 (0.86-1.34)
Sweden*	12 (10–16)	1.16 (1.02–1.30)	4 (2-9)	1.07 (0.80-1.39)
Denmark	7 (6–8)	1.45 (1.35–1.56)	1 (0.7–3)	1.54 (1.24–1.90)
U.K.				
Scotland	10 (7–13)	1.26 (1.08-1.44)	2 (1-5)	1.30 (1.00-1.66)
England	11 (10–12)	1.20 (1.13-1.29)	3 (2-5)	1.17 (0.97-1.42)
Western and Central Europe				
Germany*	15 (10–21)	1.04 (0.83-1.25)	_	_
Switzerland*	23‡	0.8‡	3‡	1.2‡
France*	24‡	0.8‡	8‡	1.2‡
Southern Europe				
Spain*	20 (17–23)	0.88 (0.79-0.97)	8 (6-11)	0.84 (0.70-1.02)
Italy*	18	0.94	4	1.08
Eastern Europe				
Slovenia	17 (3–16)	1.45 (0.99-1.92)	0	_
Slovakia	7 (4–11)	1.45 (1.17–1.74)	5	1.0
Poland*	7 (5–10)	1.45 (1.25-1.66)	2 (1-7)	1.30 (0.95-1.71)
Estonia	8 (4–17)	1.38 (0.98–1.78)	2 (1-4)	1.30 (1.03–1.63)
Europe†	16 (15–18)	Reference	5 (3–7)	Reference

RR confidence intervals were not calculated if there were no cases in one age group. $\star < 20\%$ of the national population covered. †The figures for Europe include cases not shown in the table because of small numbers. ‡Not age-standardised and therefore not directly comparable with the others in the table.

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Table 3. Time trends in 1 and 5-year age-standardised relative survival rate (% and 95% confidence intervals) for primary liver cancer, biliary tract cancer and pancreatic cancer patients (EUROCARE II)

	1978–1980	1981–1983	1984–1986	1987–1989	RR*
Primary liver cancer					
1-year	8 (7-10)	11	13	18 (15-21)	0.68 (0.60-0.77)
5-year	3 (2–5)	4	3	6 (4–9)	0.80 (0.66-0.97)
Biliary tract cancer					
1-year	20 (18-24)	21	26	29	0.77 (0.68-0.87)
5-year	11 (8–14)	10	12	14	0.89 (0.77–1.05)
Pancreatic cancer					
1-year	12 (11–14)	14	15	15 (14–16)	0.90
5-year	4 (3–5)	3	4	4 (3–5)	1

^{*}Relative risk of death 1987–1989 versus 1978–1980. In parenthesis 95% confidence interval—not calculated if there were no cases in one age group.

number of such cases annually. In order to provide an immediate comparison of survival differences and trends, the relative risk (RR) of death is given, calculated as the ratio of the logarithm for relative survival compared with the reference category.

RESULTS

Primary liver cancer

Intercountry differences in survival. Overall survival rates were very poor. The European weighted relative survival was 16% at 1 year and 5% at 5 years. Small differences in relative survival rates were observed among participating countries (Table 2). The 5-year relative survival rates varied from 8% (Spain) to 0% (Slovenia). The RR of death at 5 years (the European mean being the reference category), was over 20% greater in Denmark, Scotland, Estonia and Slovenia. It was

nearly 20% lower in Spain and close to the European average in other countries. There were relatively few differences in the RR of death at 1 year (Table 2).

The effect of age and gender on survival. Survival rates were similar in men and in women (Figure 1). They were slightly higher in the youngest age group in all countries except Scotland, Slovakia, Slovenia and Sweden (data not shown). The European 5-year relative survival rates were 8% (15–44 years), 5% (45–54 years), 5% (55–64 years), 5% (65–74 years) and $3\% (\geq 75 \text{ years})$.

Time trends in survival. There was an improvement in overall 1-year age-standardised relative survival rate over time (Table 3). When comparing 1987–1989 with 1978–1980 the RR of death was 0.68 (0.60–0.77). There was less change when considering the 5-year age standardised relative survival rate (RR 0.80; 0.66–0.97).

Table 4. One and 5-year relative survival rates (% and 95% confidence intervals) for biliary tract and pancreatic cancer patients by country (EUROCARE II)

	Biliary tract cancer				Pancreatic cancer			
	1-year	RR	5-year	RR	1-year	RR	5-year	RR
Northern Europe								
Finland	22 (15-32)	1.12 (0.84-1.41)	8 (3-23)	1.19 (0.71-1.68)	15 (14–16)	1.09 (0.94-1.07)	3 (1-5)	1.09 (0.83-1.36)
Sweden*	23 (19-26)	1.09 (0.97-1.22)	9 (6–16)	1.14 (0.90-1.38)	14 (13–16)	1.04 (0.96-1.12)	3 (1-5)	1.09 (0.83-1.36)
Denmark	19 (16–24)	1.23 (0.83-1.64)	4 (2-9)	1.52 (1.16–1.89)	11 (6–19)	1.16 (0.86-1.48)	2 (1-4)	1.22 (0.99-1.46)
U.K.								
Scotland	23 (16-33)	1.09 (0.82-1.37)	8 (6-11)	1.19 (1.04-1.36)	12 (11-14)	1.12 (1.04-1.21)	3 (2-4)	1.09 (0.96-1.24)
England	25 (23–27)	1.03 (0.96-1.11)	10 (7-14)	1.09 (0.91-1.27)	12 (11–13)	1.12 (1.05-1.19)	3 (2-4)	1.09 (0.96-1.24)
Western and Central Europe								
The Netherlands*	-	_	_	-	14 (10–18)	1.04 (0.88-1.20)	3 (1–7)	1.09 (0.78–1.41)
Germany*	29 (22–39)	0.92 (0.70-1.14)	16‡	0.8‡	16 (13–20)	0.97 (0.85–1.09)	4‡	_
Switzerland*	33 (27–40)	0.82 (0.67-0.98)	12‡	1.0‡	17 (13–21)	0.93 (0.80-1.07)	2 (1–5)	1.21 (1.08–1.37)
France*	38 (33–45)	0.72 (0.60-0.84)	16‡	0.8‡	21 (18–25)	0.82 (0.73-0.92)	8‡	-
Southern Europe								
Spain*	31 (27-35)	0.87 (0.77-0.98)	16 (11-22)	0.86 (0.70-1.04)	15 (12–18)	1.0 (0.88-1.12)	5 (3-7)	0.93 (0.79-1.09)
Italy*	25 (23–27)	1.03 (0.96-1.11)	9 (6–15)	1.14 (0.91-1.37)	18 (16–19)	0.90 (0.84-0.97)	4 (2-8)	1.0 (0.78-1.24)
Eastern Europe								
Slovenia	14 (12–16)	1.46 (1.34-1.59)	5 (2-10)	1.41 (1.03-1.81)	12 (10-15)	1.12 (1.0-1.24)	3 (2-5)	1.09 (0.93-1.28)
Slovakia	18 (15–22)	1.27 (1.12-1.43)	11 (7–15)	1.04 (0.85-1.24)	15 (13–17)	1.0 (0.92-1.09)	9 (6-13)	0.75 (0.62-0.89)
Poland*	13 (11–15)	1.51 (1.39–1.65)	5 (3-10)	1.41 (1.12-1.72)	11 (9-13)	1.16 (1.05-1.28)	4 (2-6)	1.0 (0.82-1.20)
Estonia	16 (11–23)	1.36 (1.08-1.64)	2 (1–7)	1.85 (1.38–2.33)	12 (9–15)	1.22 (0.97-1.27)	1 (0.1–5)	1.43 (0.82-2.1)
Europe†	26 (24–27)	Reference	12 (10–13)	Reference	15 (14–17)	Reference	4 (3–5)	Reference

Confidence intervals were not calculated if there were no cases in one age group. $\star < 20\%$ of the national population covered. †The figures for Europe include cases not shown in the table because of small numbers. ‡Not age-standardised and are, therefore, not directly comparable with the others in the table.

Biliary tract cancer

Intercountry differences in survival. The mean 1-year relative survival rate for Europe was 26% and the mean 5-year relative survival rate was 12% (Table 4). There were large variations in survival rates among participating countries. The 1-year relative survival rate varied from 13% (Poland) to 38% (France) and the 5-year relative survival rate from 2% (Estonia) to 16% (Spain). Compared with the European average, the RR of death at 5 years was over 1.3 in Denmark, Estonia, Poland and Slovenia. In other countries survival rates were close to the European average. Comparable RR of death were found at 1 year (Table 4).

The effect of age and gender on survival. In general, survival rates were similar in men and women (Figure 2). They were higher in men than in women in four countries (Spain, Sweden, Switzerland and Slovakia). The highest relative survival rate was observed in the 45–54 year age group (data not shown), after which survival rates decreased with increasing age in all countries. The European weighted 5-year relative survival rate was 16% (15–44 years), 29% (45–54 years), 19% (55–64 years), 12% (65–74 years) and 9% (\geq 75 years).

Time trends in survival. Over time, there was a slight improvement in 1-year age-standardised relative survival rate (Table 3). When comparing 1987–1989 with 1978–1980, the RR of death was 0.77 (0.68–0.87). There was less improvement in 5-year relative survival rates (RR 0.89; 0.77–1.05) (Table 4).

Pancreatic cancer

Intercountry differences in survival. European survival rates were 15% at 1 year and 4% at 5 years. Even though survival rates were low, some differences between countries were noted. One-year relative survival varied between 11% (Denmark and Poland) and 21% (France) and 5-year relative survival between 1% (Estonia) and 9% (Slovakia) (Table 4). The RR of death at 5 years was more than 20% higher than the European average in Denmark, Estonia, and Switzerland. It was lower than the European average in Slovakia. In the other countries the relative rate of death was close to the European average.

The effect of age, gender and time on survival. Survival rates were similar in both sexes (Figure 3). They were higher in the 15–44 years age group than in the other age group in all countries (data not shown). There were no changes in 1- and 5-year relative survival rates of pancreatic cancers over time (Table 3).

DISCUSSION

Primary liver cancer, pancreatic cancer and biliary tract cancer are still a great diagnostic and therapeutic challenge. Their prognosis is extremely poor. The European relative survival for the 1985–1989 period was 5% for primary liver cancer and pancreatic cancer and was 12% for biliary tract cancer. Although survival rates were very poor, variation between countries was noted, similar to the percentage of deaths within a month of diagnosis (see Table 5 of the Introduction, Berrino and colleagues, pp. 2139–2153). In general, survival rates were slightly higher in France and Spain than in other countries, although high survival rates for generally lethal cancers may also indicate incompleteness of data (see Table 4 of the Introduction, Berrino and colleagues, pp. 2139–2153). In contrast they were particularly low in Denmark,

Estonia, Poland and Slovenia. Part of these differences in survival can be explained by uncontrolled methodological differences in cancer registration and follow-up procedures. Checks on inclusion criteria and data quality in the EURO-CARE I study suggest that methodological problems can introduce only minor biases [3]. Differences in stage at diagnosis and/or a more aggressive therapeutic approach may explain the observed differences in survival. However, it should be considered that survival data may not be reliable when the proportion of DCO is very high.

Similar survival rates have been reported in North America. In the SEER programme 5-year relative survival rates in caucasian patients for the 1983–1988 period were 6% for primary liver cancer and 3% for pancreatic cancer [4]. In Osaka, the corresponding 5-year relative survival rates for the 1987–1989 period were 9 and 5% [5]. It was 11% for biliary tract cancer. These data confirm that these three sites have a poor prognosis around the world.

There were few differences in survival rates according to gender suggesting a similar distribution of stages at the time of diagnosis. Relative survival rates were higher in young adults (< 45 years of age), an age group in which these cancers were rare. A more aggressive therapy is probably administered in these young patients than in older groups. In the near future, further analyses need to take account of the subsites (particularly for cancer of the gall bladder, bile duct and ampulla of vater which are known to have different prognosis) and histology (particularly for primary liver and pancreatic cancers).

There was no change in the prognosis of pancreatic cancer over time. Considerable progress has been made in our ability to diagnose this cancer with the development of ultrasonography, computed tomography (CT) and more recently magnetic resonance imaging (MRI), endoscopic ultrasonography and percutaneous cytology [6]. These changes in the approach to diagnosing pancreatic cancer were not accompanied by any progress in the stage of diagnosis, therapeutic approach or survival, thus suggesting that when clinical symptoms become evident, pancreatic cancer is already advanced [7]. There was little improvement in the 5-year relative survival rate for biliary tract and primary liver cancers, but some improvement was noted at 1 year, particularly for primary liver cancer. This improvement could be the result of increased surveillance of patients with cirrhosis (although no evidence of improved survival was found in screening programmes aimed at an early diagnosis) [8] and the development of novel therapies (percutaneous ethanol injection, chemoembolisation, orthotopic liver transplantation and surgical resection) [9]. However, in general, the prognosis for patients with either primary liver, biliary tract or pancreatic cancer is dismal and new approaches to treatment and perhaps early diagnosis are needed.

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APPENDIX

The EUROCARE Working Group for this study is: Austria: W. Oberaigner (Cancer Registry of Tirol). Denmark: H. Storm (Danish Cancer Society). Estonia: T. Aareleid (Estonian Cancer Registry). Finland: T. Hakulinen (Finnish Cancer Registry). France: D. Pottier (Calvados Digestive Cancer Registry), J. Mace-Lesec'h (Calvados

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