La ricerca nei tumori rari

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MALATTIA RARA =

Secondo l'Unione Europea → prevalenza <5/10.000 abitanti

OMS: circa 6000 malattie

E' un gruppo di malattie ampio ed eterogeneo che riguarda tutti gli organi ed apparati dell'uomo e riconosce le più svariate cause eziopatogenetiche

IL PROBLEMA DELLE MALATTIE RARE È PROPRIO NELLA LORO…RARITÀ.

MALATTIE

"ORFANE"

(poco conosciute e poco ri-conosciute)

Difficoltà diagnostiche

Solitudine di fronte alla malattia

Scarsità di opzioni terapeutiche

Scarsità di percorsi assistenziali strutturati

Andamento cronico spesso invalidante

STATEMENT SUI TUMORI RARI

Senato della Repubblica

1. GENERALITÀ

1) I tumori rari costituiscono una famiglia eterogenea di patologie che possono colpire pressoché tutti i distretti corporei: la lista stilata da RARE-CARE (*Surveillance of Rare Cancers in Europe*) sulla base del ICD-O (*International Classification of Diseases for Oncology*), ne ha individuati circa 250, ma alla luce della sempre maggiore caratterizzazione genetica del tumore, questo numero è destinato rapidamente ad aumentare.

2) Sono considerate rare le neoplasie con incidenza annuale inferiore o uguale a 5 casi per 100.000 persone. Il numero globale dei casi di tumore raro è elevato nonostante la scarsa numerosità di ciascun tumore.

3) I tumori rari comprendono circa il 15% dei casi di tumore e possono suddividersi in:

- neoplasie pediatriche (come i carcinomi nasofaringei, della tiroide, adrenocorticali, che colpiscono prevalentemente i bambini al di sotto dei 3 anni d'età) equivalenti approssimativamente a meno dell'1% dei casi di tumore;
- neoplasie ematologiche rare (come la leucemia mieloide cronica) equivalenti approssimativamente a meno del 5% dei casi di tumore;
- neoplasie rare solide dell'adulto (come i sarcomi o il GIST, il tumore gastrointestinale stromale, i NET-tumori neuroendocrini etc.) equivalenti approssimativamente a circa il 10% dei casi di tumore.

STATEMENT SUI TUMORI RARI

Senato della Repubblica

2. CRITICITÀ

Il problema dei tumori rari è rilevante proprio in termini quantitativi, perché se è bassa l'incidenza di ciascun tumore è invece elevato il numero totale di casi di tali neoplasie: di conseguenza un gran numero di cittadini italiani ed europei soffre una serie di discriminazioni dovute alla bassa incidenza della loro malattia. Ai tumori rari sono associate una serie di difficoltà e problematiche correlate innanzitutto alla loro caratteristica di malattie rare. Le difficoltà coinvolgono tanto il percorso diagnostico-terapeutico della persona malata che l'impatto sull'efficienza del Sistema Sanitario.

Per quanto riguarda i pazienti vanno sottolineate:

- la difficoltà a reperire le competenze cliniche necessarie per la diagnosi e il trattamento della malattia, in quanto i centri che ne dispongono sono pochi e geograficamente dispersi;
- la conseguente difficoltà di accedere a un Centro di riferimento per una diagnosi clinica e patologica certa e tempestiva e ad essere assistiti con tutte le competenze necessarie (carenza di strutture specialistiche dedicate con approccio multidisciplinare, mancanza di consuetudine clinica nella maggior parte dei centri oncologici);
- la limitata disponibilità di terapie efficaci (per l'80% delle malattie rare in Europa ci sono solo uno o due farmaci disponibili), che si collega alla difficoltà dello sviluppo di trial clinici dovuto al numero esiguo di pazienti e alla potenziale carenza d'interesse nello sviluppo di nuove terapie;
- in Italia, a differenza di quanto avviene in Europa, i tumori rari non sono compresi nell'elenco delle patologie rare e non beneficiano pertanto dei vantaggi e delle misure previste per migliorare la ricerca, l'assistenza e l'accesso rapido alle terapie e alleviare la condizione dei pazienti affetti da una malattia rara

STATEMENT SUI TUMORI RARI

2.1 UNMET NEEDS E AREE DI CRITICITÀ

In via preliminare sono state identificate 3 aree maggiori di criticità che meritano di essere approfondite in vista di una possibile individuazione degli obiettivi prioritari per il Gruppo di

5. AREE DI CRITICITÀ E STRATEGIE DI INTERVENTO

clinico necessario per

'o

STUDI CLINICI

L'esiguo numero di studi clinici sui tumori rari rende difficile dimostrare l'efficacia delle differenti opzioni terapeutiche e dunque costruire una base di evidenza per la pratica clinica.

Il mancato sviluppo del farmaco nell'indicazione rara è dunque una problematica che attende una risposta, anche se sviluppare un farmaco che ha già l'approvazione in un'altra applicazione implica vie diverse e facilitate, visto che tutto il problema legato al controllo della safety può essere considerato, in linea di principio, già risolto.

dalle corsie preferenziali previste dalla legislazione europea e italiana per i farmaci destinati alle patologie rare ("farmaci orfani").

Il tempo, infatti, è un fattore fondamentale per i pazienti colpiti da tumori rari: per queste malattie progressive a esito fatale, avere accesso al farmaco in tempi ragionevoli può significare aver salva la vita o allungare la sopravvivenza.

Surveillance of Rare Cancers in Europe

RARECARE

RARECARE will estimate the burden of rare cancers in Europe. Its aim is to provide an operational definition of “rare cancer” and a list of cancers meeting that definition. Then the project will provide cancer burden indicators (incidence, survival, prevalence and mortality), based on population-based cancer registry data, on rare cancers across Europe.
RARECARE will assess the quality and comparability of rare cancer data between cancer registries. The project develop strategies for the diffusion of information among all the key players involved in Europe-wide surveillance on and treatment of rare cancers (clinicians, patients, health planners and researchers).

RARECARE is co-funded by the European Commission (EC) from 01/04/2007 to 31/03/2010 through its Public Health and Consumer Protection Directorate (DG SANCO), PHEA programme, and contributes among other projects to the creation of networks of action for rare diseases.

The Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy) is the leading organization and more than 15 European Institutions and Organizations participate in the project as associated or collaborating partners.

Surveillance of Rare Cancers in Europe

RARECARE

What are the aims and expected outputs of the RARECARE project?

Aims:

•To provide an operational definition of "rare cancers", and a list of cancers that meet this definition

•To estimate the burden of rare cancers in Europe

•To improve the quality of data on rare cancers

•To develop strategies and mechanisms for the diffusion of information among all the key players involved in Europe-wide surveillance on and treatment of rare cancers

Results:

•Incidence, survival, prevalence and mortality for all rare cancers will be estimated

•Data quality will be analysed for a subset of cancers, by confirming the diagnostic data and, if possible, analysing additional data on stage and treatment

•A web-site on rare cancers will be designed to disseminate the results of the project, and in particular, to inform clinicians, patients and health planners

Rare cancers are not so rare: The rare cancer burden in Europe

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A B S T R A C T

Purpose: Epidemiologic information on rare cancers is scarce. The project Surveillance of Rare Cancers in Europe (RARECARE) provides estimates of the incidence, prevalence and survival of rare cancers in Europe based on a new and comprehensive list of these diseases.
Materials and methods: RARECARE analysed population-based cancer registry (CR) data on European patients diagnosed from 1988 to 2002, with vital status information available up to 31st December 2003 (latest date for which most CRs had verified data). The mean population covered was about 162,000,000. Cancer incidence and survival rates for 1995–2002 and prevalence at 1st January 2003 were estimated.
Results: Based on the RARECARE definition (incidence <6/100,000/year), the estimated annual incidence rate of all rare cancers in Europe was about 108 per 100,000, corresponding to 541,000 new diagnoses annually or 22% of all cancer diagnoses. Five-year relative survival was on average worse for rare cancers (47%) than common cancers (65%). About 4,300,000 patients are living today in the European Union with a diagnosis of a rare cancer, 24% of the total cancer prevalence.
Conclusion: Our estimates of the rare cancer burden in Europe provide the first indication of the size of the public health problem due to these diseases and constitute a useful base for further research. Centres of excellence for rare cancers or groups of rare cancers could provide the necessary organisational structure and critical mass for carrying out clinical trials and developing alternative approaches to clinical experimentation for these cancers.

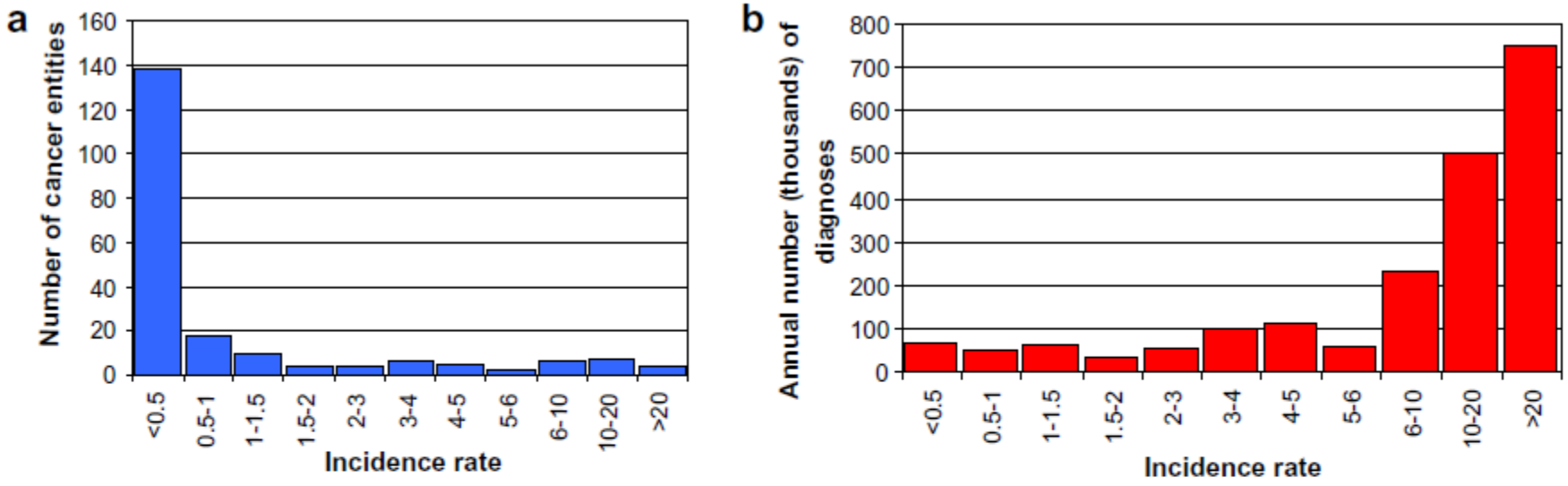

Fig. 1 – Distribution of number of cancer types (1a) and annual number of diagnoses (1b) in EU27 according to categories of incidence rate.

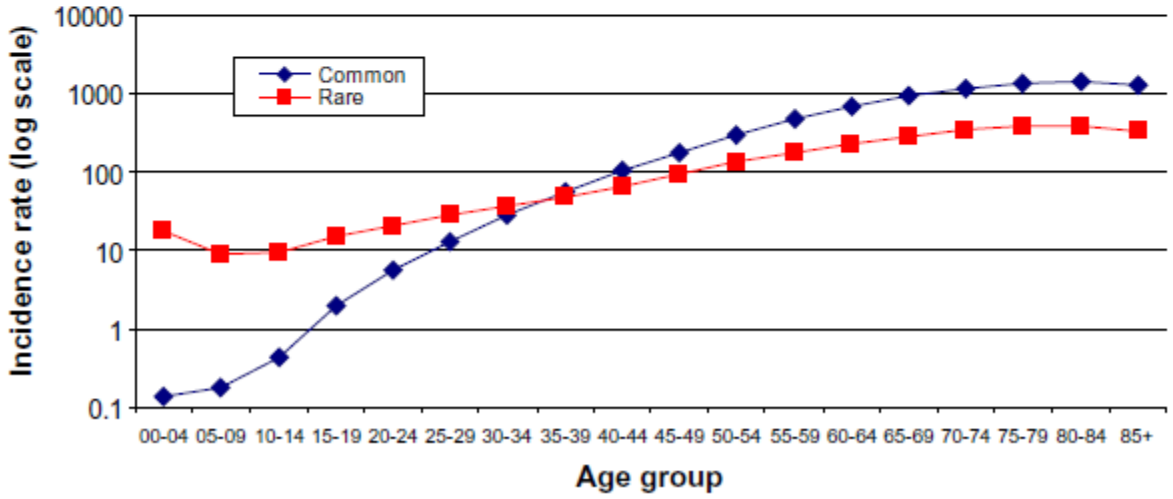

Fig. 2 – RARECARE estimates of age-specific incidence rates for rare and common cancers in EU 27.

Carcinoma of endocrine organs: Results of the RARECARE project

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Abstract The rarity or the asymptomatic character of endocrine tumours results in a lack of epidemiological studies on their incidence and survival patterns. The aim of this study was to describe the incidence, prevalence and survival of endocrine tumours using a large database, which includes cancer patients diagnosed from 1978 to 2002, registered in 89 population-based cancer registries (CRs) with follow-up until 31st December 2003. These data give an unique overview of the burden of endocrine carcinomas in Europe.

A list of tumour entities based on the third International Classification of Diseases for Oncology was provided by the project Surveillance of rare cancer in Europe (RARECARE) project. Over 33,594 cases of endocrine carcinomas were analysed in this study.

Incidence rates increased with age and were highest in patients 65 years of age or older. In 2003, more than 315,000 persons in the EU (27 countries) were alive with a past diagnosis of a carcinoma of endocrine organs. The incidence of pituitary carcinoma equalled four per 1,000,000 person years and showed the strongest decline in survival with increasing age. Thyroid cancer showed the highest crude incidence rates (four per 100,000 person years) and was the only entity with a gender difference: (female-to-male ratio: 2:9) Parathyroid carcinoma was the rarest endocrine entity with two new cases per 10,000,000 person years. For adrenal carcinoma, the most remarkable observations were a higher survival for women compared to men (40% compared to 32%, respectively) and a particularly low relative survival of 24% in patients 65 years of age or older.

European Journal of Cancer (2012) **48**, 1923–1931

Five-year relative survival (%) by cancer entity for endocrine cancers. Period survival analysis 2000–2002 46 cancer registries included.

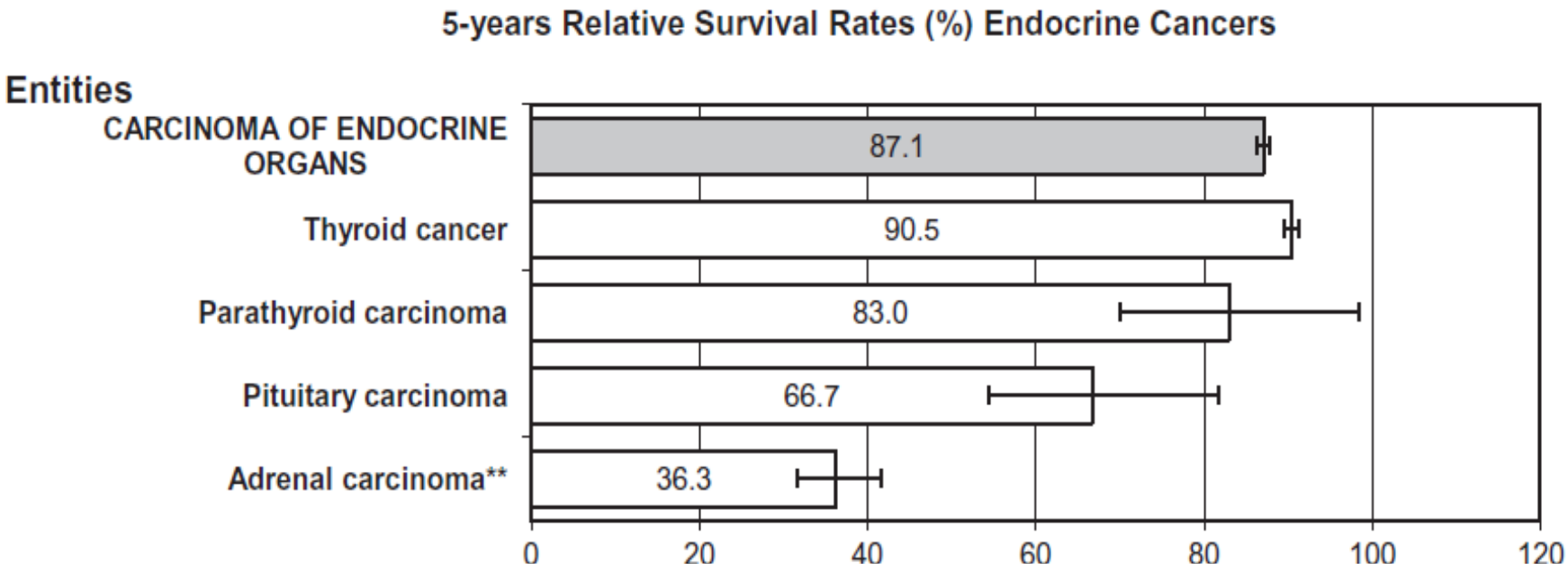


Table 5

Five year relative survival (%)[a] of Endocrine carcinomas by gender and age category. Period survival analysis 2000–2002.

Cancer entity	Sex				Age (yrs)						Overall (46 CRs)	
	Male		Female		0–24		25–64		65+			
	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE
Carcinoma of endocrine organs	80	0.97	90	0.45	95	0.97	94	0.33	64	1.2	87	0.42
Pituitary carcinoma	63	10	70	9.0	100	0.00	76	8.2	48	10	66	6.4
Thyroid cancer	85	0.98	92	0.43	99	0.58	96	0.30	69	1.3	90	0.41
Parathyroid carcinoma	80	12	84	9.1	NE	NE	73	10.5	89	11.2	81	6.9
Adrenal carcinoma[b]	32	3.6	40	3.4	39	8.8	42	3.1	24	4.2	36	2.5

NE = Not enough data to calculate.

SE = Standard Error.

Rare cancers list April 2010

NEUROENDOCRINE CARCINOMAS	**2.52**	**20,466**
Well differentiated endocrine tumours, carcinoid	**0.37**	**2,961**
Well differentiated endocrine tumours, atypical carcinoid	**0.00**	**6**
Poorly differentiated endocrine carcinoma (lung excluded)	**0.52**	**4,225**
Small cell endocrine carcinoma	0.342	2,446
Large cell endocrine carcinoma	0.514	3,674
Mixed endocrine-exocrine carcinoma	**0.00**	**17**
Endocrine carcinoma of Thyroid gland	**0.22**	**1,772**
Medullary carcinoma, NOS	0.221	1,579
Mixed medullary-follicular carcinoma	0.001	6
Well differentiated endocrine carcinoma, not functioning of Pancreas and Digestive tract	**1.25**	**10,152**
Carcinoid tumor, NOS	1.26	9,005
Islet cell carcinoma	0.034	245
Well differentiated endocrine carcinoma, functioning of Pancreas and Digestive tract	**0.02**	**200**
Insulinoma, malignant	0.014	98
Glucagonoma, malignant	0.003	24
Somatostatinoma, malignant	NE	0
Gastrinoma, malignant	0.006	46
VIP-oma	0.001	8
Other ectopic hormone producing tumours	NE	0
Endocrine carcinoma of Skin	**0.13**	**1,082**
Merkel cell carcinoma	0.12	985

Rare cancers list April 2010

CARCINOMA OF ENDOCRINE ORGANS	**4.16**	**33,757**
Carcinomas of Pituitary gland	**0.04**	**333**
Pituitary carcinoma, NOS	0.009	69
Carcinomas of Thyroid gland	**3.68**	**29,803**
Papillary adenocarcinoma, NOS	2.632	18,821
follicular carcinoma, NOS	0.724	5,173
Pleomorphic carcinoma	0.001	4
Undifferentiated/anaplastic carcinoma	0.203	1,459
Mucoepidermoid carcinoma	0.001	9
Mucinous carcinoma	0.00	3
Spindle cell tumour with thymous-like differentiation (SETTLE)	0.00	1
Carcinoma showing thymus-like differentiation (CASTLE)	NE	0
Carcinomas of Parathyroid gland	**0.02**	**179**
Parathyroid carcinoma	0.007	57
Carcinoma of adrenal gland	**0.18**	**1,471**
Adrenal cortical carcinoma	0.073	520

Survival from rare cancer in adults: a population-based study

*Gemma Gatta, Laura Ciccolallo, Ian Kunkler, Riccardo Capocaccia, Franco Berrino, Michel P Coleman, Roberta De Angelis, Jean Faivre, Jean Michel Lutz, Carmen Martinez, Torgil Möller, Risto Sankila, and the EUROCARE Working Group**

Summary

Background Rare cancers are a challenge to clinical practice, and treatment experience, even in major cancer centres to which rare cancers are usually referred, is often limited. We aimed to study the epidemiology of rare cancers in a large population of several countries.

Methods We analysed survival by age, sex, subsite, and morphology in 57 144 adults with 14 selected rare cancers diagnosed 1983–94. Variations in survival over time and between European regions were also assessed for variations in quality of care. We also estimated the adjusted relative excess risk of death for every rare cancer.

Findings Overall 5-year relative survival was good (ie, >65%) for placental choriocarcinoma (85·4% [95% CI 81·4–89·5]), thyroid medullary carcinoma (72·4% [69·2–75·5]), ovarian germ-cell cancer (73·0% [70·0–76·0]), lung carcinoid (70·1% [67·3–72·9]), and cervical adenocarcinoma (65·5% [64·3–66·6]); intermediate (ie, 35–65%) for testicular cancer at age 65 years or older (64·0% [59·3–68·7]), sarcoma of extremities (60·0% [58·9–61·2]), digestive-system endocrine cancers (55·6% [54·9–56·3]), anal squamous-cell carcinoma (53·1% [51·5–54·8]), and uterine sarcoma (43·5% [42·0–44·9]); low for carcinoma of adrenal-gland cortex (32·7% [28·3–37·2]) and bladder squamous-cell carcinoma (20·4% [18·8–22·0]); and poor for angiosarcoma of liver (6·4% [1·8–11·0]) and mesothelioma (4·7% [4·3–5·2]). Survival was usually better for women than men and poor in those aged 75 years or older. Survival significantly improved over time for ovarian germ-cell cancer, sarcomas of extremities, digestive-system endocrine tumours, anal squamous-cell carcinoma, and angiosarcoma of liver. Survival in northern Europe was higher than in the other geographic groupings for most cancers.

Interpretation Because effective treatments are available for several of the rare cancers we assessed, further research is needed to ascertain why survival is lower in some European countries than in others, particularly in older patients. Audit of best practice for rare cancers with treatment protocols would be useful.

Lancet Oncol 2006; 7: 132–40

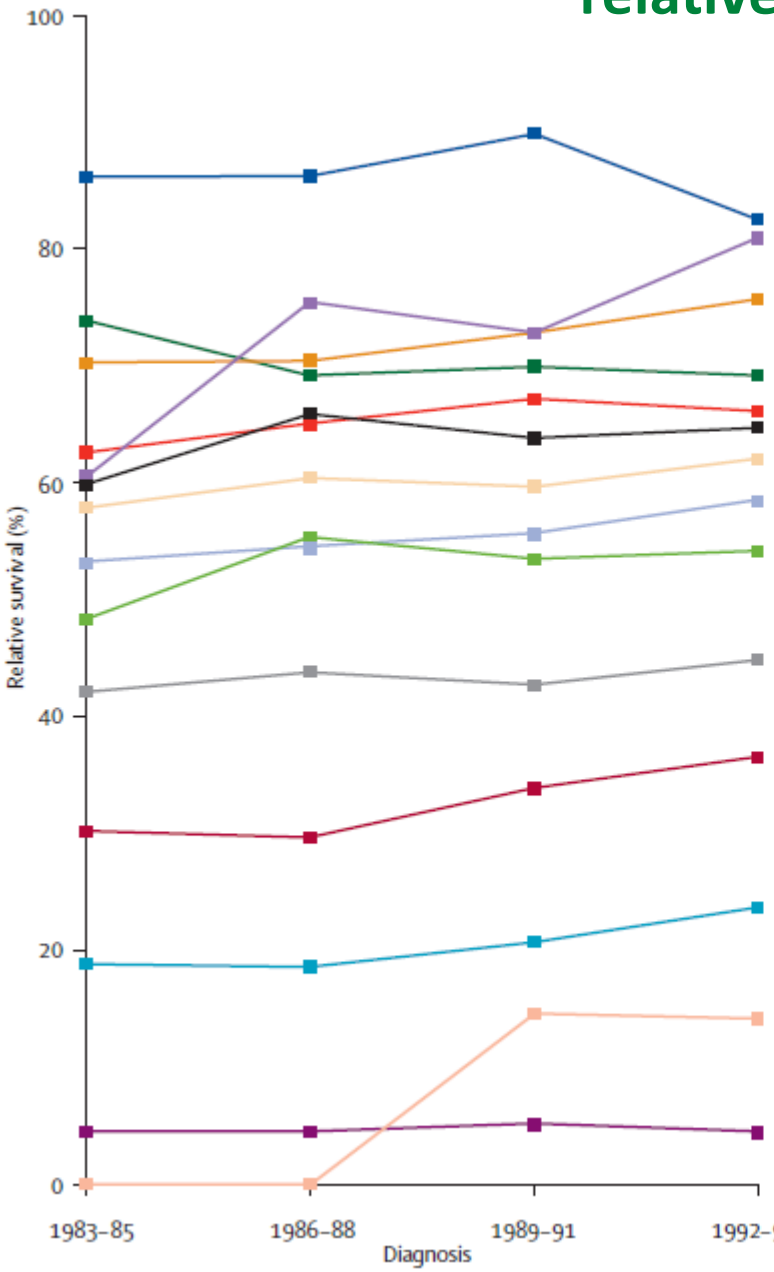
5-year relative survival and adjusted relative excess risk of death by age and sex

	Age									Sex*					
	15–54 years			55–74 years			≥75 years			Women			Men		
	n	Survival, % (95% CI)	RER†	n	Survival, % (95% CI)	RER (95% CI)	n	Survival, % (95% CI)	RER (95% CI)	n	Survival, % (95% CI)	RER†	n	Survival, % (95% CI)	RER (95% CI)
Adenocarcinoma of uterine cervix	5041	77·6 (76·4–78·8)	1	2623	50·1 (47·9–52·2)	2·82 (2·60–3·07)	1022	29·0 (25·2–32·8)	5·62 (5·06–6·25)	..	..	..	..	..	..
Anal squamous-cell carcinoma	974	64·6 (61·4–67·7)	1	2773	53·4 (51·2–55·5)	1·41 (1·25–1·60)	1639	41·2 (37·6–44·8)	2·35 (2·05–2·69)	3477	55·0 (53·0–57·1)	1	1909	49·5 (46·7–52·4)	1·30 (1·19–1·42)
Angiosarcoma of liver	38	8·0 (0–16·8)	1	75	6·9 (0·5–13·2)	1·18 (0·73–1·89)	25	0·0	2·02 (0·99–4·09)	66	9·8 (1·8–17·7)	1	72	3·3 (0–7·9)	1·71 (1·09–2·66)
Sarcoma of uterus	1868	63·6 (61·3–65·9)	1	2670	32·6 (30·6–34·5)	2·59 (2·35–2·85)	1148	29·5 (25·9–33·1)	3·24 (2·88–3·64)	..	..	..	..	..	..
Sarcoma of extremities	4618	65·7 (64·3–67·1)	1	3468	56·4 (54·5–58·4)	1·73 (2·60–3·16)	1926	46·3 (42·8–49·9)	2·86 (1·11–1·27)	4621	62·3 (60·6–64·0)	1	5391	58·1 (56·5–59·7)	1·19 (1·11–1·27)
Testicular cancer (age ≥65 years)	..	..	..	560‡	70·4 (65·2–75·7)	1	383	49·5 (40·9–58·1)	1·71 (1·32–2·22)	..	..	..	..	..	..
Mesothelioma	1854	8·6 (7·3–9·9)	1	6397	3·9 (3·4–4·4)	1·34 (1·27–1·42)	2298	3·0 (2·2–4·1)	1·72 (1·60–1·85)	1896	8·1 (6·8–9·5)	1	8653	3·9 (3·5–4·4)	1·15 (1·08–1·21)
Placental choriocarcinoma	171§	91·4 (87·1–95·8)	1	91¶	81·6 (73·4–89·8)	2·28 (1·14–4·58)	46‖	74·3 (61·2–87·4)	4·17 (1·97–8·85)	..	..	..	..	..	..
Medullary carcinoma of thyroid	579	82·5 (79·2–85·8)	1	399	61·8 (56·2–67·4)	2·74 (2·10–3·58)	122	44·5 (31·2–57·9)	5·20 (3·62–7·47)	647	78·2 (74·4–82·1)	1	453	63·7 (58·5–68·9)	1·86 (1·46–2·37)
Squamous-cell carcinoma of bladder	322	32·7 (27·4–38·0)	1	1826	21·5 (19·4–23·6)	1·35 (1·16–1·56)	1575	14·2 (11·7–16·6)	1·88 (1·62–2·19)	1738	18·0 (15·9–20·2)	1	1985	22·6 (20·3–24·9)	0·85 (0·78–0·92)
Adrenal-cortex carcinoma	229	37·1 (30·6–43·6)	1	224	27·9 (21·4–34·3)	1·34 (1·06–1·70)	46	32·6 (14·4–50·9)	1·59 (1·05–2·41)	286	32·3 (26·5–38·1)	1	213	33·3 (26·3–40·4)	0·99 (0·79–1·24)
Digestive-system endocrine tumours	2219	74·6 (73·6–75·6)	1	3788	48·6 (47·7–49·5)	2·26 (2·05–2·50)	1686	38·2 (36·5–39·9)	3·58 (3·19–4·01)	4028	58·1 (57·2–59·0)	1	3665	52·7 (51·8–53·7)	1·19 (1·10–1·28)
Lung carcinoid	613	84·3 (81·2–87·4)	1	717	60·9 (56·7–65·1)	2·97 (2·33–3·78)	113	33·7 (21·7–45·7)	8·24 (5·88–11·54)	731	78·1 (74·5–81·7)	1	712	61·6 (57·4–65·8)	2·08 (1·69–2·56)
Ovarian germ-cell cancer	796	82·8 (80·1–85·5)	1	142	22·9 (15·4–30·3)	6·81 (5·17–8·97)	40	22·3 (3·8–40·8)	10·56 (6·77–16·47)	..	..	..	..	..	..

RER=relative excess risk: adjusted for follow-up, age, diagnosis period, geographic group, sex (excluding uterine, placental, and gonadal sites), subsite (for uterine sarcoma of extremities, mesothelioma and digestive-system endocrine cancer), and morphology (for uterine sarcoma, adenocarcinoma of cervix, testicular cancer, mesothelioma, digestive-system endocrine
†Reference category. ‡65–74 years (reference category). §15–29 years (reference category). ¶30–39 years. ||≥40 years.

Lancet Oncol 2006; 7: 132–40

5-year relative survival from rare cancer by period of diagnosis, and relative excess risk of death



	Relative excess risk					
	1986–88	(95% CI)	1989–91	(95% CI)	1992–94	(95% CI)
Placental choriocarcinoma	1·15	(0·50–2·62)	0·99	(0·40–2·41)	1·38	(0·61–3·15)
Ovarian germ-cell cancer	0·70	(0·50–0·98)	0·74	(0·54–1·03)	0·57	(0·40–0·80)
Medullary carcinoma of thyroid	1·06	(0·75–1·50)	0·92	(0·65–1·32)	0·88	(0·62–1·25)
Lung carcinoid	1·12	(0·80–1·55)	0·98	(0·70–1·36)	1·07	(0·79–1·45)
Adenocarcinoma of uterine cervix	0·97	(0·87–1·08)	0·91	(0·82–1·02)	0·96	(0·86–1·07)
Testicular cancer at age ≥65 years	0·84	(0·58–1·23)	1·00	(0·70–1·45)	1·11	(0·78–1·59)
Sarcoma of extremities	0·91	(0·83–1·00)	0·92	(0·84–1·01)	0·87	(0·79–0·95)
Digestive-system endocrine tumours	0·92	(0·82–1·02)	0·95	(0·85–1·05)	0·83	(0·74–0·92)
Anal squamous-cell carcinoma	0·81	(0·71–0·92)	0·88	(0·78–1·00)	0·85	(0·75–0·96)
Sarcoma of uterus	0·99	(0·89–1·10)	0·95	(0·85–1·05)	0·92	(0·83–1·02)
Adrenal-cortex carcinoma	1·19	(0·86–1·65)	1·01	(0·75–1·37)	0·96	(0·70–1·33)
Squamous-cell carcinoma of bladder	1·00	(0·90–1·12)	0·98	(0·87–1·09)	0·93	(0·83–1·04)
Angiosarcoma of liver	0·87	(0·48–1·58)	0·53	(0·28–0·99)	0·52	(0·30–0·89)
Mesothelioma	1·04	(0·97–1·11)	0·98	(0·92–1·05)	0·97	(0·91–1·04)

Lancet Oncol 2006; 7: 132–40

Burden of testicular, paratesticular and extragonadal germ cell tumours in Europe

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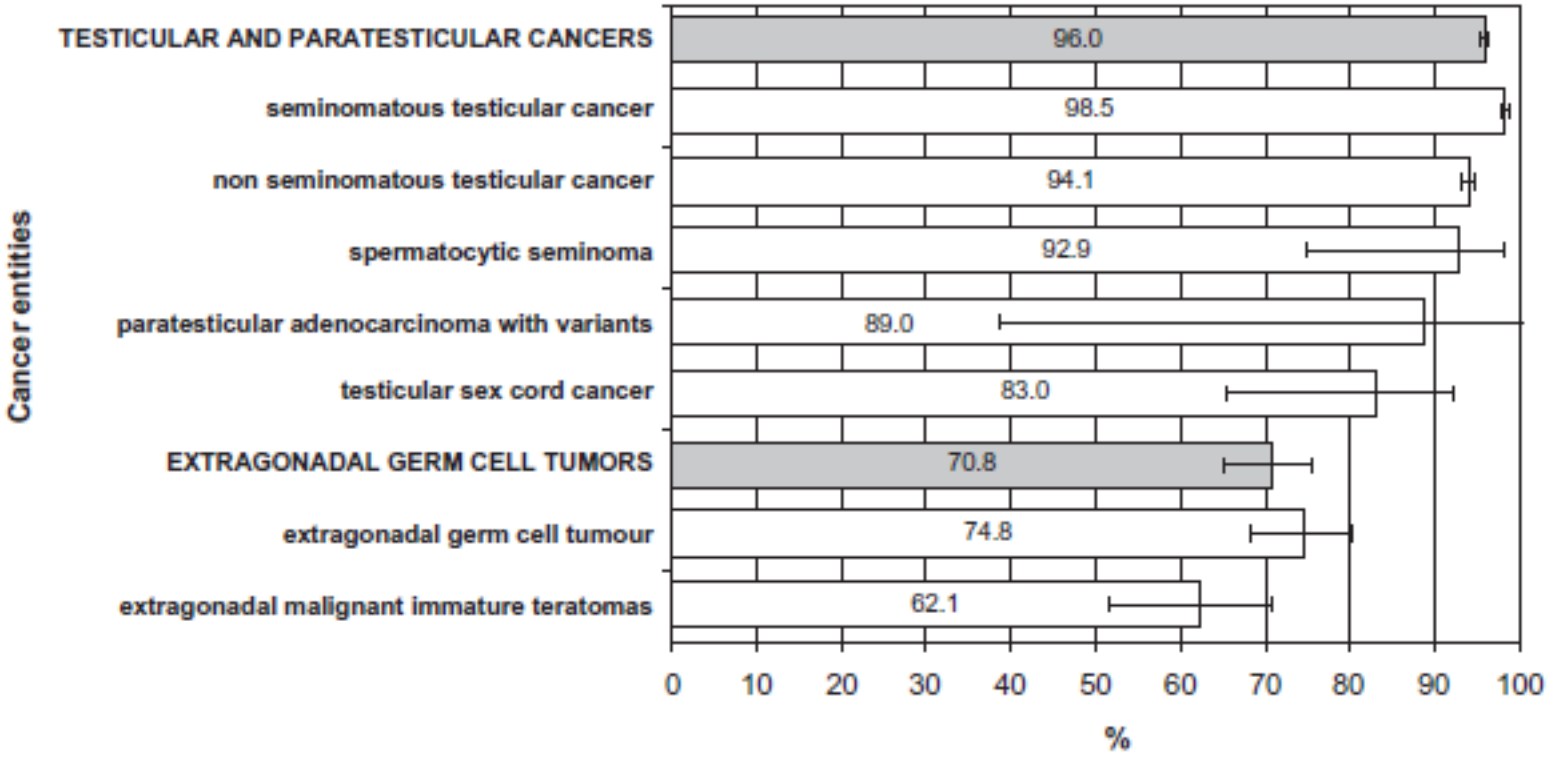
Table 2 – Observed cases with crude incidence (rate per million/year) and standard errors (SE) in Europe. Rates and SE by sex and age, with estimated incident cases in Europe (EU27). Cases diagnosed 1995–2002 in 64 European CRs.

Entity	EU overall			Sex						Age						Estimated cases in EU27 per year
				Male		Female		0–14		15–24		25–64		65+		
	Observed cases 1995–2002	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	
TESTICULAR AND PARATESTICULAR CANCERS	25,357	31.52	0.20	64.53	0.41			1.09	0.09	36.30	0.59	48.03	0.33	6.49	0.23	15,679
Paratesticular adenocarcinoma with variants	12	0.01	0.00	0.03	0.01			NE	NE	NE	NE	0.02	0.01	0.04	0.02	7
Non-seminomatous testicular cancer	9754	12.12	0.12	24.82	0.25			0.86	0.08	26.98	0.51	15.70	0.19	0.67	0.07	6031
Seminomatous testicular cancer	13,777	17.12	0.15	35.06	0.30			0.08	0.02	7.08	0.26	29.44	0.26	3.19	0.16	8518
Spermatocytic seminoma	221	0.27	0.02	0.56	0.04			NE	NE	0.07	0.03	0.35	0.03	0.50	0.06	137
Teratoma with malignant transformation	11	0.01	0.00	0.03	0.01			NE	NE	0.01	0.01	0.02	0.01	0.01	0.01	7
Testicular sex cord cancer	177	0.22	0.02	0.45	0.03			0.04	0.02	0.16	0.04	0.29	0.03	0.24	0.04	109
EXTRAGONADAL GERM CELL TUMOURS	1019	1.27	0.04	1.87	0.07	0.69	0.04	1.73	0.11	2.24	0.15	1.13	0.05	0.42	0.06	630
Extragonadal malignant immature teratoma	335	0.42	0.02	0.58	0.04	0.26	0.03	0.73	0.07	0.63	0.08	0.34	0.03	0.15	0.03	207
Extragonadal germ cell tumour	684	0.85	0.03	1.29	0.06	0.43	0.03	0.99	0.08	1.60	0.12	0.79	0.04	0.27	0.05	423

NE = Not estimated (observed cases = 0).

Five –year relative survival (%) for testicular,paratesticular and extragonadal germ cell tumors ihn Europe in 2000-2002



- Five-year relative survival was 96% for testicular/paratesticular cancer and 71% for extragonadal germ cell cancer; the proportions cured were 95% and 69%, respectively.
- We found limited variation in survival between European regions except for non-seminomatous testicular cancer, for which five-year relative survival ranged from 86% in Eastern Europe to 96% in Northern Europe.
- Survival for all cancer types considered decreased with increasing age at diagnosis.
- Further investigation is required to establish the real reasons for the lower survival in Eastern Europe.
- Considering the high prevalence of these highly curable cancers, it is important to monitor patients long-term, so as to quantify treatment-related risks and develop treatments having limited impact on quality of life.

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European disparities in malignant digestive endocrine tumours survival

IJC
International Journal of Cancer

C. Lepage[1], L. Ciccolallo[2], R. De Angelis[3], A.M. Bouvier[1], J. Faivre[1], G. Gatta[2] and The EUROCARE working group

5-Year Relative Survival Rates of MDET According to Sex, Age, Location and Cellular Differentiation

	UK	Eastern Europe	Western Continental Europe	Northern Europe	Total
Overall	42.5 (1.3)	37.6 (3.0)	53.6 (2.0)	60.3 (2.5)	47.5 (1.0)
Males	42.7 (1.9)	28.1 (3.9)	48.3 (2.7)	63.0 (3.9)	45.5 (1.4)
Females	42.4 (1.8)	47.9 (4.4)	59.1 (2.8)	58.4 (3.4)	49.4 (1.4)
<65 years	53.2 (1.9)	41.9 (3.6)	58.9 (2.5)	71.2 (3.2)	50.4 (1.3)
65–74 years	34.0 (2.4)	28.7 (6.3)	46.3 (3.9)	49.6 (4.6)	34.4 (1.8)
≥75 years	27.8 (2.8)	27.3 (8.7)	44.5 (5.1)	44.3 (6.2)	32.4 (2.3)
Oesophagus	5.3 (1.3)	1.1 (2.7)	10.4 (4.8)	8.9 (4.5)	5.7 (1.3)
Stomach	34.3 (4.5)	36.5 (6.6)	49.9 (5.8)	74.4 (7.7)	45.6 (3.0)
Small intestine	58.3 (2.7)	55.1 (7.2)	64.2 (3.8)	62.0 (3.9)	60.3 (1.9)
Colon/rectum	57.0 (2.5)	49.9 (5.3)	67.6 (3.5)	63.0 (4.7)	59.6 (1.8)
Pancreas	39.7 (3.5)	8.5 (3.5)	38.8 (4.1)	49.3 (6.8)	37.1 (2.3)
Liver/gall bladder	22.2 (7.2)	16.5 (8.4)	31.9 (8.8)	15.7 (10.3)	24.2 (4.6)
Differentiated	56.9 (1.6)	48.0 (3.6)	60.3 (2.1)	62.5 (2.6)	58.1 (1.1)
Small-cell	7.7 (1.3)	6.3 (2.6)	11.3 (3.1)	7.4 (3.8)	8.1 (1.1)

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Excess Hazard Ratio (EHR) of Death within 5 Years of Diagnosis, with 95% Confidence Interval (CI), Among Patients with Mdet, by Prognostic Group

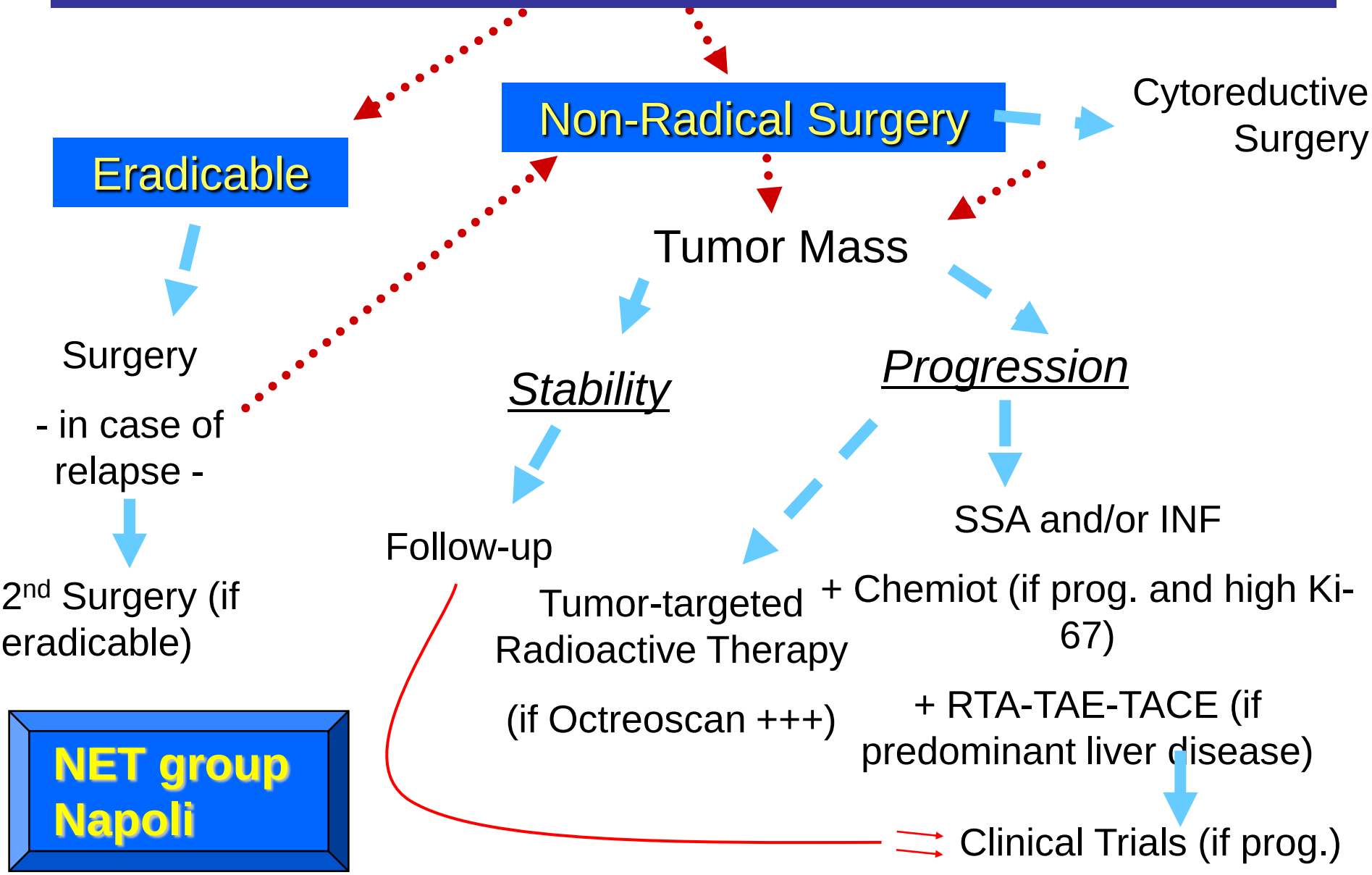
	EHR	95% CI	p^1
Gender			
Males	1		
Females	0.89	0.81; 0.97	0.012
Age			
<65 years	1		
≥65 years	1.91	1.74; 2.11	<0.001
Country			
United Kingdom	1		
Eastern Europe	1.38	1.18; 1.62	<0.001
Western Continental Europe	0.83	0.74; 0.94	0.002
Northern Europe	0.84	0.71; 0.98	0.025
Subsite			
Small intestine	1		
Oesophagus	1.59	1.31; 1.93	<0.001
Stomach	1.17	0.97; 1.40	0.103
Colon/rectum	0.97	0.84; 1.13	0.720
Liver/gall bladder	2.23	1.74; 2.85	<0.001
Pancreas	1.96	1.68; 2.28	<0.001
Differentiation			
Small-cell	1		
Well differentiated	0.27	0.24; 0.31	<0.001

[1]Likelihood ratio test.

In conclusion, MDET comprise a heterogeneous group of rare neoplasms with widely differing prognostic features. Our results reveal that for MDET, as for many other cancer sites,2 there are wide variations in survival from one European country to another. These variations are independent of MDET characteristics (differentiation, site) and of the age and sex of the patients. However, in this study, no data were gathered on the management or stage at diagnosis of MDET. It has been suggested that poorer access both to adequate diagnostic facilities, leading to advanced stage at diagnosis, and also to treatment services were key factors in the lower survival rates found for all solid tumours in Eastern Europe. An efficient health system is particularly important in dealing with MDET because of the difficulty of diagnosis and of the complexity of treatments.

Int. J. Cancer: 126, 2928–2934 (2010) © 2009 UICC

Algoritmo terapeutico dei Tumori Neuroendocrini Ben Differenziati



Molecular targeted agents in neuroendocrine tumors

Agent	Status
VEGF monoclonal antibody	
Bevacizumab	In phase-III development.
mTOR inhibitor	
RAD001 (Everolimus)	In phase-III development.
Temserolimus	Phase-II completed.
VEGF tyrosine kinase inhibitor	
Sunitinib	Phase-II completed.
Vatalanib	Phase-II in progress.
Sorafenib	Phase-II in progress.
PDGFR, kit, abl inhibitor	
Imatinib	Phase-II completed. RR
EGFR inhibitor	
Gefitnib	Phase-II completed.
Other	
Bortezomib	Phase-II completed.

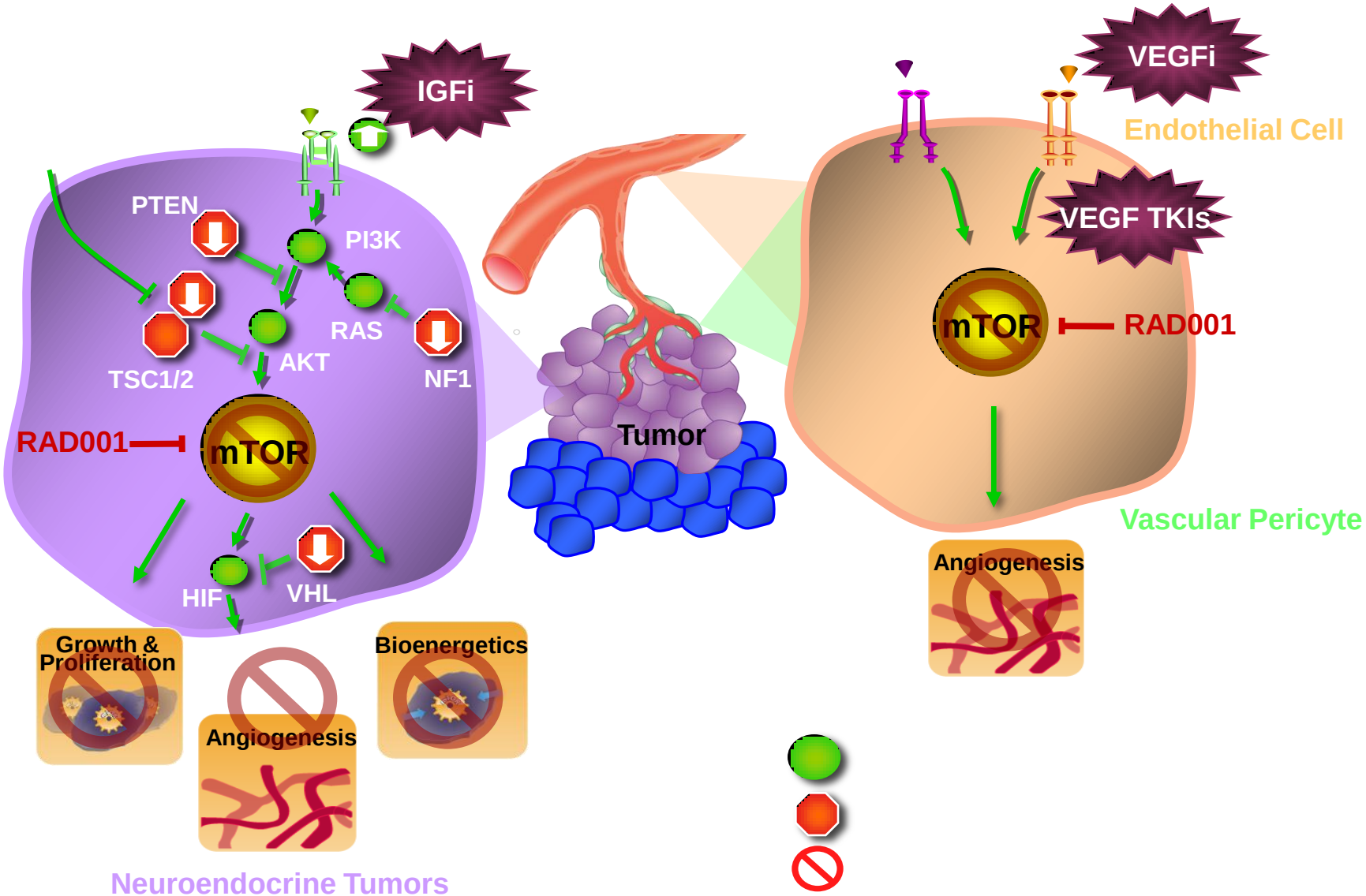
VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor.

Yao, Best Practice and Research Clinical Endocrinology & Metabolism, 2007

Target therapy nei NET: farmaci in studio

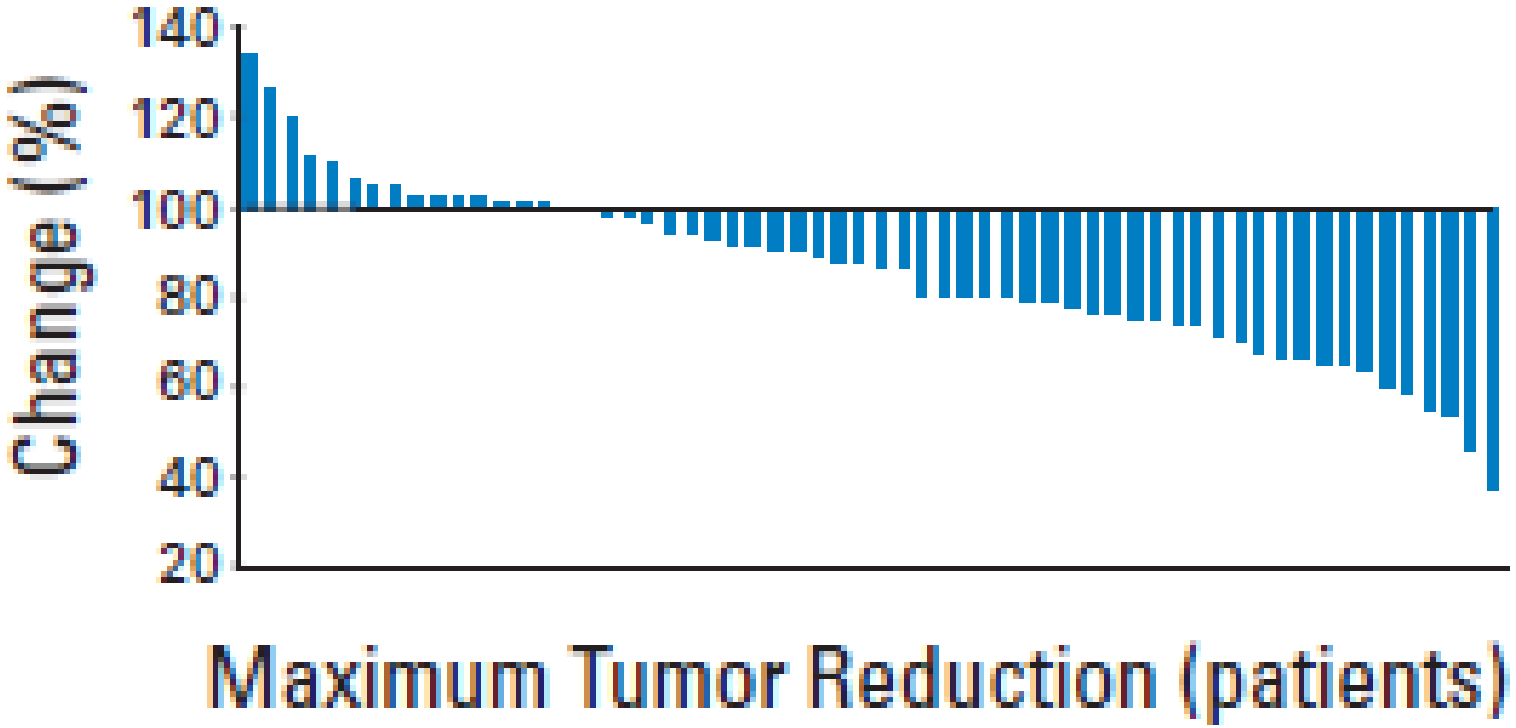
- Inibitori pathway VEGF
  - Sunitinib
  - Sorafenib
- Inibitori pathway mTOR
  - RAD001 (Everolimus)

RAD001 - mTOR pathway



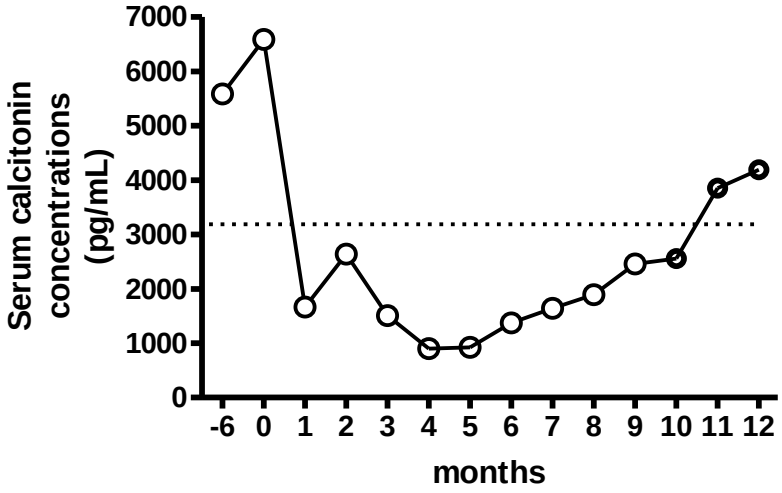
Efficacy of RAD001 (Everolimus) and Octreotide LAR in Advanced Low- to Intermediate-Grade Neuroendocrine Tumors: Results of a Phase II Study

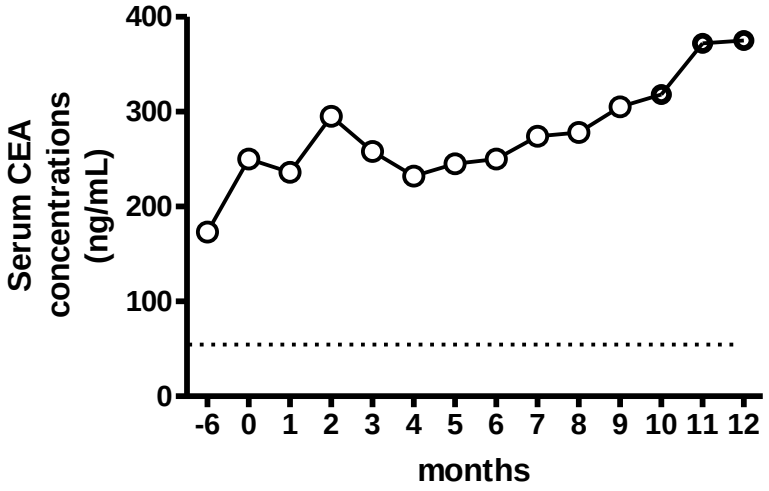
James C. Yao, Alexandria T. Phan, David Z. Chang, Robert A. Wolff, Kenneth Hess, Sanjay Gupta, Carmen Jacobs, Jeannette E. Mares, Andrea N. Landgraf, Asif Rashid, and Funda Meric-Bernstam



Yao et al. JCO 2008

CMT





The Antiproliferative Effect of Pasireotide LAR Alone and in Combination with Everolimus (RAD001) in Patients with Progressive Medullary Thyroid Cancer (MTC): A Single-Center, Open-Label, Phase II, Proof-of-Concept Study

Antongiulio Faggiano and Annamaria Colao
Department of Molecular and Clinical Endocrinology and Oncology, Federico II University, Naples, Italy

Background

Medullary thyroid cancer (MTC) is a well-differentiated neuroendocrine tumor (NET) of the thyroid parafollicular cells and expression of somatostatin receptor subtypes sst1, sst2 and/or sst5 have been shown in majority (~80%) of patients with MTC. Pasireotide (SOM230) is a novel, multi-receptor targeted somatostatin analogue with high-binding affinity for $sst_{1,2,3}$ and sst_5, and has antisecretory and potential antitumor properties. Everolimus, an inhibitor of mTOR (a central regulator of growth/proliferation, cellular metabolism and angiogenesis) and has shown antitumor benefit in patients with NET, either alone or in combination with octreotide LAR.

Methods

Patients with progressive metastatic or persistent postoperative MTC and evidence of biochemical progression (escalating serum calcitonin levels) will receive pasireotide LAR 60 mg/month for 6 months with efficacy evaluated every 3 months. Patients exhibiting progressive disease at 3 months will then be administered oral everolimus 10 mg/day as combination therapy. The primary endpoint is the effect of pasireotide LAR on progression-free survival (PFS), according to RECIST. Secondary endpoints include PFS with pasireotide LAR + everolimus, safety, and change in serum calcitonin and carcinoembryonic antigen levels. Patients achieving benefit (stable disease or better) with monotherapy or combination therapy at 6 months may enroll in an optional extension phase.

Results

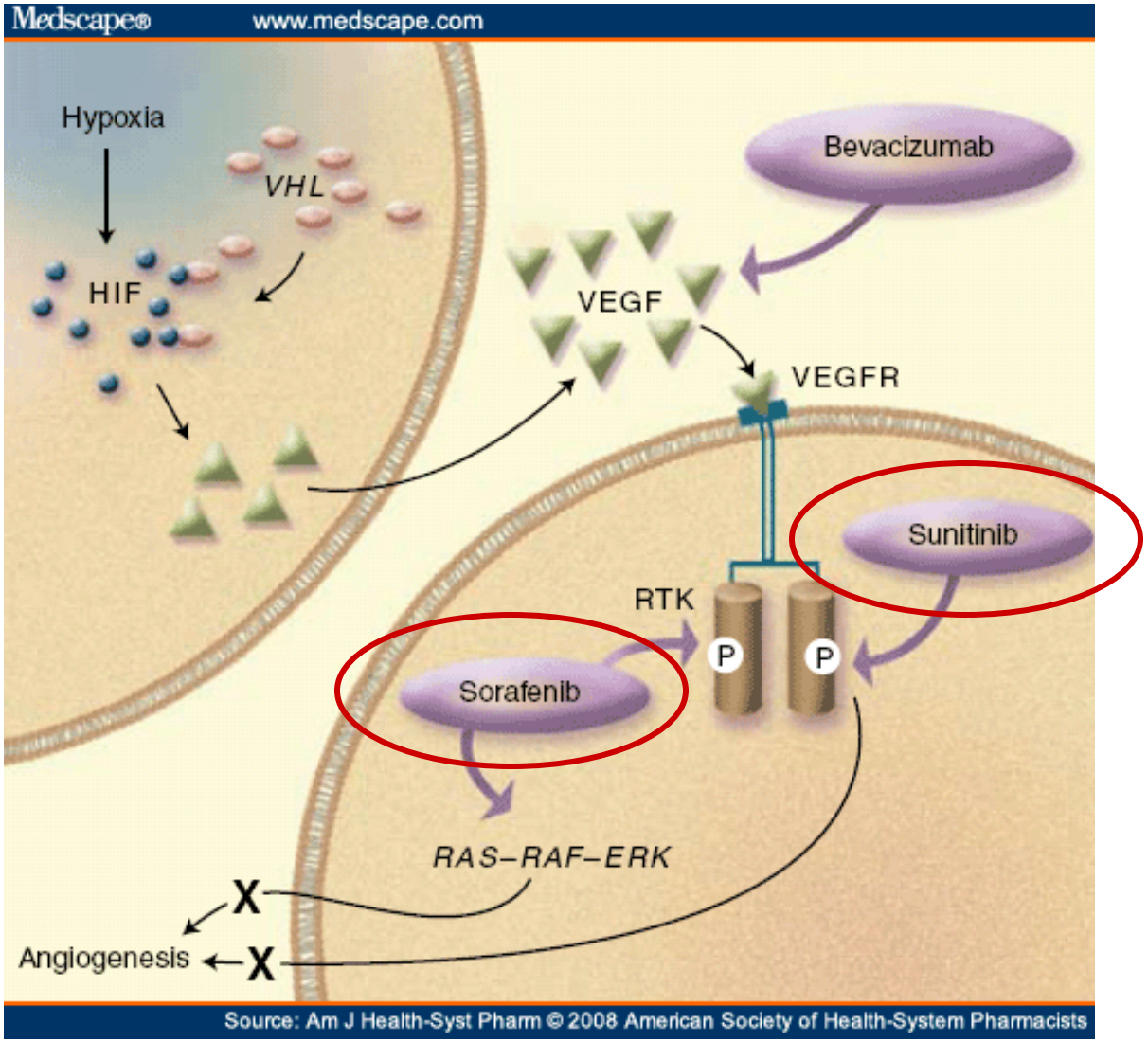
20 patients are expected to be enrolled. In December 2009, the study protocol received institutional review board approval and the trial commenced enrollment. Recruitment is expected to be completed in June 2010, with the last patient visit estimated in December 2010. Study results are anticipated in 2011.

Conclusions

This study will provide evidence of the antiproliferative potential of pasireotide LAR alone and in combination with everolimus in patients with progressive, metastatic or persistent postoperative MTC. As there is no established treatment for patients with persistent postoperative MTC, an efficacious medical therapy would be invaluable.

Poster presented at the American Society of Clinical Oncology, Annual Meeting, 4–8 June 2010, Chicago, IL, USA

sunitinib/sorafenib - VEGF pathway



Sunitinib - 37.5 mg a day continuous daily dosing
Phase III - sunitinib vs placebo - multicenter study

in patients with progressive metastatic or locally advanced well differentiated pancreatic endocrine carcinomas (171 pts randomized)

Efficacy	SU vs Placebo
➢Median PFS	11.4 vs 5.5 months
➢ORR	9 vs 0%
➢Median OS	Not reached
Safety	
➢Serious AE	27 vs 42%
➢Quality of life	No significant difference in the global health-related QoL

aspetti fondamentali

-Il RAD001 è un farmaco efficace e sicuro per il trattamento di pazienti con NET avanzato in progressione

-Tra gli anti-angiogenetici il sunitinib sembra avere il miglior profilo di efficacia nei NET

-La tossicità è accettabile e gestibile senza dover interrompere la terapia nella maggior parte dei pazienti

aspetti da sviluppare

-Efficacia di nuovi farmaci in trial clinici controllati

-Necessità di valutare gli aspetti economico-sanitari delle diverse strategie terapeutiche dei NET

Review Article

Adrenocortical Carcinoma: Current Therapeutic State-of-the-Art

Amir H. Lebastchi, John W. Kunstman, and Tobias Carling

Adrenocortical carcinoma (ACC) is a rare, aggressive malignancy that generally conveys a poor prognosis. Currently, surgical resection is considered the lone curative treatment modality. In addition, the low prevalence of ACC has limited effective clinical trial design to develop evidence-based approaches to ACC therapy. The proper role of radio- and chemotherapy treatment for ACC is still being defined. Similarly, the molecular pathogenesis of ACC remains to be fully characterized. Despite these challenges, progress has been made in several areas. After years of refinement, an internationally accepted staging system has been defined. International collaborations have facilitated increasingly robust clinical trials, especially regarding agent choice and patient selection for chemotherapeutics. Genetic array data and molecular profiling have identified new potential targets for rational drug design as well as potential tumor markers and predictors of therapeutic response. However, these advances have not yet been translated into a large outcomes benefit for ACC patients. In this paper, we summarize established therapy for ACC and highlight recent findings in the field that are impacting clinical practice.

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Ongoing Clinical Trials that test the Target Therapies.

Study	Target	ID	Purpose	Status
Mitotane with or without *IMC-A12* in treating patients with recurrent, metastatic, or primary adrenocortical cancer that cannot be removed by surgery	*IGF1R*	NCT00778817	This randomized phase II trial compares the combination of mitotane and IMC-A12 with mitotane alone in the treatment of recurrent, metastatic, or primary adrenocortical cancer that cannot be removed by surgery	Recruiting
A study of *OSI-906* in patients with locally advanced or metastatic adrenocortical carcinoma (GALACCTIC)	*IGF1R*	NCT00924989	A multicenter, randomized, double-blind, placebo-controlled, phase III study of single-agent OSI-906 in patients with locally advanced/metastatic adrenocortical carcinoma who received at least 1 but no more than 2 prior drug regimens	Ongoing not recruiting
Phase II trial of *ZD1839* (*Iressa*) in patients with nonresectable adrenocortical carcinoma	*VEGFR*	NCT00215202	This phase II trial investigates the effect of Iressa in patients with nonresectable adrenocortical cancer who have previously been treated with one other form of systemic therapy (either Mitotane or chemotherapy).	Completed
Phase II Study of *Axitinib* (AG-013736) With Evaluation of the VEGF-Pathway in Metastatic, Recurrent or Primary Unresectable Adrenocortical Cancer	*Multikinase* (i) *VEGFR* (ii) *PDGFR* (iii) *KIT*	NCT01255137	To evaluate the effectiveness of axitinib in individuals who have adrenocortical cancer that is inoperable and has not responded to standard treatments	Recruiting
Sunitinib in Refractory Adrenocortical Carcinoma (SIRAC)	*Multikinase* (i) *VEGFR* (ii) *PDGFR* (iii) *KIT*	NCT00453895	The primary objective of this trial is to estimate the response (defined as progression-free survival of $\geq$12 weeks) rate associated with Sunitinib treatment in patients advanced ACC progressing after cytotoxic chemotherapy	Unknown
Sorafenib Plus Paclitaxel in adreno-cortical-cancer patients (PAXO)	*Multikinase* (i) *RAF* (ii) *VEGFR* (iii) *PDGFR* (iv) *KIT*	NCT00786110	The aim of this phase II trial is to evaluate the clinical benefit and toxicity of the combination of Sorafenib plus metronomic chemotherapy in patients with locally advanced or metastatic ACC who progressed after first or second line chemotherapy.	Unknown
Clinical trial of *Dovitinib* in first-line metastatic or locally advanced non-resectable adrenocortical carcinom	*FGFRs*	NCT01514526	Non-randomized, phase II clinical trial, that investigates the use of Dovitinib in adult patients with metastatic or locally [illegible] adrenocortical carcinom	Recruiting
Cixutumumab in treating patients with relapsed or refractory solid tumors	*IGF1R*	NCT00831844	Phase II trial that studies well cixutumumab work [illegible] relapsed or refractory solid tumors, including ACC	

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Review Article

Adrenocortical Carcinoma: Current Therapeutic State-of-the-Art

Amir H. Lebastchi, John W. Kunstman, and Tobias Carling

"ACC remains a rare malignancy that has seen little improvement in overall mortality over the past two decades. Until recently, standard of care was based only on individual opinion and occasionally expert consensus. Over the past decade, international collaboration has begun to improve the management of these patients and the molecular understanding of the disease. The development of standardized staging criteria and the gradual accrual of clinical trials in treating ACC, especially with the release of the first randomized phase III trial in ACC, exemplifies the ongoing progress in clinical care of these patients. Similarly, as the genetic understanding of adrenal tumorigenesis continues to progress, more targets for future drug development are identified and evaluated. As these discoveries are translated into clinical practice, ACC therapy will move beyond historical modalities to the benefit of patients everywhere."

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CONCLUSION

- 22% of all cancers diagnosed in the EU27 each year are rare. In absolute terms, this is slightly more than half a million new rare cancer cases each year, while 4,300,000 rare cancers are prevalent in the population.
- 30% of Europeans with a rare cancer have one of the particularly rare forms that affect <1/100,000 and this is important, because low incidence is amajor obstacle to conducting clinical trails to develop effective treatments.
- One way to overcome this obstacle would be to establish centres of excellence for rare cancers and international collaborative groups to network centres across the EU to thereby achieve necessary organisational structure, critical mass and patients for carrying out clinical trials, developing alternative study designs and methodological approaches to clinical experimentation and improving accuracy and standardisation of staging procedures for rare cancers.

Gatta G,et al. Eur J Cancer. 2011