National Cancer Registry Ireland **Cancer Trends**

Soft Tissue Sarcomas

Case numbers and subtype definitions

Sarcomas are a group of uncommon cancers that originate from mesenchymal cells as opposed to more well-known cancers that develop from epithelial tissue. Soft tissue sarcomas (STS) form in cartilage, fat, muscle, blood vessels and in the fibrous, connective & supportive tissues of the body. There are dozens of histological types of STS but they can be broadly grouped into 18 main subtypes based on cell type and location. These groups were described recently following research on rare cancer incidence in Europe (RARECARE[1,2]) and are listed in Table 1. An average of 176 cases of STS was diagnosed per year in Ireland from 1994 to 2012, representing just over 1% of all invasive cancers. Age standardised incidence rates averaged 4.9 cases per 100,000 women and 4.1 cases per 100,000 men. In addition, averages of 6 cases of Kaposi sarcoma per year and (since 2005) 20 gastrointestinal stromal tumours (GIST) per year were diagnosed. These fall outside the RARECARE STS group definition and so are listed separately here.

Table 1. Annual average numbers of soft tissue sarcomas (STS) by RARECARE histological subtype[1,2], 1994–2012

	Annual average	% all STS	M/F ratio	Rate ~
head & neck	10	6%	1.8	0.24
limbs	36	20%	1.3	0.90
superficial trunk	17	9%	1.5	0.42
mediastinum	<1	<1%	0.6	0.01
heart	<1	1%	1.1	0.02
breast	7	4%	0	0.38
uterus	28	16%	-	1.44
paratestis	<1	<1%	-	0.03
other genitourinary#	11	6%	0.3	0.30
other viscera	10	6%	1.3	0.27
peritoneum & retroperitoneum	6	3%	1.2	0.15
pelvis	9	5%	1.1	0.22
skin	17	10%	1.6	0.42
paraorbit	<1	<1%	0.8	0.01
brain & nervous system	6	3%	1.1	0.15
embryonal rhabdomyosarcoma	4	2%	1.5	0.10
alveolar rhabdomyosarcoma	2	1%	1.6	0.05
Ewing sarcoma of soft tissue	1	1%	2.6	0.03
other & unspecified	9	5%	1.2	0.23
TOTAL STS	**176**		**0.8**	**4.48**
GIST*	20	-	1.3	0.45
Kaposi sarcoma*	6	-	8.1	0.26

#vulva, vagina, ovary, penis, prostate, testis, kidney, renal pelvis, ureter, bladder, urethra
**Gastrointestinal Stromal Tumours (GIST) & Kaposi sarcoma not included in overall STS grouping as defined by RARECARE[1]. GIST identified by an individual histological code (M-8936) from 2005 onwards only.*
~ rate per 100,000 per year (European age standardised, sexes combined except for breast, uterus [females], paratestis & Kaposi sarcoma [males])

Over 90% of all STS were diagnosed symptomatically. However 12% of heart sarcomas were diagnosed incidentally or at autopsy. Almost all tumours were microscopically confirmed; the lowest proportions of histologically confirmed cases were for brain & nervous system tumours (89%) and Kaposi sarcoma (96%).

Over half of all STS were diagnosed in the limbs, uterus, skin and superficial trunk; tumours in the limbs alone representing 1 in 5 of all STS (Table 1). STS as a group overall were more common in females than in males but (excluding sex-specific tumours) Ewing sarcoma, alveolar & embryonal rhabdomyosarcomas, head & neck, skin (and Kaposi) sarcomas were more common in males.

For the most part, the names of the STS subtypes also indicate the position of the tumour. However some subtypes were defined by histology and found at a range of locations in the body, notably embryonal and alveolar rhabdomyosarcomas (Table 2). Over two-thirds of all STS in the limbs were in the legs and hips. 41% of STS in "other viscera" were gastro-oesophageal specifically and for GIST in particular (not tabulated) 63% were located in the stomach and 24% in the small intestine.

Table 2. Percentage distribution of anatomical tumour sites for selected STS subtypes, 1994–2012, N = annual average

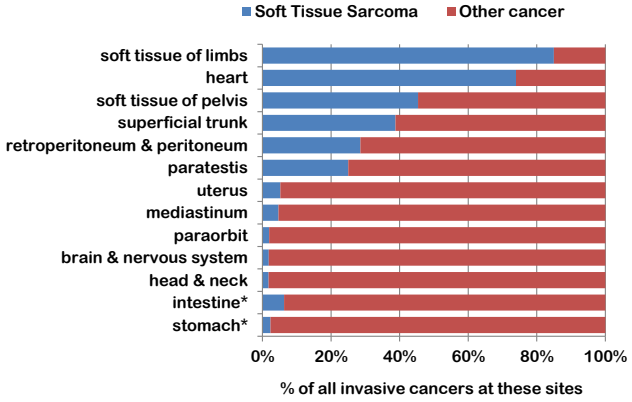
	%		%
LIMBS	**N=36**	**BRAIN & NERVOUS SYSTEM**	**N=6**
upper limb & shoulder	29%	brain & CNS	40%
lower limb & hip	71%	peripheral nerves	58%
		thyroid & endocrine	2%
SKIN	**N=17**	**EMBRYONAL RHABDOMYOSARCOMA**	**N=4**
face & ears	20%	head & neck	19%
scalp & neck	13%	eye	16%
trunk	29%	brain & CNS	2%
upper limb & shoulder	20%	skin	1%
lower limb & hip	16%	cervix & uterus	3%
unspecified	2%	other gynaecological	4%
		male genital	16%
OTHER VISCERA	**N=10**	kidney & bladder	3%
oesophagus & stomach	41%	connective & other soft tissue	34%
small intestine	27%	other & unspecified	2%
colorectal	14%		
liver & gallbladder	8%	**ALVEOLAR RHABDOMYOSARCOMA**	**N=2**
pancreas	3%	head & neck	13%
other digestive	4%	colorectal	3%
other & unspecified	3%	connective & other soft tissues	67%
OTHER GENITOURINARY#	**N=11**	other gynaecological	3%
ovary	55%	male genital	3%
other gynaecological	12%	thyroid & endocrine	3%
male genital	11%	other & unspecified	3%
kidney & bladder	23%		

#vulva, vagina, ovary, penis, prostate, testis, kidney, renal pelvis, ureter, bladder, urethra

STS were represented by 67 different cell types (excluding GIST & Kaposi sarcoma), but 65% of all STS were made up of just 10: leiomyosarcoma (20%), unspecified sarcoma (9%), Mullerian mixed tumour (8%), dermatofibrosarcoma (7%), malignant fibrous histiocytoma (6%), endometrial stromal tumour, liposarcoma, phyllodes tumour, hemangiosarcoma and spindle cell tumours (3% each). Histological composition by topographically-defined subtype is summarised in Appendix I.

STS as a proportion of all invasive cancers varied considerably between anatomical sites. While 85% of all soft tissue tumours in limbs and 75% of all heart tumours were sarcomas, STS represented a very small proportion of tumours at most other sites (Figure 1). Although uterine sarcomas were the 2nd most common STS subtype, they only formed 5% of all cancers in the uterus. GIST represented only 2% of all stomach and 6% of all small intestine tumours. STS represented <0.5% of all cancers in the breast and skin as well as in the 'other genitourinary' and 'other viscera' sites.

Figure 1. Proportion of all invasive tumours which were soft tissue sarcomas (or GIST) by body site 1994-2012*

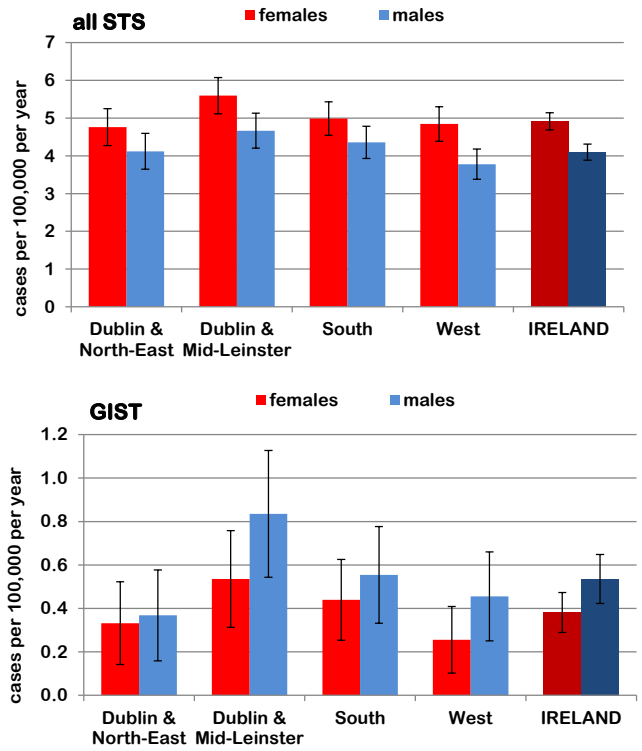


* intestine & stomach show % GIST specifically for cases diagnosed 2005-2012 only

Geographic distribution

Rates of STS varied somewhat between regions but there were no significant differences in incidence between areas for either sex (Figure 2). Female rates were higher than male rates in all regions, likely due to the high proportion of female specific cancers in the overall STS grouping. Incidence rates for GIST were highly variable, reflecting the low number of cases and in contrast to all STS, incidence here was higher in males than in females.

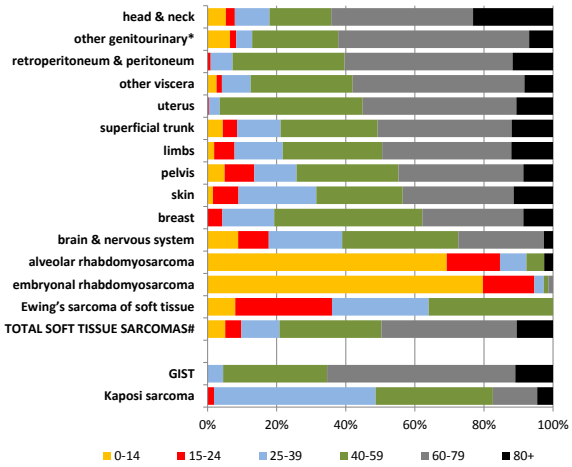
Figure 2. Incidence rates (EASR) of all STS (1994–2012) and GIST (2005–2012) by HSE region of residence



Age profile

Half of all STS patients were under 60 years of age at diagnosis, compared to just one-third of all invasive cancer patients. Rhabdomyosarcomas were diagnosed mostly in children (aged under 15) and a third of all Ewing sarcomas were diagnosed in under 25 year olds (Figure 3). Just under half of all Kaposi sarcoma patients were aged between 25 and 39. Most of the other subtypes had an older age profile with 23% of head & neck STS in particular diagnosed in patients aged 80 or older.

Figure 3. Percentage age distribution of STS by histological subtype[1], 1994–2012



*vulva, vagina, ovary, penis, prostate, testis, kidney, renal pelvis, ureter, bladder, urethra
Total STS as per RARECARE definitions (excludes GIST & Kaposi Sarcoma)

Time trends in incidence

Incidence rates of STS have fluctuated from year to year with rates in recent years close to those calculated during the mid 1990's. However in both sexes, rates showed an initial increase during the 1990's followed by a later decline in incidence (Figure 4, Table 3).

Figure 4. Incidence rates (EASR) for all STS 1994-2012

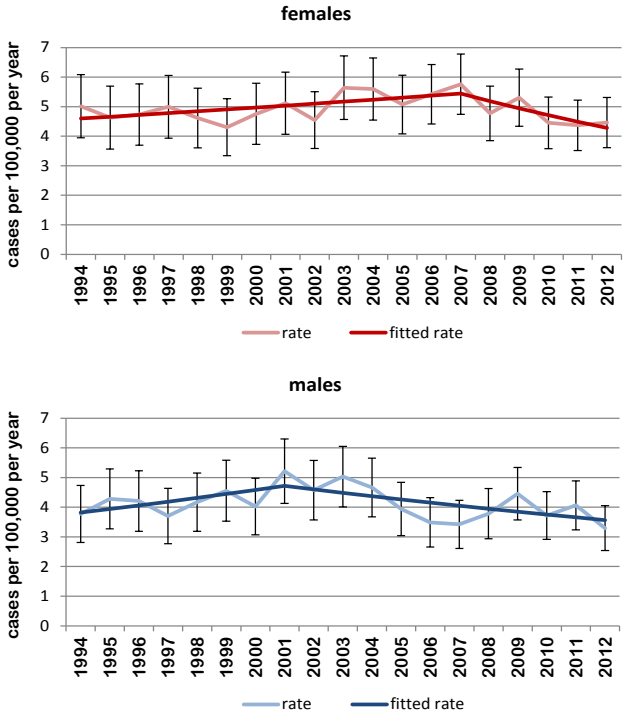


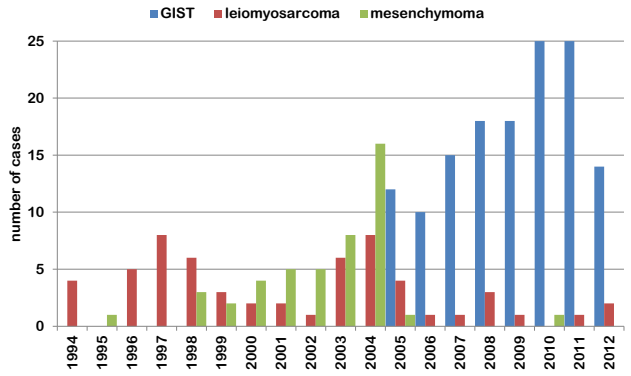
Table 3. Incidence rates (EASR per 100,000) for STS in 1994 & 2012, peak incidence and annual % change (95% confidence intervals) in rates for both males and females

	females	males
rate 1994	5.0	3.8
peak rate*	5.8	5.2
rate 2012	4.5	3.3
annual % increase**	1.3 (0.1, 2.5)	3.1 (-1.6, 7.9)
annual % decline**	-4.7 (-9.1, -0.1)	-2.5 (-4.6, -0.5)

*2007 for females, 2001 for males ** trend to/from peak rate

This trend in incidence rates is likely influenced by the changes in the diagnosis and registration of some tumours, particularly gastrointestinal stromal tumours (GIST). Throughout the 1990's gastrointestinal sarcomas that are now recognised as GIST were likely to have been diagnosed and registered as other STS subtypes, notably leiomyosarcomas and mesenchymomas (Figure 5). However with advances in diagnostic techniques, these tumours are now recognised as a distinct entity and, since 2005, have been registered as such. Improvements in detection methods have also resulted in an increase in recorded incidence of GIST[3]. Because GIST are excluded from the overall STS total, the true trend in STS incidence is unclear.

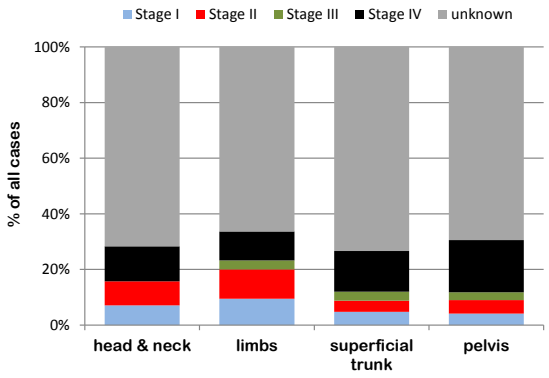
Figure 5. Number of sarcomas diagnosed in the gastro-oesophageal and small intestinal tract, 1994-2012 by histological type



Tumour stage

5th edition TNM tumour staging (used by NCR up to 2012) did not apply to most STS subtypes (e.g. STS of breast, uterus or intestinal tract), and only 14% of all STS were assigned a tumour stage. For the four most common subtypes that included sarcomas for which TNM staging was applicable, over two-thirds of all cases were still of unknown stage (Figure 6). Stage IV made up the largest proportion of staged tumours.

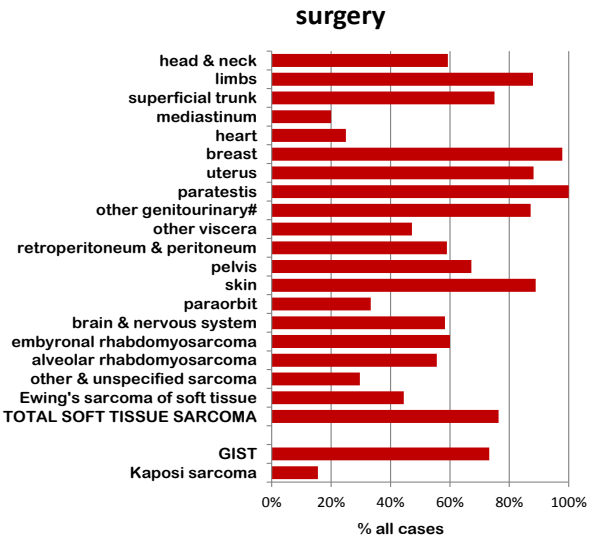
Figure 6. Percentage distribution of tumour stage for STS subtypes where TNM staging applied, 1994-2012



Treatment[4]

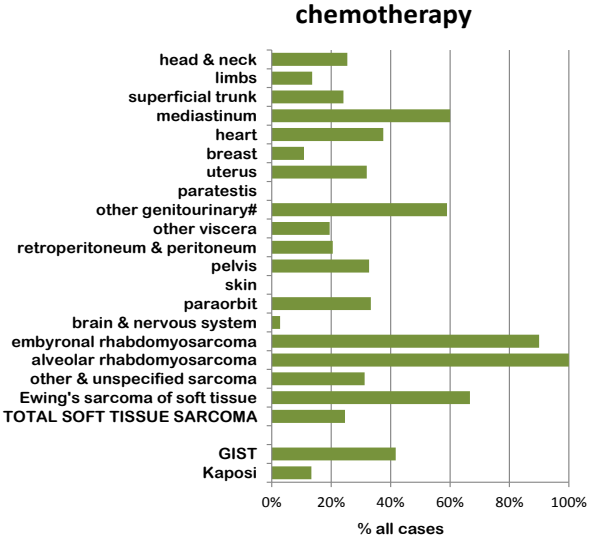
As a group overall, 78% of STS diagnosed between 2007 and 2012 had tumour-directed surgery, 25% had chemotherapy and 38% had radiotherapy, with just 11% of all patients not having any tumour directed treatment (Figure 6a-d). Over 75% of all patients diagnosed with STS in the limbs, superficial trunk, breast, uterus, paratestis, genitourinary system and skin had surgical removal of their tumour (Figure 6a). In addition 73% of GIST were surgically removed. Only 1 of 5 mediastinal STS, 1 of 3 paraorbital STS and 2 in 8 patients diagnosed with heart sarcomas had tumour-directed surgery. Treatment of Kaposi sarcoma is complicated by the fact that most patients have impaired immune systems and the low percentage directly treated may be due to other non-cancer directed treatment, such as antiretroviral therapy being preferred[5].

Figure 6a. Treatment of soft tissue sarcomas, GIST and Kaposi sarcoma, 2007-2012[4]: surgery



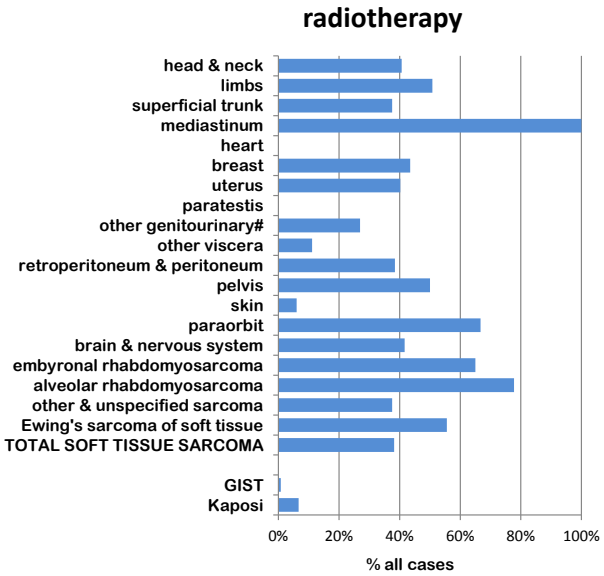
Chemotherapy was the main treatment for patients (mostly children aged under 15) diagnosed with rhabdomyosarcoma with 25 of 29 patients treated (Figure 6b). 6 of the 9 patients diagnosed with Ewing sarcoma of soft tissue had chemotherapy. Chemotherapy was comparatively rare for patients with limb STS with just 14% treated.

Figure 6b. Treatment of soft tissue sarcomas, GIST and Kaposi sarcoma, 2007-2012[4]: chemotherapy



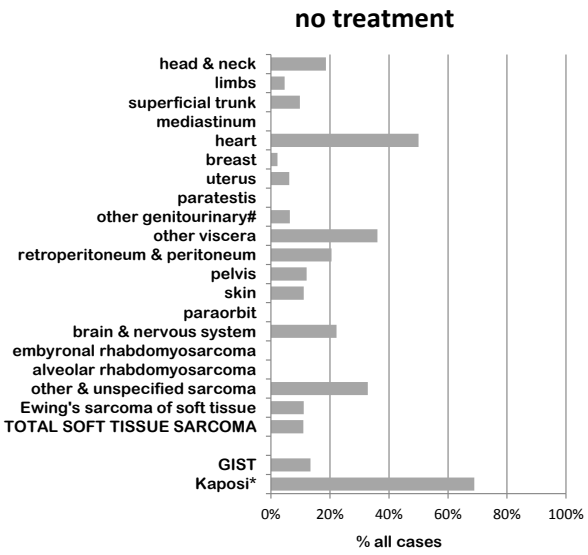
All 5 patients with mediastinal STS had radiotherapy and over half of patients with STS in the limbs, pelvis, paraorbit as well as Ewing sarcoma and rhabdomyosarcoma also had radiotherapy.

Figure 6c. Treatment of soft tissue sarcomas, GIST and Kaposi sarcoma, 2007-2012[4]: radiotherapy



Only a small proportion of all STS patients had no tumour-directed therapy and less than 20% of most individual subtypes were not treated. However 50% of heart sarcomas (4 of 8 patients) were not treated and approximately one-third of patients with STS in the digestive system (other viscera) and other unspecified sites were also untreated.

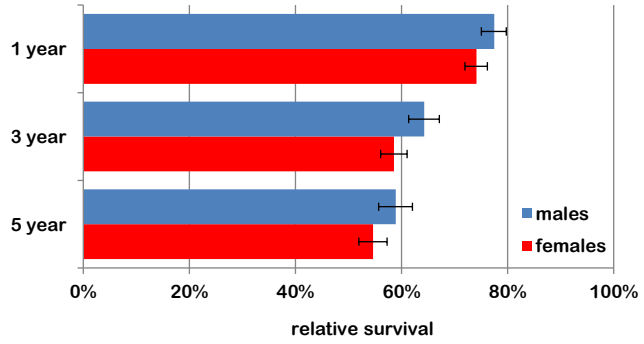
Figure 6d. Treatment of soft tissue sarcomas, GIST and Kaposi sarcoma, 2007-2012[4]: no tumour directed therapy



Survival

Relative survival (RS) for all STS combined at 1 year was 75.6% (95%CI: 74.0%-77.1%), at 3 years was 61.1% (95%CI 59.1%-62.9%) and at 5 years was 56.5% (95%CI 54.4%-58.5%). For the STS grouping overall, survival was better for males than for females (Figure 7). These figures exclude GIST and Kaposi sarcoma.

Figure 7. One-, three- and five- year relative survival (with 95% confidence intervals) for all soft tissue sarcomas diagnosed in men and women 1994-2011[6] (excluding GIST & Kaposi sarcoma)



Relative survival varied considerably between STS subtypes (Table 4). STS of the skin had the highest survival of all, with 5-year RS of 91%. Breast STS (mostly phyllodes tumours) and GIST had the next highest survival with 81% and 78% RS at 5 years respectively. Poorest survival was observed for female patients diagnosed with genitourinary STS with 5-year RS of just 23%. RS was also poor for patients diagnosed with Ewing sarcoma of soft tissue or with peritoneal or uterine sarcomas. 5 year RS for STS in the limbs, the most common subtype overall was 68% (65% in males and 71% in females). The higher RS for all STS combined in males (Figure 7) is likely to be influenced by the different composition of subtypes between the sexes, notably the comparatively poor survival of some female specific cancers.

Table 4. One-, three- and five-year relative survival (RS) estimates for soft tissue sarcoma subtypes and GIST, 1994-2011[6]

	1 year	3 year	5 year
head & neck	81.8 (74.7-87.4)	68.3 (59.6-76.1)	59.5 (49.7-68.7)
limbs	87.1 (84.0-89.7)	73.1 (68.9-76.9)	67.8 (63.1-72.2)
superficial trunk	75.7 (70.2-80.5)	58.8 (52.4-64.7)	56.8 (50.1-63.2)
breast (females only)	91.3 (84.7-95.3)	85.4 (77.4-91.2)	81.1 (71.9-88.2)
uterus (females only)	66.9 (62.6-71.0)	46.3 (41.6-50.9)	43.2 (38.3-48.0)
other genitourinary# (females only)	57.1 (49.1-64.5)	34.7 (27.0-42.6)	23.4 (16.3-31.3)
other viscera	76.0 (68.8-81.9)	63.4 (55.3-70.8)	55.9 (47.3-63.9)
retroperitoneum & peritoneum	59.0 (48.5-68.2)	51.8 (40.9-62.0)	39.0 (28.0-50.2)
pelvis	77.1 (69.3-83.2)	57.9 (49.0-66.1)	56.2 (46.7-65.0)
skin	94.3 (90.5-96.9)	91.1 (86.1-95.0)	91.0 (85.2-95.7)
brain & nervous system	73.1 (63.2-80.9)	56.5 (45.8-66.1)	51.5 (40.4-61.7)
embryonal rhabdomyosarcoma	88.5 (78.2-94.1)	73.1 (60.6-82.2)	66.3 (53.2-76.5)
alveolar rhabdomyosarcoma	82.7 (66.5-91.7)	56.9 (39.7-71.1)	51.5 (34.4-66.4)
Ewing sarcoma of soft tissue	63.7 (40.4-80.0)	37.4 (17.0-58.0)	37.5 (17.0-58.2)
TOTAL soft tissue sarcoma	75.6 (74.0-77.1)	61.1 (59.1-62.9)	56.5 (54.4-58.5)
GIST*	90.4 (83.2-95.0)	86.5 (77.3-93.0)	78.0 (64.8-88.0)

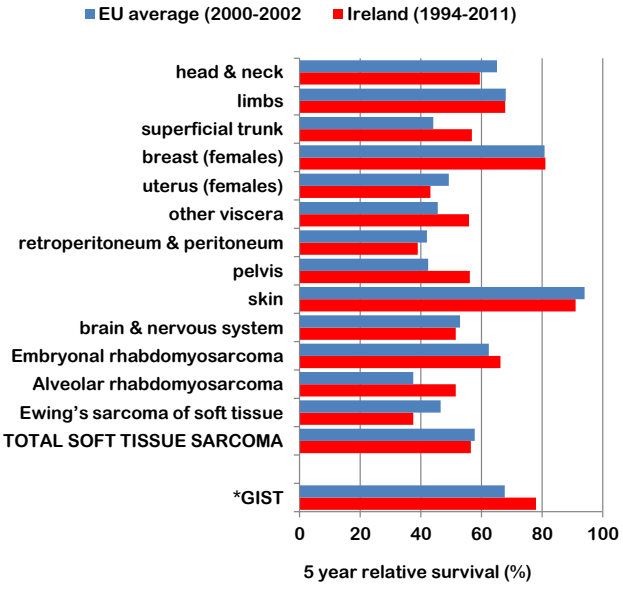
#vulva, vagina, ovary, kidney, renal pelvis, ureter, bladder, urethra
**GIST (2005-2011 cases only)*

International comparisons of incidence and survival

RARECARE reported an incidence rate of 3.8/100,000/year for STS diagnosed between 1995 and 2002 for Ireland & the UK overall[2]. However the rate for northern Europe (4.7/100,000/year) is closer to that found here (4.5/100,000/year). Note however, that differences in diagnosis years and changes in GIST coding over time complicate these comparisons.

RARECARE also reported a 5 year relative survival for all European STS of 57.8%, which is close to that found here (56.6%)[2]. Relative survival values here were similar to those reported in the European study for several subtypes, particularly STS of limbs, breast and brain & nervous system (Figure 7). Survival was poorer than the European average for Ewing sarcoma of soft tissue and uterine sarcomas in particular, but was higher than the European average for alveolar rhabdomyosarcoma, STS of pelvis and superficial trunk and GIST. RARECARE[2] commented that many GIST were previously coded as intestinal leiomyosarcomas. As GIST is identified by a specific ICDO3 code (M-8936) introduced only in 2000, European figures represent GIST coded directly as such and selected historical cases coded originally as intestinal leiomyosarcomas but reviewed and later recoded to GIST.

Figure 7. Five year relative survival in Ireland and Europe overall for all STS, the more common subtypes and GIST



Prevalence

Of all 3,327 patients diagnosed with STS during the 19 year period between 1994 and 2012, 1,545 or 46% were known to be alive on 31/12/2012. Almost 57% of all STS survivors were female and 60% of all patients had lived at least 10 years following their diagnosis (Table 5a). The majority of patients were aged between 40 and 79 at the end of 2012; 12% were aged specifically between 60 and 79 and had survived at least 10 years following their diagnosis (Table 6b). In addition, 118 patients (58 females and 60 males) with GIST were still alive at the end of 2012 representing 75% of all GIST patients diagnosed since 2005,

Over 40% of survivors diagnosed with rhabdomyosarcomas and breast STS had lived at least 10 years post diagnosis while almost 1 in 5 patients still alive after a diagnosis of peritoneal or brain & nervous system STS or Ewing sarcoma had been diagnosed within the previous year (Figure 8).

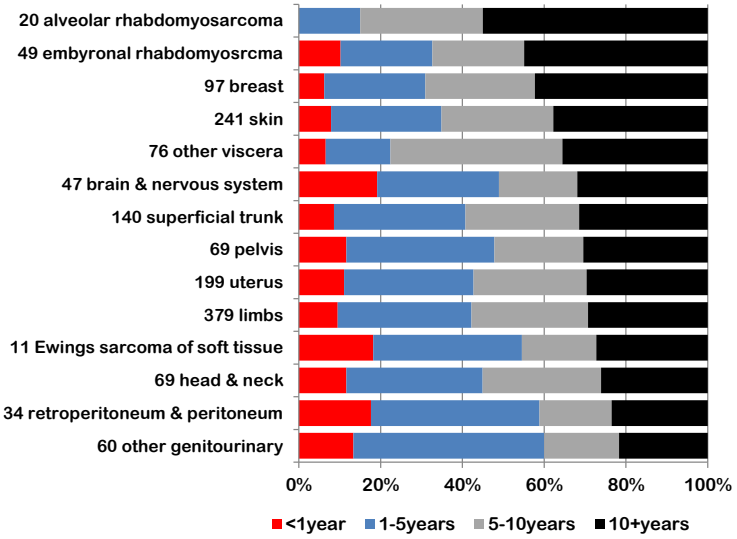
Table 5a. Number of STS patients diagnosed since 1994 and alive on 31/12/2012; by age group and time since diagnosis

	Females	Males	Total
Age at end 2012	29	30	59
0-14 years	28	43	71
15-24 years	105	88	193
40-59 years	272	204	476
60-79 years	336	229	565
80+ years	106	75	181
Time since diagnosis			
<1 year	100	61	161
1-5 years	252	217	469
5-10 years	244	174	418
10+ years	280	217	497
Total survivors	876	669	1545

Table 5b. Proportion of all STS patients diagnosed since 1994 and alive on 31/12/2012; by age group and time since diagnosis

	<1 year	1-5 years	5-10 years	10+ years	Total 19 years
Age group	1%	2%	1%	0%	**4%**
0-14 years	0%	1%	1%	2%	**5%**
15-24 years	1%	4%	3%	4%	**12%**
40-59 years	3%	10%	8%	10%	**31%**
60-79 years	4%	10%	11%	12%	**37%**
80+ years	1%	3%	3%	5%	**12%**
All ages	**10%**	**30%**	**27%**	**32%**	**100%**

Figure 8. Prevalence of the most common STS subtypes by period since diagnosis, patients diagnosed since 1994 & alive 31/12/2012



**numbers indicate number of patients alive on 31/12/2012*

References and notes

1. RARECARE. The surveillance of rare cancer in Europe. Website: http://www.rarecare.eu/rarecancers/rarecancers.asp
2. Stiller C.A et al, 2013. Descriptive epidemiology of sarcomas in Europe.: Report from the RARECARE project. Eur J Cancer. 49:684-695.
3. Rubio-Casadevall J et al 2014. Temporal trends of incidence and survival of sarcoma of digestive tract including Gastrointestinal Stromal Tumours (GIST) in two areas of the north-east of Spain in the period 1981-2005: a population-based study. Clin Transl Oncol 16(7): 660-667
4. Treatment for cases diagnosed between 2007 and 2012 only to reduce effects of any changes in treatment patterns over a longer time period.
5. National Cancer Institute 2014. Kaposi sarcoma treatment (PDQ). http://www.cancer.gov/cancertopics/pdq/treatment/kaposis/Patient
6. Cases diagnosed 1994-2011, followed up to 31/12/2012.

Appendix 1: Histological composition of some of the main (site-defined) sarcoma subtypes

(n=total number of cases diagnosed 1994-2012)