

# Hematopoietic stem cell transplantation for solid tumors in Europe

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On behalf of the Accreditation Committee of the European Group for Blood and Marrow Transplantation (EBMT) in cooperation with the Working Party on Solid Tumours (STWP) and the Working Party on Pediatric Diseases (PDWP)

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**Background:** Hematopoietic stem cell transplants (HSCT) are discussed as treatment options for patients with solid tumors. Transplant numbers have changed substantially over the last decade, few controlled studies are available and different opinions prevail. Objective information on current practice is needed.

**Patients and methods:** Data from 27 902 HSCT for solid tumors (2% allogeneic, 98% autologous), collected by the European Group for Blood and Marrow Transplantation (EBMT) activity survey from 1991 to 2002 were used to assess trends, transplant rates and coefficient of variation of transplant rates in Europe.

**Results:** Transplant numbers increased from 536 in 1991 to 4154 in 1997 and decreased to 1913 in 2002. Indications were neuroblastoma (2504 HSCT; 9%), glioma (662 HSCT; 2%), soft tissue sarcoma (1253 HSCT; 4%), germ cell cancer (3291 HSCT; 12%), breast cancer (13 524 HSCT; 48%), Ewing's sarcoma (1896 HSCT; 7%), lung cancer (387 HSCT; 1%), ovarian cancer (845 HSCT; 3%) and other solid tumors (3540 HSCT; 14%). Allogeneic cells were used in <20 cases up to 1997; since then allogeneic HSCT increased to 159 in 2002, mainly for renal cell carcinoma. Low coefficients of variation in transplant rates (<60%) are observed for Ewing's sarcoma (<56.5%), suggesting consensus for this indication.

**Conclusions:** These data give an overview on current practice of HSCT for solid tumors in Europe. They provide objective information for health-care providers and patient counselling.

**Key words:** donor type, Europe, hematopoietic stem cell transplants, solid tumors, transplant rates

## Introduction

Intensive chemotherapy supported by hematopoietic stem cell transplantation (HSCT) has been considered a useful approach for patients with chemo-radiosensitive malignancies for many years. Hematopoietic stem cells could overcome the dose-limiting marrow toxicity of more intensive regimens [1–8]. Triggered by preliminary positive, retrospective and prospective data in the early 1990s, enthusiasm has fostered HSCT as a treatment approach for breast cancer, and transplant numbers have increased massively over several years for breast cancer and other tumors alike. This trend was supported by positive prospective randomized trials in hematological malignancies with a parallel increase in transplant numbers for lymphomas and leukemias [9–13]. A change in attitude occurred in 1997. Doubts on initial reports, failures of prospective controlled studies to document an advantage of HSCT in breast cancer, and rising awareness of the need for evidence brought about this change. HSCT numbers for

breast cancer declined [14]. For other indications transplants continued, based in part on results of controlled studies, such as for neuroblastoma [15], or in the context of such studies. Definitive answers are still lacking. Optimal information is not available.

Patients and treating physicians in contrast depend on an optimum of information for treatment decisions today. Large comprehensive observational databases provide an instrument to reflect current strategies. Taking the annual European Group for Blood and Marrow Transplantation (EBMT) activity survey as a basis, we therefore present a detailed analysis of current practice of HSCT for solid tumors in Europe, including changes over time in transplant numbers and differences in transplant rates between European countries over the last 12 years. The results describe current thinking of specialist teams in Europe.

## Patients and methods

### Data collection, selection and validation

Data derived for these analyses come from the EBMT activity surveys introduced in 1990 [16]. All EBMT members and affiliated non-members receive an annual survey sheet on which they report numbers of patients by indication, stem cell source and donor type for the past year. This report includes data

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from 1991 up to and including 2002. This analysis includes solid tumors defined and classified in 1991 as neuroblastoma, glioma, soft tissue cancer, germ cell cancer, breast cancer, Ewing’s sarcoma, lung cancer, ovarian cancer and other solid tumors. Lung cancer and ovarian cancer were introduced as new variables in 1997 (Table 1). Specific information on melanoma or renal carcinoma has only been introduced in 2002.

The EBMT survey forms an integral part of a prospective quality assurance program conducted by the EBMT (<http://www.ebmt.org>). Validation of data includes returning a computer printout of entered data to the reporting teams, cross-checking with national transplant registries and onsite visits.

**Participating countries and teams**

The report is based on 636 teams from 39 European countries. The numbers have increased from 143 teams in 1990 to the current status [16]. For the 2002 report, there were responses from 586 teams. Twenty-six contacted teams chose for unknown reasons not to reply, or failed to do so, despite several efforts to reach them. No major transplant team in Europe is missing from the list. Of the 586 teams reporting HSCT in 2002, 331 (57%) do both allogeneic and autologous transplants; 230 teams (39%) restrict their activity to autologous, eight teams (1%) to allogeneic transplants only. Seventeen contacted teams (3%) did not perform transplants in 2002.

Contacted teams are listed in the Appendix in alphabetical order according to country, city and EBMT center code. This can be viewed online at [www.annonc.oujournals.org](http://www.annonc.oujournals.org). Information reached us that no blood or marrow transplants were performed in Albania, Andorra, Armenia, Azerbaijan, Bosnia-Herzegovina, Georgia, Iceland, Liechtenstein, Malta, Moldavia, Monaco, San Marino and the Vatican during this time period.

**Definitions**

*Transplants.* Transplants were defined by the EBMT (<http://www.EBMT.org>) as the infusion of hematopoetic stem cells following a conditioning regimen with the intention of replacing the existing hematopoiesis by injected stem cells. The information in this analysis is restricted to first transplants, e.g. refers to individual patients not to transplant numbers. Patients in planned double or triple transplant programs are counted only once.

*Transplant rates.* Transplant rates were defined as the number of HSCT per 10 million inhabitants. They were computed for each disease indication, donor type and country. For each disease indication, transplant rates were assessed for all HSCT and separately for autologous and allogeneic HSCT. Population data were obtained from the US Census Office (<http://www.census.gov>).

*Coefficient of variation.* Transplant rates from those countries with more than 300 HSCT in 2002 (Austria, Belgium, Czech Republic, France, Germany, Italy, The Netherlands, Poland, Spain, Sweden, Turkey and the UK) were used to calculate the coefficient of variation (CV) of transplant rates for each disease indication. It was calculated as previously defined [17] by computing mean and standard deviations as follows:  $CV (\%) = (\text{standard deviation}/\text{mean}) \times 100$ . Low CVs reflect little variation in transplant rates, high CVs high variation in transplant rates between the selected countries.

*Team density.* Team densities were defined as the number of transplant teams in participating countries per 10 million inhabitants.

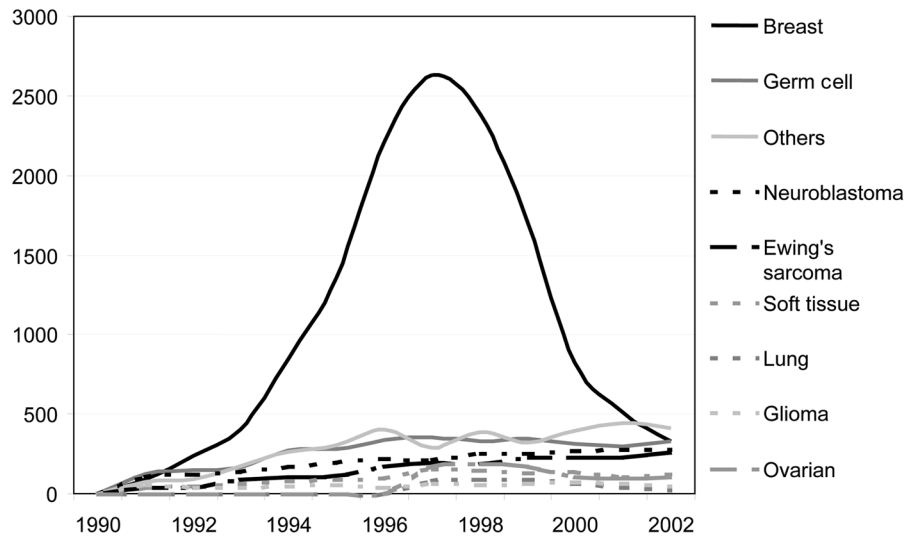
**Statistical analysis**

Mean, median and standard deviations of numerical variables were calculated on an Excel spreadsheet. Groups were compared with chi-square tests.

**Table 1. Hematological stem cell transplants for solid tumors in Europe, 1991–2002**

Year	Neuroblastoma		Glioma		Soft tissue		Germ cell		Breast cancer		Ewing’s sarcoma		Lung cancer		Ovarian cancer		Others		Total				
	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Total		
1991	102	3	56	0	41	0	120	0	94	0	41	3	44	n.a.	n.a.	n.a.	n.a.	74	2	76	528	8	536
1992	120	4	41	0	53	0	149	0	242	0	35	5	40	n.a.	n.a.	n.a.	n.a.	89	1	90	729	10	739
1993	137	4	43	0	66	1	168	0	400	1	87	0	87	n.a.	n.a.	n.a.	n.a.	168	3	171	1068	9	1077
1994	173	3	49	0	83	0	271	1	845	1	104	6	110	n.a.	n.a.	n.a.	n.a.	263	2	265	1787	13	1800
1995	196	1	55	0	85	4	283	0	1356	9	117	1	118	n.a.	n.a.	n.a.	n.a.	299	2	301	2382	17	2399
1996	215	3	43	0	101	0	335	3	2213	4	166	3	169	n.a.	n.a.	n.a.	n.a.	396	6	402	3465	19	3484
1997	206	5	67	0	160	0	349	1	2629	3	198	2	200	82	0	171	0	280	4	284	4139	15	4154
1998	250	6	55	1	149	2	331	1	2382	8	184	2	186	87	0	188	3	381	6	387	3996	29	4025
1999	251	0	62	0	131	1	348	1	1697	15	225	2	227	87	1	173	1	301	22	323	3259	43	3302
2000	265	3	76	1	136	5	307	3	824	17	223	4	227	63	0	104	7	320	73	393	2294	113	2407
2001	277	2	62	0	104	5	292	2	512	21	224	3	227	42	0	100	8	333	108	441	1917	149	2066
2002	274	4	50	1	119	7	324	2	330	14	256	5	261	25	0	109	10	291	116	407	1754	159	1913
Total	2466	38	2504	659	3	662	1228	25	1253	93	13524	1860	36	1896	386	1	845	3195	345	3540	27318	584	27902

Allo, allogeneic; auto, autologous; n.a., not available.



**Figure 1.** Numbers of hematopoietic stem cell transplants (HSCT) for solid tumors in Europe according to main disease categories from 1991 to 2002. Allogeneic and autologous HSCT combined.

## Results

### Numbers and donor type of HSCT for solid tumors from 1991 to 2002

A total of 27 902 HSCT, 27 318 (98%) autologous and 584 (2%) allogeneic, were carried out in Europe from 1991 to 2002 (Table 1). There were 2504 HSCT for neuroblastoma (9%), 662 HSCT for glioma (2%), 1253 HSCT for soft tissue sarcoma (4%), 3291 HSCT for germ cell cancer (12%), 13 524 HSCT for breast cancer (49%), 1896 HSCT for Ewing's sarcoma (7%), 387 HSCT for lung cancer (1%), 845 HSCT for ovarian cancer (3%), 3540 for 'others' (13%).

The change in numbers and absolute numbers of HSCT per year for the main disease categories is presented in Table 1 and illustrated in Figure 1. There is an increase in HSCT for neuroblastoma, glioma, soft tissue sarcoma, germ cell cancer, Ewing's sarcoma and 'other' indications. There is an increase initially followed by a decrease for breast cancer, lung cancer and ovarian cancer. Transplants increased 2.6-fold for neuroblastoma, 1.1-fold for glioma, 3.0-fold for soft tissue, 2.7-fold for germ cell, 3.5-fold for breast cancer (28-fold from 1991 to 1997), 5.9-fold for Ewing's sarcoma and 5.3-fold for 'others' from 1991 to 2002.

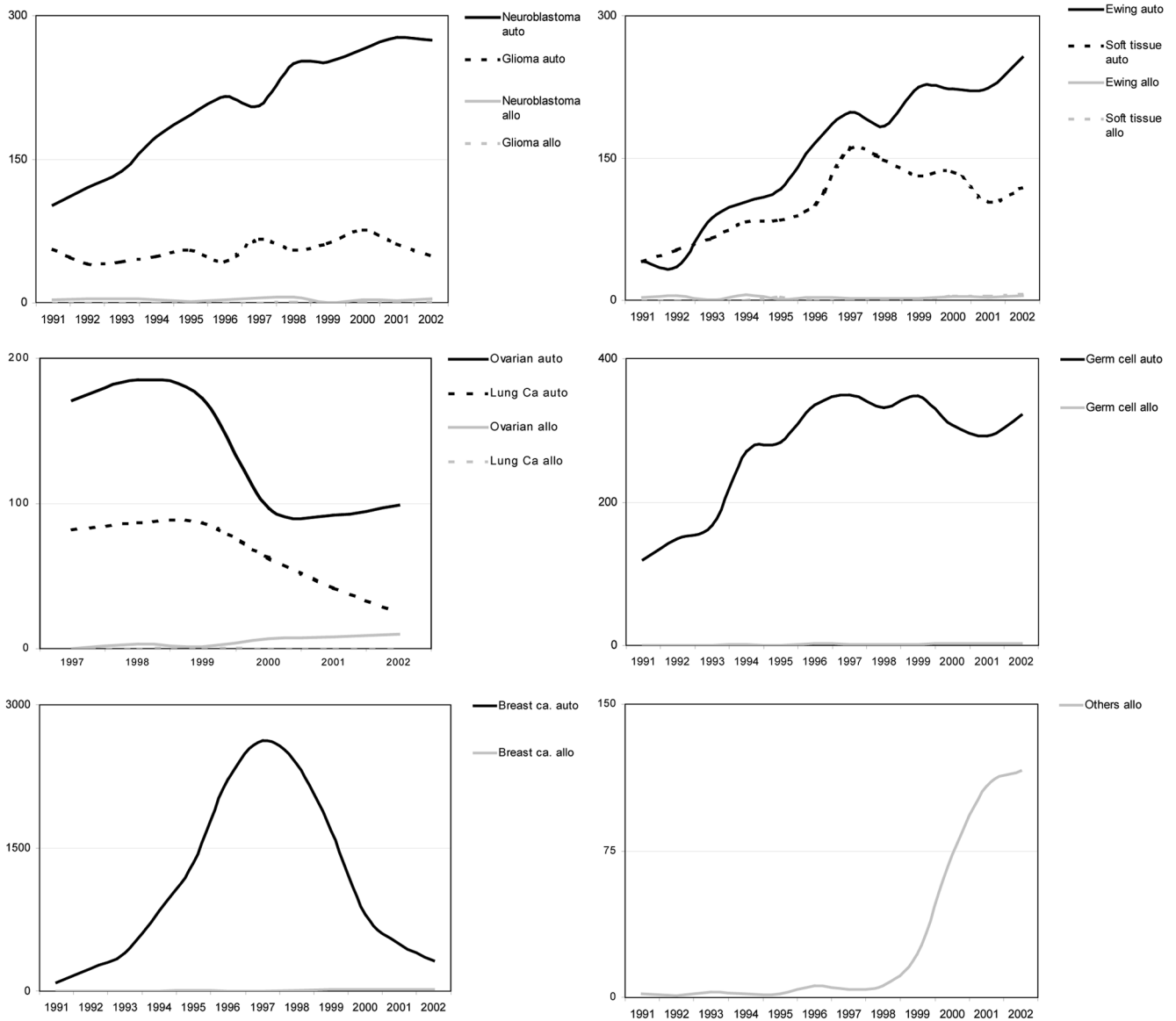
Primarily autologous HSCT were used for all indications with few allogeneic transplants, as presented in Table 1. Up to 10% allogeneic transplants were seen early in the 1990s for Ewing's sarcoma with a decline thereafter. The proportion of allogeneic HSCT is increasing again in the most recent years for soft tissue sarcoma, breast cancer, ovarian cancer and 'others', with a total 159 allogeneic HSCT in 2002. Based on this recent increase in allogeneic HSCT for solid tumors, renal cell carcinoma and melanoma were introduced as specific new variables to the activity survey in 2002.

### Trend over time

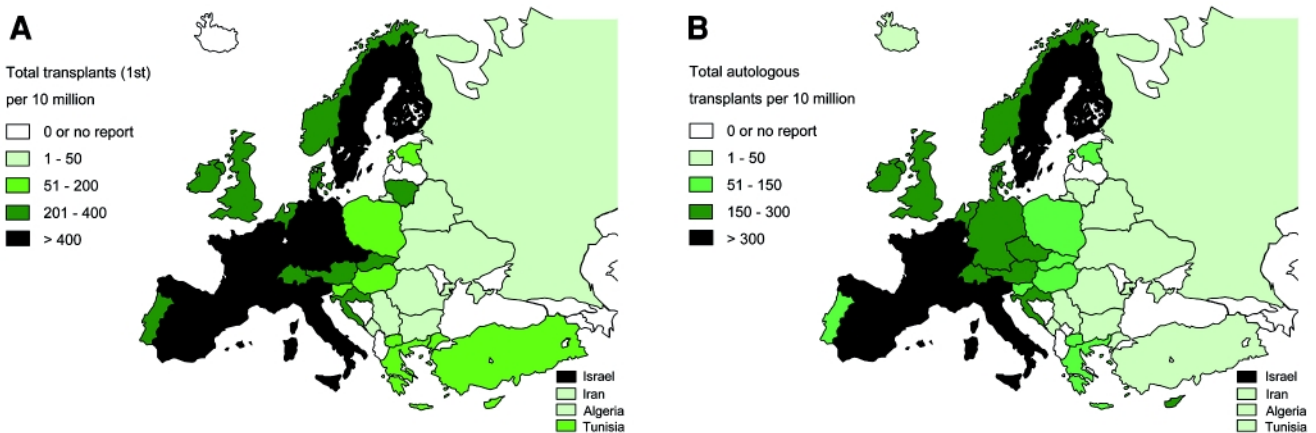
This evolution of transplant numbers over time for allogeneic and autologous HSCT is best illustrated by separation into disease subcategories (Figure 2). Different trends can be observed. There is a continuous steady increase in autologous HSCT for neuroblastoma (Figure 2A) and Ewing's sarcoma (Figure 2B). For glioma (Figure 2A), soft tissue sarcoma (Figure 2B) and germ cell tumors (Figure 2D), numbers have been stable over the observation period. This is in sharp contrast to the evolution in breast cancer (Figure 2E), ovarian (Figure 2C) and lung cancer (Figure 2C). The increase up to 1997 is followed by a sharp decrease. For allogeneic HSCT the numbers remain low in all disease indications with the exception of other disease categories (Figure 2F). A marked increase is observed over the last 3 years and is primarily due to renal cell carcinoma (80 HSCT in 2002), breast cancer (14 HSCT in 2002) and colon cancer (nine HSCT in 2002).

### Transplant rates in European countries

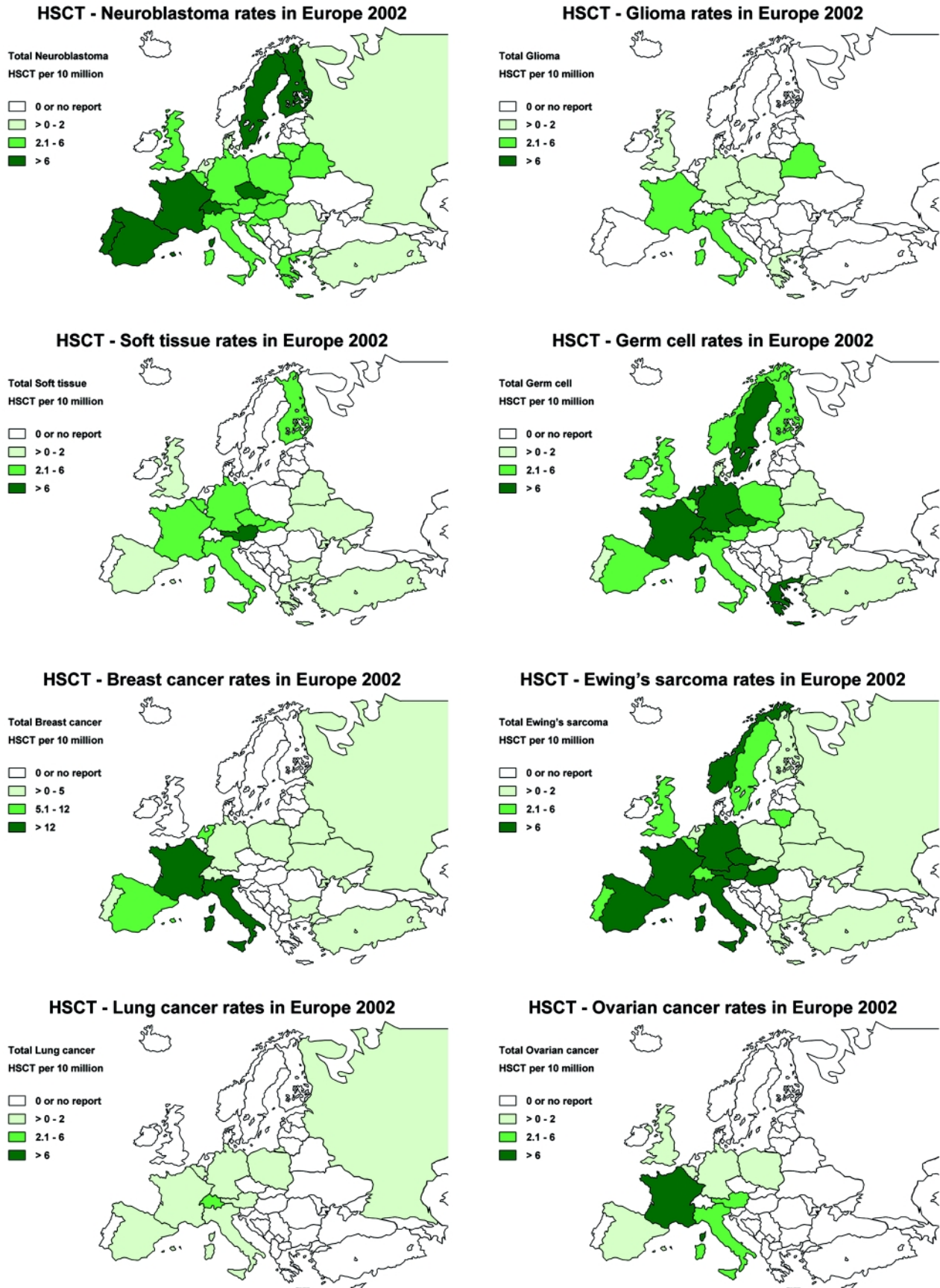
Transplant rates differed markedly between European countries, as reflected by the distribution of the total 20 207 HSCT in Europe in 2002 (Figure 3). Transplant rates for all transplants (Figure 3A), including both allogeneic and autologous HSCT, varied from 0 (several countries) to more than 400 per 10 million inhabitants (several countries). The same basic difference in transplant rates between eastern and western European countries was observed if autologous transplants only were considered (Figure 3B). In addition, there was a marked over- or under-representation for certain disease indications (Figure 4). Neuroblastoma (Figure 4A), germ cell cancer and Ewing's sarcoma (Figure 4F) were represented in similar proportions in all European countries. In contrast, some tumors, such as glioma (Figure 4B), lung cancer (Figure 4G) or ovarian cancer (Figure 4H) showed preferential distribution in



**Figure 2.** Transplant numbers for solid tumors in Europe for 1991–2002 according to disease and donor type. (A) Neuroblastoma and glioma. (B) Ewing’s sarcoma and soft tissue sarcoma. (C) Ovarian cancer and lung cancer. (D) Germ cell tumors. (E) Breast cancer. (F) ‘Other’ solid tumors.



**Figure 3.** Transplant rates in European countries, 2002. Shades reflect numbers of hematopoietic stem cell transplants (HSCT) per 10 million inhabitants. (A) All indications and all donor types. (B) Autologous HSCT.



**Figure 4.** Transplant rates for solid tumors in Europe, 2002. Shades reflect numbers of transplants for individual indications per 10 million inhabitants. Transplant rates for: (A) neuroblastoma; (B) glioma; (C) soft tissue; (D) germ cell cancer; (E) breast cancer; (F) Ewing's sarcoma; (G) lung cancer; (H) ovarian cancer.

**Table 2.** Coefficient of variation in transplant rates for solid tumors according to disease indication in Europe 2002

	Mean TR	SD	CV	Country with max. TR	Country with min. TR
Ewing	4.8	2.7	56.5	Italy (9.7)	Turkey (0.4)
Neuroblastoma	5.1	3.2	62.9	Sweden (10.1)	Turkey (0.1)
Germinal cancer	5.9	4.0	68.1	Germany (16.3)	Turkey (1.0)
Soft tissue	2.6	2.7	103.6	Austria (8.5)	NL, PL, S (0)
Glioma	0.8	0.9	111.2	France (2.2)	B, NL E, S, T (0)
Lung cancer	0.5	0.6	127.2	Italy (1.6)	CZ, NL, S, T, UK (0)
Ovarian cancer	1.8	2.8	152.4	France (9.3)	CZ, NL, S, T (0)
Breast cancer	5.1	8.5	166.4	Italy (25.6)	A, B, CZ, S, UK (0)

Twelve countries with >300 HSCT in 2002 (A, B, CZ, F, G, I, NL, PL, Sp, Sw, T, UK).

A, Austria; B, Belgium; CV, coefficient of variation; CZ, Czech Republic; F, France; G, Germany; I, Italy; NL, The Netherlands; PL, Poland; SD, standard deviation; E, Spain; S, Sweden; T, Turkey;

TR, transplant rate (see text for definitions).

selected countries, e.g. France for ovarian cancer or Switzerland for lung cancer.

### Coefficient of variation

These visual differences in transplant rates for the individual disease indications were quantified by the coefficient of variation. In order to adjust for the economic impact, this analysis was restricted to 12 countries with >300 HSCT in 2002 (Table 2). They performed a total 17 237 HSCT (all indications) in 2002 with total transplant rates from 62 (Turkey) to 578 (Italy) (median 534 transplants per 10 million inhabitants). Solid tumor transplant rates differed substantially with numbers for neuroblastoma from 0.1 (Turkey) to 10.1 (Sweden) (median 5.5 per 10 million inhabitants), for glioma from 0 (several countries) to 2.2 (France) (median 0.4 per 10 million inhabitants), for soft tissue from 0 (several countries) to 8.5 (Austria) (median 2.3 per 10 million inhabitants), germ cell cancer from 1.0 (Turkey) to 16.3 (Germany) (median 4.5 per 10 million inhabitants), breast cancer from 0 (several countries) to 25.6 (Italy) (0.6 median per 10 million inhabitants), Ewing's sarcoma from 0.4 (Turkey) to 9.7 (Italy) (median 5.3 per 10 million inhabitants), lung cancer from 0 (several countries) to 1.6 (Italy) (median 0.2 per 10 million inhabitants), ovarian cancer from 0 (several countries) to 9.3 (France) (median 0.7 per 10 million inhabitants), 'other' solid tumors from 1.8 (Turkey) to 22.6 (Italy) (median 7.9 per 10 million inhabitants).

This variation of transplant rates, as exemplified by the CV, is listed in detail for all disease indications in Table 2. Variation is lowest for Ewing's sarcoma (56.5) and neuroblastoma (62.9) and is highest for breast cancer (166.4) and ovarian cancer (152.4). It permits classification of disease into categories with high consensus (CV <60%), intermediate consensus (CV 55–100%) and low consensus (CV >100%) among the specialist teams concerning indications for HSCT. By using this approach, neuroblastoma and Ewing's sarcoma could be considered as accepted indications for

autologous HSCT. All other indications cannot be regarded as established indications for HSCT.

### Discussion

These data reflect current practice of HSCT for solid tumors in Europe today, point to the changes in transplant rates over the last decade and illustrate similarities and discrepancies between European countries. They illustrate the continuing increase for some disease categories, stable situations for others, as well as increase and decrease for indications, such as breast cancer, lung cancer and germ cell tumors. In general these trends reflect the prevailing considerations of transplant physicians and specialists in the field concerning the advantage or disadvantage of HSCT: they point to consensus on the advantage of HSCT or the need for prospective studies. Stable low numbers reflect the experimental status of the procedure and decreasing numbers the advent of alternative therapies or a disadvantage of HSCT. In this context, it is comforting to see that low CVs of  $\leq 75\%$  coincide also with those indications where prospective randomized studies have indicated a clear advantage, i.e. neuroblastoma or Ewing's sarcoma [15, 18–20].

Other interpretations for high CVs are possible, as illustrated by the difference in transplant rates for indications, such as lung cancer or glioma. These differences reflect the impact of the presence or absence of ongoing active study protocols by the respective national or regional study groups [21, 22]. As such, a lower transplant rate might reflect the absence and a higher transplant rate the presence of a specific national study group protocol. Little or no information exists with regard to these aspects.

There are several reasons for current trends in Europe regarding autologous HSCT in solid tumors. The scenario of breast cancer deserves some specific comments or suggestions: in the early and mid-1990s impressive data from phase II trials as well as from registries accelerated the growth in number of autotransplants for this disease [1]. When the first results from phase III studies became available, a wave of pessimism began to appear and the number of patients undergoing high-dose chemotherapy began to

drop [2–4, 14]. Most recent results remain ambiguous and the value of HSCT in breast cancer still needs to be determined in selected categories. HSCT might be an effective tool in the treatment of solid tumors in some subsets of patients [23–25].

Ninety-eight per cent of all HSCT were autologous transplants. A few allogeneic HSCT were performed in the early 1990s but then largely abandoned. Transplant-related mortality was considered to be too high despite some documented graft-versus-tumor effects. Interest was renewed with the introduction of reduced intensity conditioning transplants and the first successful reports in solid tumors [26–30]. Concepts of allogeneic HSCT for solid tumors do not rely on high-dose chemotherapy and tumor load reduction but rather on a graft-versus-tumor effect [26]. New categories of solid tumors, i.e. immunosensitive malignancies, became a target of such therapies. Focus in 1990, at the time of introduction of the EBMT activity survey, was on chemo-sensitive malignancies; hence, typically immunosensitive malignancies, such as melanoma or renal cell carcinoma, were not reported in detail but summarized as ‘others’. This has now been changed with the introduction of renal cell carcinoma, melanoma and colon cancer as subentities in the survey.

Comprehensive surveys like the EBMT survey, reaching >95% of activity in the field, can provide an objective analysis of current practice [9]. By restriction to transplants, not outcome, rapid data collection can be attained on a broad basis. Only prospective randomized studies can provide evidence on outcome differences. Prospective randomized studies, however, take time. Additional years are required for data analysis and for the generation of sufficient observation time. This is specifically necessary if early events, e.g. transplant-related mortality, are offset later on by reduced relapse rate. Teams and experts in the field might change their procedure before results are known. In these situations, the EBMT activity survey has already become a standard instrument to assess transplant rates and differences between European countries. With the variation in transplant rates, difference in opinions between transplant specialists can be quantified. Data in 2002 suggest there is consensus on autologous HSCT as an indication for Ewing’s sarcoma and near consensus on neuroblastoma and germinal cancer in Europe.

This present analysis does not give any data on outcome. This information is gathered elsewhere and published separately. This survey concentrates on rapid description of the current *status quo*. It reflects current practice of HSCT for solid tumors in Europe, gives information on consensus or dissension among specialists in the field and provides an objective basis for patient counselling and health-care planning.

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