Chapter 17
The Burden of Rare Cancers in Europe

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Abstract The burden of rare tumors in Europe is still unknown and no generally accepted definition of them exist. The Surveillance of Rare Cancers in Europe project (funded by the European Commission) aimed at providing a definition of "rare cancer", a list of cancers and rare cancer burden indicators, based on population-based cancer registry data, across Europe. An international consensus group agreed that incidence is the most appropriate indicator for measuring rare cancers frequency and set the threshold for rarity at 6/100,000/year. The list of rare cancers was based on the International Classification of Diseases for Oncology (ICD-O 3rd edition) and it was hierarchically structured in 2 layers based on various combinations of ICD-O morphology and topography codes: layer (1) families of tumors (relevant for the health care organisation) and layer (2) tumors clinically meaningful (relevant for clinical decision making and research). The burden indicators were estimated and are provided in this chapter.

Keywords Rare tumor · Population based cancer registry · Incidence · Prevalence · Survival

17.1 Introduction

According to the European Union (EU) definition, cancers are classified in the group of rare diseases when their prevalence in the general population is less than 50 out of 100,000 persons [4]. Patients with rare cancers are faced with the same challenges as other patients living with a rare disease just because their condition is rare. Rare cancers are often misunderstood, misdiagnosed, or poorly investigated, and there are usually few treatment options [17].

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Rare cancers are a challenge to clinical practice. Delay in diagnosis and suboptimal treatment outcomes are common for rare cancers due to a lack of knowledge among physicians and pathologists, a limited expertise in the management of rare cancers (also because of the limited number of cases), a poor referral rates from general practitioners and pathologic misdiagnosis. Outcomes for rare cancers could be improved through the establishment of reference networks however, few networks or centers of expertise exist across the EU and funding is not available to cover the increased costs associated with the organization of these networks [6].

Exchange of experience, information and data on rare cancers is low. Information about rare cancers, their treatment options and where to obtain appropriate treatment is in many cases not readily available to patients.

Clinical studies are more difficult to conduct in rare cancers due to the low number of patients. This makes it difficult to demonstrate the effectiveness of different therapeutic options and build a comprehensive evidence-base for practice. For many rare cancers, research is confined to case reports or small retrospective series, for which substantial selection bias occurs and total experience is commonly too limited for any firm conclusions on management to be made. Therefore, medicines have to be often used off label.

Population-based survival study [10] reports large variations in survival over time and across Europe, with poorer outcome among older patients and in eastern European countries.

In spite of these problems, substantial advances in the treatment of some rare cancers have occurred in the recent past. Childhood lymphatic leukaemia was practically invariably fatal until the years 1970s, while nowadays has a cure proportion of 80% or more [8]. For adult cancers, gastrointestinal stromal sarcomas have increased their survival rate from 30 to 75% [16]; anal squamous-cell carcinoma have improved outcome in the 1980s thanks to the introduction of fluorouracil and radiotherapy in the protocol of treatment [15].

Since the EU Orphan Drug Regulation [5] entered into force, 20 of the 46 medical products that have been designated as orphan drugs have received marketing authorisation for a rare cancer indication [6].

These results are due to international efforts aimed at strengthening scientific excellence in research and treatment, promoting incentives for research and development of orphan drugs, clinical trials and collaboration in the field of rare cancers.

The European LeukemiaNet (http://www.leukemia-net.org) and the Scandinavian Sarcoma Group (http://www.ssg-org.net/), are good examples of the benefits of such efforts and networks in the field of rare tumors. The LeukemiaNet integrates the leading leukemia trial groups (CML, AML, ALL, CLL, MDS, CMPD), their interdisciplinary partners (diagnostics, treatment research, registry, guidelines), industry and Small and Medium Enterprises (SME) across Europe to form a cooperative network for advancements in leukemia related research and health care. It cares for some ten thousand patients. The Scandinavian Sarcoma Group (SSG) was formed in 1979 by physicians and scientists from the Scandinavian countries with a primary interest in tumors of connective tissues. The goal of the SSG is to advance the care

of patients with sarcoma and to increase knowledge of all aspects of the biology of these tumors, including basic and clinical research. The SSG has developed treatment protocols for different sarcoma types and participates in international clinical trials.

These networks, as many others, provide good examples of what works for rare cancers:

1. integration of local, national and European centres of expertise into European reference networks in order to provide the necessary *organisational structures for clinical research*, *early transfer of research data into clinical practice* and *clinical management of rare cancers*;
2. exchange of experience, information, data and best practices;
3. development of consensus guidelines on multi-disciplinary treatment;
4. engagement of all stakeholders including representatives of patients.

In this context, to start addressing rare cancers challenges, it is essential to have a clear picture of which are the rare tumors as well as to have information on their frequency and outcome figures. Considering that the burden of rare tumors in Europe is still unknown and no generally accepted definition of them exist, the aims of this chapter are:

1. to provide a definition and a list of rare tumors;
2. to estimate the indicators of rare tumors in Europe: incidence, prevalence, survival. Estimates will be provided for rare malignant tumors diagnosed during the period 1995–2002.

17.2 Criterion for Defining Rare Tumors

According to the official EU definition, rare tumors are identified in the same way as rare diseases, i.e. as those conditions whose prevalence is lower than 50/100,000.

However, prevalence has shortcomings as a measure for rarity for tumors, although we acknowledge its appropriateness for non-neoplastic diseases. Many of these are chronic conditions, so prevalence, which reflects the total number of cases at any given time in a population truly renders the burden that a disease poses at a population level. On the contrary, tumors are subacute diseases in which everything tends to happen once. In the natural history of a tumor, there will be one potentially eradicating surgery, one local radiation therapy, one first chemotherapy and each of these will take place in a definite time intervals. Thus, the total amount of resources that tumors mobilize are proportional to the yearly rate of new diagnoses (incidence) and not to the total amount of persons with previous cancer diagnosis (prevalence), some of them been cured. Incidence, which reflects the yearly number of new cases occurring in a population might thus be a better indicator to describe the burden posed by a tumor.

The prevalence of a disease depends on two time-dependent characteristics which are independent of one another: incidence and survival. With the prevalence threshold adopted as a definition, some commonly-occurring diseases for which the survival is very poor, such as most cancers of stomach, pancreas, lung will be defined as rare since the proportion of the general population who are survivors is very low. By contrast, some neoplasms that occur very infrequently ("rare" in the sense of incidence) but which have very good survival, such as cancer of testis, will be defined as common on the basis of prevalence, because although they occur infrequently, most people who develop the disease survive for long periods.

For these reasons, incidence seems to be a more useful indicator to select a threshold for rarity in the case of tumors, as opposed to non-neoplastic diseases. In addition it is worth stressing that:

- the incidence of tumors tends to change in a more predictable manner than prevalence and it is more closely connected to the cause of the diseases;
- the incidence is a direct measure of the burden imposed by the need for the first line cancer treatment;
- the number of patients amenable to enter a clinical study is reflected by cancer incidence.

It should be clear, however, that the conventional definition of rare diseases has regulatory implications, including those on orphan drugs. In addition, evolution of therapies may well affect the definition of rare cancers in the future. For example, if oncologists will manage to deliver anticancer therapies in a chronic way, overcoming the currently limiting factor of tumor resistance, prevalence would become a much more useful indicator of frequency. At the moment, this is not the case, although an evolution towards more chronic anti-cancer therapies is in place. Thus, in this chapter, we will consider incidence as the frequency indicator of tumors' rarity.

17.3 List of Rare Cancers

Usually, cancer statistics are provided for broad cancer categories, based on the anatomic site of the malignancies as defined by the International Classification of Diseases (ICD) codes. Rare tumor entities, because of their specific problems related to the health care organisation and to the clinical management, might be more appropriately defined as a combination of topographical and morphological characteristics, as defined by the International Classification of Diseases for Oncology (ICD-O) [13].

The ICD-O list of tumor entities have a pathologic basis however, to have a clinical meaning the tumor entities have to be grouped. This grouping exercise, necessary to identify a list of clinically relevant rare tumor entities, was carried out in the framework of the EU funded project Surveillance of Rare Cancers in

Europe (RARECARE) by an international group of experts, including oncologists (European Society for Medical Oncology – http://www.esmo.org/), epidemiologists, pathologists and organizations of patients (European Cancer Patient Coalition – http://www.ecpc-online.org/). The group had the possibility to estimate incidence and prevalence for different combination of tumor entities from the RARECARE project database including data from all the European CRs participating to the project. The group of experts met three times drawing a provisional list of rare tumors, that was subsequently validated with the engagement of local and international experts by e-mail exchanges and through the project web site. The complete list of rare cancers, including the topography and morphology codes that define the entities, is available on the RARECARE project website (www.rarecare.eu).

17.3.1 The Structure of the Rare Cancers List

A rare tumor will be problematic per se, i.e. due to its low frequency, under the perspective of clinical decision-making and the perspective of the health care organization.

Clinical decision-making is more problematic in the case of a rare tumor because clinical studies on that tumor are more difficult to carry out so the quality of available evidence tends to be limited. Under this perspective, a liposarcoma or a bronchioloalveolar lung carcinoma are similar because the feasibility of clinical studies on both conditions is equally affected by their low frequency.

Also the *organization of health care* is more problematic in the case of a rare tumor because the direct clinical expertise of any oncologist will be limited in comparison to the one that they have on common cancers so some kind of centralized patient referral needs to be implemented (towards centres or networks of excellence). Under this perspective a liposarcoma and a bronchioloalveolar lung carcinoma are not alike because the former belongs to a family of tumors which are rare as such, while the latter is a lung tumor i.e. it belongs to a family of common tumors. Any community oncologist deals everyday with lung tumors and will be aware of bronchioloalveolar carcinoma while this will not be the case for any sarcoma. In fact, centralized patient referral is generally recommended for sarcomas but not for lung tumors. A bronchioloalveolar carcinoma will be rare under the clinical decision-making but not the health care organization perspective while any sarcoma will be rare under both perspectives.

In order to respond to these issues, the list of rare tumours was hierarchically structured in two layers based on various combinations of ICD-O morphology and topography codes. The *first layer* denotes the main families of tumors identified according to a consensus-based clinical perspective. This partitioning should be mainly useful for patient referral purposes i.e. it is relevant under the health care organization perspective. A family of tumors generally finds its own referral pattern.

The *second layer* denotes tumors relevant from the clinical, mainly the therapeutic, decision-making perspective (ICD-O coded entities have been grouped on the basis of their similar clinical management). This partitioning should be

mainly useful for clinical purposes, e.g. for clinical studies, etc. The two layers simply group the ICD-O codes in a clinically sound fashion at a different level of depth. Under the clinical decision-making perspective, tumors partitioning have to be as detailed as required by the diversity of treatments. Under the health care organization perspective, the level of detail may be lower.

17.3.2 First Layer: Families of Cancers Relevant for the Health Care Organization

The first criterion for grouping tumor entities was the referral pattern. According a list of the major tumors families useful for patient referral purposes was developed by the international experts involved. Thus, entities included in the first layer of the list are those relevant under the health care organization perspective (Table 17.1). As a first step, the two large groups of epithelial and not epithelial tumors were disentangled and, within them, broad anatomic categories were identified. The long list of the epithelial group of tumors, that are usually treated by different oncology specialists, is closely related to the organization of health care. For instance the epithelial tumors of nasal cavity and sinuses, of nasopharynx, of major salivary glands, of hypopharynx and larynx, of orpharynx and of oral cavity and lip are treated by the head and neck oncologists even if they have different prognosis and will need different medical and surgical approaches. Similar considerations are suitable also for tumors of the digestive organs, tumors of the respiratory system and intra-thoracic organs, female/male genital organs, urinary tract, hematologic malignancies, and so on. In all these cases, the expertise is defined by the anatomical group of sites and the treatment will be more or less centralized depending on the rarity of tumors.

Table 17.1 Crude annual incidence rates, 5-year relative prevalence proportion and survival by first layer of malignant tumor entity

Crude incidence rate × 100,000	Tumor entity	5-year relative survival (%)	15-year prevalence × 100,000
>50	Epithelial tum of breast	81	594
	Epithelial tum of lung	11	85
>20–50	Epithelial tum of skin	98	474
	Epithelial tum of prostate	75	474
	Epithelial tum of colon	53	233
	Lymphoid malignant diseases	55	172
	Epithelial tum of bladder	66	133
>10–20	Epithelial tum of stomach	22	46
	Epithelial tum of rectum	53	102
	Malignant skin melanoma	84	135
	Epithelial tum of pancreas	4	8
	Epithelial tum of kidney	57	65

Table 17.1 (continued)

Crude incidence rate × 100,000	Tumor entity	5-year relative survival (%)	15-year prevalence × 100,000
>10–20	Epithelial tum of corpus uteri	80	100
>7–10	Epithelial tum of ovary and fallopian tube	38	48
	Epithelial tum of esophagus	11	8
≥6–7	Epithelial tum of hypopharynx and larynx	55	36
	Epithelial tum of liver and intrahepatic bile tract (IBT)	6	9
	Epithelial tum of cervix uteri	67	58
≥5–6	Glial tum of Central Nervous System (CNS) and pineal gland	20	15
≥4–5	Epithelial tum of oral cavity and lip	59	29
	Soft tissue sarcoma	56	43
	Epithelial tum of gallbladder and extrahepatic biliary duct	13	7
	Carcinoma of endocrine organs	85	41
≥2–4	Acute myeloid leukemia and related precursor neoplasms	20	8
	Tum of testis and paratestis	95	43
	Myeloproliferative neoplasms	60	29
	Epithelial tum of oropharynx	37	12
	Neuro endocrine tumors	51	19
≥1–2	Epithelial tum of vulva and vagina	61	13
	Malignant mesothelioma	6	3
	Epithelial tum of pelvis urether and urethra	54	10
	Myelodisplastic syndrome	37	4
	Epithelial tum of major sal glands and sal gland type tum	65	10
	Epithelial tum of anal canal	56	7
<1	Bone sarcoma	61	6
	Epithelial tum of small intestine	25	2
	Malignant melanoma of uvea	73	5
	Epithelial tum of penis	72	5
	Malignant melanoma of mucosa	30	2
	Epithelial tum of nasopharynx	49	2
	Mixed epithelial and mesenchymal tum of uterus	38	?
<1	Epithelial tum of nasal cavity and sinuses	48	2
	Non epithelial tum of ovary	63	3

Table 17.1 (continued)

Crude incidence rate × 100,000	Tumor entity	5-year relative survival (%)	15-year prevalence × 100,000
	Kaposi sarcoma	64	2
	Extragonadic embryonal neoplasms	77	4
	Myelodisplastic myeloproliferat diseases	23	1
	Adnexal carcinoma of skin	87	3
	Non glial tum of CNS and pineal gland	53	2
	Epithelial tum of thymus	57	1
	Epithelial tum of eye and adnexa	80	1
	Malignant meningiomas	62	1
	Epithelial tum of trachea	12	< 1
	Extragonadal germ cell tum	69	2
	Non-glial tum of nerves, autonomic nervous system and paraganglia	64	2
	Gastrointestinal stromal sarcoma	71	< 1
	Histiocytic and dendritic cell neoplasms	72	< 1
	Epithelial tum of middle ear	42	< 1
	Trophoblastic tum of placenta	90	< 1
	Glial tum of nerves, autonomic nervous system and paraganglia	87	< 1

Tum = Tumor; Sal = Salivary.

17.3.3 Second Layer: Cancer Entities Relevant for Clinical Decision Making and Research

Within each of the first layer entities, a set of second layer entities was defined according to their relevance from the clinical (basically the therapeutic) decision-making perspective. For instance among the epithelial tumors of the oesophagus, which may be considered a relatively common tumor, few entities (see Table 17.2) can be identified with different natural history and different therapeutic approaches. These are: the squamous cell carcinomas, the adenocarcinomas, the salivary gland type tumor and the undifferentiated carcinoma.

Under the clinical decision making perspective, all the epithelial tumors of the oesophagus are rare. For all of them, effective curative treatment does not exist also because the majority of patients get a diagnosis when the disease is already at an advanced stage. The surgical ablation is indicated for localised lesion. Radiotherapy, as well as multi-chemotherapy, have been proposed alone or in combination with surgery. Prognostic factors include stage at diagnosis, patient's general health, morphological and molecular feature of the tumor. For squamous cell carcinoma

Table 17.2 Crude annual incidence rates, 5-years relative survival prevalence proportion and for three groups of tumor entities

Layer	Tumor entity	Crude incidence rate × 100,000	5-year relative survival (%)	15-year prevalence × 100,000
1	Epithelial tumors of oesophagus	7.49	10.65	11.1
2	Squamous cell carcinoma and variants of oesophagus	3.39	10.67	4.9
2	Adenocarcinoma and variants of oesophagus	2.83	11.74	5.2
2	Salivary gland type tumors of oesophagus	0.01	9.56	0.01
2	Undifferentiated carcinoma of oesophagus	0.07	7.28	0.07
1	Epithelial tumors of liver and intrahepatic bile tract (IBT)	6.28	8.8	5.5
2	Hepatocellular carcinoma of liver and IBT	3.1	11.7	3.5
2	Cholangiocarcinoma of IBT	0.83	5.5	0.7
2	Adenocarcinoma and variants of liver and IBT	0.21	5.4	0.2
2	Undifferentiated carcinoma of liver and IBT	0.02	3.6	0.01
2	Squamous cell carcinoma and variants of liver and IBT	0.01	9.6	0.01
2	Bile duct cystadenocarcinoma of IBT	0.00	12.1	0.00
1	Epithelial tumors of cervix uteri	6.07	66.6	58.9
2	Squamous cell carcinoma and variants of cervix uteri	4.28	67.3	41.9
2	Adenocarcinoma and variants of cervix uteri	1.01	66.7	9.0
2	Undifferentiated carcinoma of cervix uteri	0.03	34.1	0.2

the depth of invasion and for adenocarcinoma the presence of lymphatic metastasis should also be considered. Clinical trials should be conducted taking into account the different histotypes [12, 14].

17.3.4 Limitations and Advantages of the Proposed Cancer Entities Grouping

The list of entities described in this chapter is based on tumor entities classified using topography and morphology. We are aware that this is just a subset of many

other possible features that contribute to the clinical presentation of a clinical case. In addition to being affected by a given tumor, a patient will have a specific stage of the disease, which, along with his/her sex, age, genetic patrimony, and several other factors (including concurrent diseases), will eventually determine treatment. In the era of molecular targeted therapies, the molecular profile will be relevant as well. We can foresee that disease entities will be increasingly defined on the basis of other features in addition to conventional pathologic aspects. It follows that many different clinical presentations may tend to become rare even when the tumor is common, simply because the number of characteristics which define the case will be high.

The choice of basing the definition of rare tumor only on topography and morphology was made for two reasons. The first reason is *to follow existing tumor classifications*. Any list of rare tumors will always be a subset of a standard list of tumors. International agencies preside over such classifications, constantly updating them, and genetic and molecular profile is more and more relevant to tumor partitioning in such classifications. This list of rare tumors is based on the ICD-O (3rd edition) classification [13] because this is the worldwide recognized classification of tumors. The second reason is *data availability*. Cancer registry data, the only data available to calculate population-based incidence and prevalence indicators, refer to cases classified only according to ICD-O. Other, even attractive, classification criteria such as biomarkers or gene expression cannot be used for any quantitative description of cancer burden.

17.4 Definition of the Cutpoint

Clinically defined cancer entities are classified as rare if their frequency falls below a given threshold level. As discussed in the previous paragraph, there is unanimous agreement among oncology specialists and epidemiologists that the most appropriate frequency measure for cancer is the crude incidence rate in the general population. The definition of an incidence threshold value, under which a given entity should be considered as rare is necessary arbitrary. However, several practical and important decisions depend on the threshold or cut point value. From the point of view of the health care organization, the management of rare cancers is different from the one of common tumors since rare entities should have a centralized treatment. From the research perspective, innovative clinical study designs should be considered when well-powered randomised trials are not feasible due to the low incidence. In addition, according to the EU Directive on orphan drugs [5], specific incentives are available to promote research and development of rare cancers.

Therefore, the choice of an appropriate cut point has been accurately considered on the basis of several issues. A brief description of the main issues considered follow.

17.4.1 How Many Cancer Diagnoses Refer to Rare Cancers?

In order to be of practical use, the concept of rare cancer cannot include the majority, or even a large proportion, of all cancers. In a setting of limited resources, provision of incentives for the study and management of a subset of cancers is as more effective as more precisely targeted and smaller is the number of affected patients. Using the RARECARE database (see paragraph 17.5), Fig. 17.1 provides the proportion or rare cancer patients over all cancer patients that would be selected as a function of the incidence cut point. For instance, an incidence cut point of 1 × 100,000 per year would select a subset of cancer entities affecting about 5.5% of all cancer patients. With a cut point of 10 × 100,000 per year, a wider set of entities would be classified as rare, corresponding to a proportion of 27% of all cancer diagnoses. A well chosen cut point should provide a balance between being too selective (i.e. less that 10% of patients) and too inclusive (more than 30% of patients). This balance could be provided choosing an incidence threshold between 3 and 12 × 100,000.

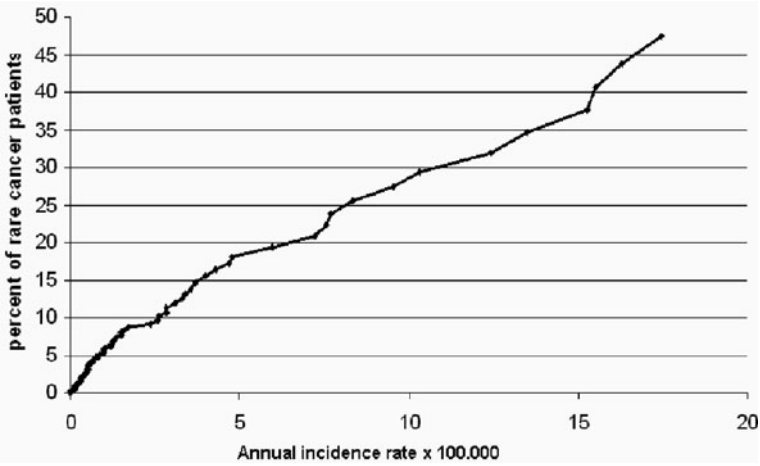

Fig. 17.1 Percent of cancer patients diagnosed with rare cancers, according to the definition of rarity

17.4.2 Does Rarity Affects the Possibility to Carry Out Effective Research?

Randomised clinical trial (RCT) is the standard study design required for research on new treatments. The number of patients included in the study, and the related statistical power, is one of the crucial characteristic for a good trial. The possibility to enrol a high proportion of all the incident cases is therefore of major importance to decide on the feasibility of a clinical trial. Unfortunately, with the exception of childhood cancers, it is usually very difficult to enrol more than 10% of the eligible patients in a given population. If the treatment under study regards a rare cancer, a

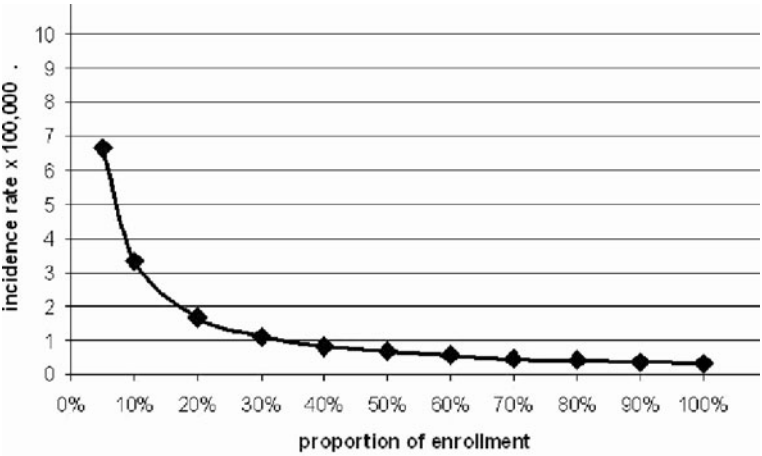

Fig. 17.2 Annual incidence rate necessary to recruit at least 500 patients in 3 years in a 50 million country

single hospital would take too much time to enrol a sufficient number of patients to ensure the required statistical power, and multicentre studies have to be planned. These are generally more difficult than single-centered studies, since common protocols for treatment and data collection and analysis have to be previously agreed on. This process is even more difficult for large multinational studies, because legal constrains arise on the circulation of data and biological material. The possibility to carry out a RCT for a given cancer, with enrolment of 500 patients in three years within a large country of 50 million inhabitants has therefore been considered to support the discussion on the decision of the cut point value.

In Fig. 17.2, the minimum incidence level required to make possible such a study was plotted against the expected proportion of enrolment. With incidence of 1 × 100,000 per year, an enrolment proportion of 33% should be reached in order to carry out the study. With an incidence below 6 × 100,000, a proportion of at least 5% would be necessary. Cancers with incidence greater than 10 × 100,000 do not create particular problems under this point of view. This criterion suggest an incidence cut point ranging between 3 and 6 × 100,000.

17.4.3 Is Clinical Decision Making More Difficult?

Assessing in an objective way the minimum rate of new diagnoses necessary to reach a sufficient experience in the clinical management of patients is difficult since it depends, among others, on the complexity of the disease and of the treatment and on the individual response variability. On the basis of the developed list of cancer entities the experts of the RARECARE group have systematically discussed their experience and their perception of the problems in the clinical management of

the various entities. This analysis has been particularly addressed to cancers with incidence rate between 3 and 10 × 100,000.

In conclusion, *an incidence cut point of 6 × 100,000 has been identified as the appropriate value to define rare cancers or a group of rare cancers*. This means (Fig. 17.1) to consider as rare about 20% of all cancers that arise in the general population. Almost all cancers defined as rare on the basis of the incidence based criterion are rare also according to the European prevalence-based definition of rare disease. Five cancers: poorly differentiated endocrine carcinoma of lung, adenocarcinomas of lung, squamous cell carcinomas of lung, adenocarcinomas of stomach and pancreatic adenocarcinoma are classified as common (according to their incidence) while, due to their low survival have a prevalence rate below 50 per 100,000.

17.5 Assessing Rare Cancers Burden

Information and health care statistics for cancer are better than for most other diseases, both because there is a long history of epidemiological studies and because population-based cancer registries (CRs) have provided an invaluable source of information for decades. Epidemiologic indicators of frequency such as incidence, prevalence and mortality, and indicators of outcome like relative survival are all available from population-based cancer registries and disseminated by the scientific literature, web sites and electronic tools. Incidence and survival figures based on CRs data are routinely available in the Cancer Incidence in Five Continents (CI5C) published by the International Agency for Research on Cancer (IARC http://www.iarc.fr) and through the EUROCARE (Survival of Cancer Patients in Europe) project monographs. Survival for the European patients has been provided by the EUROCARE project (http://www.eurocare.it/) since 1995. Prevalence was estimated by the Globocan software [9] to which contributed also the EUROPREVAL project [2]. However, all these projects describe the burden of broad cancer categories defined on the basis of anatomic site of the malignancy as defined by the ICD-O codes for topography [13]. On the contrary, specific objective of the RARECARE project is to provide basic epidemiologic indicators for rare cancers based on morphology and topography. This project, based on the data collected from 90 CRs in 21 European countries, gives a unique opportunity to study the epidemiology of rare tumors in a large population from various countries. RARECARE gathered CRs data on patients diagnosed from 1978 up to 2002, with vital status information available up to 31st December 2003 or later. To our knowledge, no similar large-scale analyses of rare tumours have been reported. A systematic presentation of rare cancer indicators is provided in Table 17.1 which includes only cancer groups listed in layer 1. Those included in layer 2 were removed for brevity however, few examples of layer 1 and 2 entities are reported in Table 17.2. The full list of rare cancers is available on the RARECARE project website: www.rarecare.eu.

17.5.1 Indicators of the Burden of Rare Cancers: Incidence, Survival, Prevalence

All the frequency indicators were calculated by the RARECARE project and expressed as crude rates. The frequency of each gender specific cancer was assessed in the general population. Therefore incidence rates were estimated as the number of new cases occurring in the considered period 1995–2002 over the total number of person years lived by the general population in the same period. Relative survival was estimated by the Hakulinen method [11]. Prevalence is expressed as the proportion of patients alive at the index date of 1 January 2003 with a diagnosis of tumour received any time in the last 15 years over the total population. It was estimated by the counting method [2], based on CRs incidence and follow-up data from 1988 to 2002. Only 22 CRs covered the entire period and were therefore included in the analysis.

Figure 17.3 shows the distribution of incidence rates of all the groups of tumors belonging to the first layer, those relevant for the health care organization, ranked from the highest to the lowest. As expected, the two most frequent tumors are (Table 17.1) the epithelial tumor of breast and of the lung, with annual incidence rates higher than 50 per 100,000. By contrast, slightly less than half of the tumor entities have their annual incidence rates lower than 1 per 100,000.

All the common entities are epithelial tumors of the most common sites, with the exception of skin melanoma and the group of lymphoid disease, including lymphomas and lymphatic leukemias. All the other entities are rare.

For almost all common entities, 5-year survival was more than 50%, exception were the epithelial tumors of pancreas (5-year survival 4%), oesophagus (5-year survival 11%), lung (5-year survival 11%), liver (5-year survival 8%), ovary (5-year

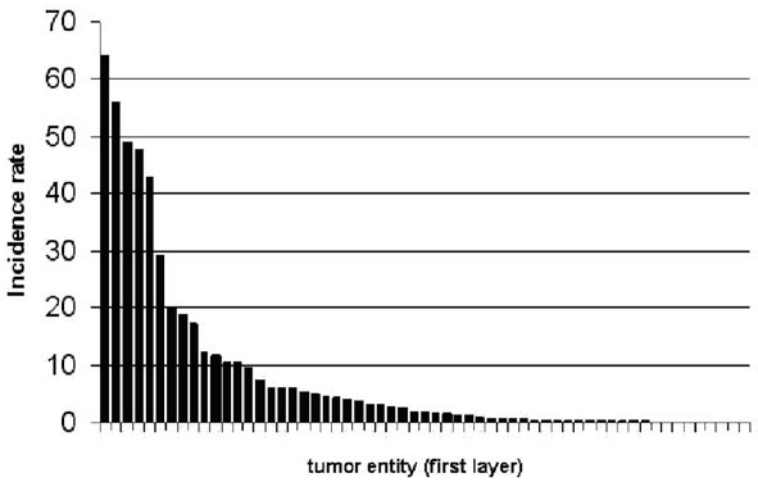

Fig. 17.3 Annual incidence rates ranging of groups of tumor entities (first layer)

survival 38%), and stomach (5-year survival 22%). For the rare entities survival variation was larger and many tumors had a poor prognosis: 5-year survival was less than 50% for the majority of rare entities. Fifteen-year prevalence (per 100,000) ranged between slightly less than 600 (epithelial tumor of breast) to less than 1.

The data in Table 17.1 clearly show how much prevalence of a specific cancer depends on prognosis. Within rare tumors, the highest prevalence was observed for testicular cancers (prevalence 43, 5-year survival 95%), soft tissue sarcomas (prevalence 43, 5-year survival 56%) and carcinomas of the endocrine organs (prevalence 41, 5-years survival 85%). There are very few rare tumors with prevalence higher than 50 per 100,000 i.e. the threshold of the EU definition of rare diseases [4], and few common tumor entities have a prevalence under 50 due to their poor prognosis.

It is worth mentioning that groups of common cancers might include rare tumour entities which are relevant for the clinical decision making perspective. Three examples of this situation are presented in Table 17.2. The oesophageal tumors as well as the liver and cervix epithelial tumors, have an incidence rate close to the threshold adopted of 6 per 100,000. However, the epithelial tumors of the oesophagus includes four rare clinically defined entities. Five-year survival figures vary from 9% for the adenocarcinoma to 6% for the undifferentiated carcinoma. The epithelial tumors of the liver and intrahepatic bile tract include different rare tumor entities relevant from the clinical management. The most frequent histotypes are the hepatocarcinoma and the colangiocarcinoma. These two different clinical entities have both a bad prognosis, lower for the cholangiocarcinoma. Adenocarcinomas of liver have low survival similar to that observed for cholangiocarcinoma. The other three entities present very few cases and can be considered as exceptional.

Epithelial tumors of cervix uteri comprise 2 rare tumor entities relevant from the clinical perspective: squamous cell carcinoma and adenocarcinoma.

17.6 Final Considerations and Future Directions

The RARECARE project, on the basis of population based cancer registries data provided an operative definition of rare cancer, a list of tumour entities from which is possible to select rare entities and the most important epidemiologic indicators (incidence, prevalence and survival) of rare tumors in Europe. The RARECARE project assured a wide engagement of oncologists, pathologists, cancer epidemiologists and patients advocacy groups in all its activities thus the conclusion of the project were extensively discussed and agreed on. We proposed a definition of rare cancer based on incidence and we developed a list of rare entities, using an incidence threshold of 6/100.000. However, we also acknowledge the importance of prevalence for health planning purposes, therefore this important measure was provided for all the tumor entities included in the rare cancer list. No important differences were found in identifying rare tumors on the basis of the incidence rate as opposed to the European definition of rare diseases based on prevalence [4].

This is the first time that CRs data are used to estimate epidemiologic indicators for rare tumors thus, the results obtained should be consolidated and widely utilised.

Bias in our results might arise because of variations in data quality and comparability. However, the analysis of the major indicators of the quality of cancer-registry data [3] – i.e., proportion of cases reported as death-certificate only, microscopically verified, and lost to follow-up – suggest a high-quality dataset. Information on morphology is commonly available from CRs, however in depth quality control should be done on the validity and completeness of such data. This important task was included among the aims of the RARECARE project. Actually, we are working on data quality revising a sample of selected rare tumors to assess the effect of such revision on incidence and survival rates. We hope that the results of rare cancer data quality analyses will contribute to increase the awareness on this critical topic among CRs.

Another important task is the dissemination of the results. These data should reach all the relevant stakeholders in order to support the best effective research into rare cancers and the best provision of care to patients. The list of rare cancers could be important for:

- establishing networks on rare cancers (European reference network),
- identifying tumor entities where a focus on treatment and timely diagnosis is essential,
- investigating the off-label use in rare cancers,
- supporting a greater involvement of disease-oriented research communities in the mechanisms developed by regulatory bodies to provide advice to the pharmaceutical industry on the development of new agents for use in rare cancers,
- developing alternative methodologies for rare cancer research,
- involving patients in the clinical decision-making process.

What will be the future of such experience?

Although information on patients access to care in the different European countries is not widely available, previous studies reported substantial regional differences in survival from rare cancers, particularly for those that respond well to treatment. Furthermore, a survey on the availability of orphan drugs in Europe, conducted by EURORDIS (European Organisation for Rare Diseases) in 2007, showed that access to recently approved orphan drugs is very limited and it varies significantly across the EU member states [7]. These results are of great concern and further investigations are needed to understand the reasons of survival differences across the European countries. Population-based studies may contribute to address this critical issue and it is our intention to carry out additional survival studies also to contribute to ameliorate the equity of care in rare cancer. Accurate population-based information on cancer patient survival is indispensable for effective cancer control. While clinicians need survival from clinical series to evaluate the efficacy of their treatments, only population-based survival comparisons can provide information on the effectiveness of health care systems. Population-based cancer registration is also necessary for monitoring cancer incidence and for estimating cancer prevalence

which are required for health care planning and resource allocation [1]. Policy and economic investments to ensure equal access to care to rare cancer patients have to be foreseen and we will work for providing evidence on which base such important decisions.

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