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ORIGINAL ARTICLE

Rare tumors: A comprehensive analysis of cancer

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Summary

Purpose: *To evaluate differences between the data from project "Surveillance of Rare Cancers in Europe" (RARECARENet) and the data from the Institute of Oncology "Prof. Dr. Ion Chiricuta" (IOIC).*

Methods: *Data from the institutional cancer registry of IOIC through 2012 to 2013 and the data published in RARECARENet project were compared.*

Results: *There were 14,127 cases in the IOIC cancer registry but only 13632 complied with the RARECARENet categories. Of these, 7382 (54%) were common, 5975 (44%) were rare, and 275 (2%) were in the "Other" category compared to RARECARENet (64%, 22%, 14%; p<0.01). From a total of 65 tumor categories, 34 (2.3%) should be given special treatment for rare tumors. Comparing the cases of the IOIC with the data of the RARECARENet project, 14 out of 65 categories showed significant structural differences and these represented 81% of our cases. 44.7% of cancers were rare compared to only 22% at the level of the European project (p<0.01).*

Conclusion: *Globally, Oncology Institute "Prof.Dr. Ion Chiricuta" receives a large number of rare tumors. There are differences between RARECARENet and IOIC, but these differences are probably due largely to the fact that IOIC receives the largest number of rare tumors from the surrounding area.*

Key words: *rare tumors, RARECARE, RARECARENet, Monte-Carlo method*

Introduction

Identifying rare tumors is a serious problem to avoid postponing the diagnosis, applying inappropriate treatments, or lack of information coming from clinical trials. Progress can only be achieved in an approach that goes over the borders of the countries of Europe and beyond [1-5].

The definition of a rare event is relative, and leads to different definitions depending on the criteria applied (incidence, prevalence or number of cases) [6]. However, the best-known initiative concerning "rare tumors" is developed around the project "Surveillance of Rare Cancers in Europe" known as RARECARE [7] and then after the update as RARECARENet [8]. The initiative has been materialized by the emergence of a series of synthesis works of Gatta et al. in 2011 [9] and 2017 [1] followed by developments on the major families of rare tumors: urogenital [10], head and neck [11], neuroendocrine tumors [12], thoracic cancers [13]. Classification in RARECARE is governed by the pair topographical code and morphological code. Based on this pair, tumors are classified into three levels [7,9]. Level 1 is the broadest and contains large tumor families. It generally is splitted into several disjunctive components of level 2. However, the reunion components of level 2 is generally more reduced. Supplementary level 1 usually contains tumors that raise suspicions of wrong identification or that can not be classified histologically clear. For example, morphologi-

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cal codes that are not sufficiently characterized 8000 (Malignant Neoplasm) and 8001 (Malignant Cells) are found at level 1, but never at level 2 or 3. To make the exposure clearer, we have introduced an entity that contains all these exceptions and which we call "Other or badly classified" or "Other" briefly. Epithelial tumors of nasal cavity and sinuses for example have 17.3% of cases in "Other" category. Globally the category "Other" represents 14% of the total number of cases. Level 2 or clinical level includes tumors perceived by the clinician as a single disease. Tumors at this level are understood as classes that are subject to the same decisional criteria for treatment and their terminology is used in clinical trials. Of course there are situations in which level 1 is the same as level 2, or in other words, level 1 does not decompose except in one class of level 2 class (eg. nephroblastoma, retinoblastoma, hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma, olfactory neuroblastoma, odontogenic malignant tumors). Level 3 has a more descriptive role including World Health Organization (WHO) entities. It is mainly used to make clearer the WHO entities inclusion in level 2 (clinical) and when this inclusion is not well understood from definition of level 1 or 2. For example "squamous cell carcinoma with variants of cervix uteri" at level 2 is decomposed at level 3 in: squamous carcinoma; squamous cell carcinoma nonkeratinizing; squamous cell carcinoma keratinizing; papillary squamous cell carcinoma; papillary carcinoma; verrucous/warty carcinoma; basaloid carcinoma; squamous cell carcinoma spindle cell; lymphoepithelial carcinoma; transitional cell carcinoma; glassy cell carcinoma.

Rare tumors are defined as those tumors that at level 1 or 2 have a crude incidence of less than 6/100000 relative to the population of Europe. For the definition from 2011, information from 76 European cancer registries during 1995-2002 was used, covering an average population of 162 million inhabitants. This set of data along with the entire methodology will be referred to as RARECARE after the name of the project that has accumulated these registers [7]. Naturally, RARECARE evolved into RARECARENet, continuing all objectives but expanding the information base. Efforts became another rare tumor database based this time on 94 cancer registries in Europe over the period 2000-2007 [1,8] and the definition of rare tumor was updated consequently.

For the moment, Romania has not been included in RARECARENet. However, the data on Romania are partly included in EUROCARE-5 project [14-17] which is the starting point also for RARECARENet. Otherwise, in Romania the collection of data on oncology cases is regulated by law by the Ministry of Health [18]. However, the only published data we know so far about the incidence of cancers in Romania are those in the "Cancer Report in the Northwest of Romania 2012 - incidence, mortality, survival and prevalence" [19]. The quoted report refers only to six administrative regions (Cluj, Bihor, Salaj, Satu Mare, Maramures and Bistrita), with an area of 14.3% and a population of 12.9% from Romania.

The Institute of Oncology "Prof. Dr. Ion Chiricuta" (IOIC), member of the Organization for European Cancer Institute (OECI) [20] has a long tradition in the fight against cancer. It was founded in 1929 and since then has always been a reference pole at least for Romania. Having a wide addressability, it includes patients from all 42 counties of Romania.

Regarding the treatment of cancer in the public network it is concentrated in three national oncology institutes located in the most important three university centers in Romania: Bucharest, Cluj and Iasi. On the other hand, considering that the Institute from Bucharest and Cluj-Napoca were founded before the 1950s and that of Iasi only in March 2012, the cancer cases were divided at the time of the study between the Bucharest Oncological Institute and the Cluj Institute of Oncology. Also, in Romania there are no studies on rare cancers and comparisons with data from other cancer registries in Europe are missing. In this way, the objective of the study to analyze and compare data from IOIC with RARECARENet is natural.

Methods

Since 1996 IOIC maintains electronically a database of all tumors diagnosed or treated here. The database at its inception complied with the conditions recommended by the WHO for the development of cancer registries [21]. We chose to study all tumors registered in IOIC over the 2012-2013 period. This period was chosen because during this time the impact of private oncology clinics was still minor and at the end of 2011 some IOIC procedures were introduced to highlight unlikely cases and to track the evolution of patients, which raised the quality of the data. We thus had a total of 14,127 tumors. Of these cases, certain malignant tumor behavior was only for 13,632 cases (96.5%). The rest were cases that were treated as malignant but were distributed as follows: 15 (0.1%) benign cases, 131 (0.9%) with uncertain behavior and 349 (2.5%) tumors *in situ*.

We made our analysis based on RARECARENet that is more complete, but we also have references to RARECARE where we thought it fits.

In order to classify tumors from IOIC, we have matched the pair (topographical code, morphological

code) in the IOIC database with the corresponding pair in the RARECARENet classification. Several ambiguous definitions have been observed. For example, for the three cases of IOIC with ICDO-3 topographical code "C30.0 Malignant neoplasm of the nasal cavity and middle ear" with the morphological code "9364 Peripheral Neuroectodermal Tumor" we have two variants in RARECARENet "SOFT TISSUE SARCOMA / Soft tissue sarcoma of head and neck" or "SOFT TISSUE SARCOMA / Ewing's sarcoma of soft tissue". We have chosen the "SOFT TISSUE SARCOMA / Soft tissue sarcoma of head and neck " that seemed more appropriate to us. In total, there are 74 ambiguities that we have evaluated and reclassified. However, these ambiguities account for only 0.5% (74/13632).

In addition to these ambiguities we have encountered pairs (topographical code, morphological code) that are not present in RARECARENet. All these cases were re-evaluated from the patient's archive file and the results presented are after this review. We finally had 275/13632 (2%) cases of pairs (topographical code, morphological code) not present in RARECARENet.

We note that most of the missing cases in the RARECARENet classification are due to problems that go beyond the framework of the rare tumor evaluation we have proposed here. Thus, the first three groups in the order of the number of cases are: 180 cases classified in IOIC with C80.9 topographic code, *i.e.* malignant tumors with undetermined site; 15 cases with C57 code, *i.e.,* malignant tumor of the genitals, other and unspecified, and 10 cases with code C26, *i.e.* malignant tumor of digestive organs with other site and bad defined. All these problematic sites amounted to 205 cases, *i.e.* 1.5%, remaining only 70 (0.5%) potentially questionable cases from the point of view of the classification system. Next, we will analyze 13357 cases omitting all cases outside the RARECARENet classification.

Statistics

All tests were done with Excel 2013 and Mathematica 10. The differences between the averages were assessed by Student's t-test. To compare the data distribution between IOIC and RARECARENet we tried first to apply the x^2 test [23]. If the application of this test, including the addition of some corrections, was not possible due to the small number of observations, we attempted to apply the exact Fisher's test [23] or generalization [24]. If this test also was not appropriate or impossible to evaluate, we have estimated the p value using a Monte-Carlo (MC) simulation technique that we describe briefly below.

We exemplify with the 65 categories from RARECARENet. The basic model used in the simulation is that of a multinomial distribution on 65 RARECARENet categories. For simplicity, the 65 probabilities *a priori* are considered the percentages resulting from the RARECARENet database. The error is negligible due to the relative high number of cases in RARECARENet. If we denote by p_1, p_2, ..., p_{65} the probabilities *a priori* and p'_1, p'_2, ..., p'_{65} the probabilities in IOIC, then the null hypothesis to check is: H_0: $p_1=p'_1$, $p_2=p'_2$, ..., $p_{65}= p'_{65}$ *i.e.* IOIC probabilities (percentages) are the same as theoretical (*a priori*). The alternative hypothesis is H_1: at least one pair (p_1, p'_1), (p_2, p'_2), ..., (p_{65}, p'_{65}) contains different values or in other words at least one IOIC probability is different from the theoretical ones.

We denote with the n_1, n_2, ..., n_{65} the IOIC observations. As we will see below many of the n_1, n_2, ..., n_{65} values are zero, so the x^2 test can not be applied. For Fisher's exact test or generalization [24] we should consider all combinations for which the sum of the 65 categories n_1, n_2, ..., n_{65} is equal to the sum of the observations in IOIC (13657) and hence the p value is equal to the sum of all probabilities of combinations that are less than or equal to the probability to obtain the IOIC observations. The enumeration of all these combinations is many times impossible even with today's computing power.

We can, however, estimate the p value simulating repeatedly a process of extracting 13537 samples from a returning urn with 65 categories. The percentage of processes with the probability of occurrence less than that of obtaining exactly the observations in IOIC is the p value. The fact that the total number of cases in RARECARENet and IOIC is relatively high leading to small confidence intervals throughout the work p values less than or equal to 0.01 are considered significant and p values greater than 0.01 but less than 0.05 are considered to show a trend towards statistical significance.

Results

In International Classification of Diseases for Oncology (ICDO) there are 70 topographic locations but according to RARECARENet they were grouped only in 65 entities at level 1. The immediate global comparison of the totals from IOIC and RARECARENet shows a significant difference, the p-MC estimated value of p is <0.001. Further, we can study IOIC / RARECARENet percentage ratio in order to identify the categories which provide the most important difference. IOIC / RARECARENet ratio identifies three groups from the 65 categories of RARECARENet.

The first group is formed by the categories in which no cases have been observed in the IOIC: trophoblastic tumour of placenta, epithelial tumours of urethra, hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma, olfactory neuroblastoma, odontogenic malignant tumors, carcinomas of pituitary gland. Statistical significance is far from the significance threshold except for epithelial tumors of urethra for which there is a trend (p=0.03).

The 2nd group consists of the categories where the IOIC percentage is lower than the percentage of RARECARENet. For the majority of categories 21/26 the differences are statistical significant: epithelial tumours of skin (p<0.01), epithelial tumours of small intestine (p<0.01), epithelial tumours of pelvis and

ureter (p<0.01), malignant mesothelioma (p<0.01), epithelial tumours of gallbladder and extrahepatic biliary tract (EBT) (p<0.01), epithelial tumours of bladder (p<0.01), epithelial tumours of prostate (p<0.01), myeloproliferative neoplasms (p<0.01), epithelial tumours of pancreas (p<0.01), myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases (p<0.01), malignant melanoma of uvea (p<0.01), epithelial tumours of liver and intraepatic bile tract (IBT) (p<0.01), epithelial tumours of oesophagus (p<0.01), malignant melanoma of mucosa and extracutaneous (p=0.16), epitelial tumours of kidney (p<0.01), epithelial tumours of colon (p<0.01), epithelial tumour of lung (p<0.01), lymphoid diseases (p<0.01), epithelial tumours of stomach (p<0.01), carcinoma of adrenal cortex (p=0.15), acute myeloid leukemia and related precursor neoplasms (p<0.01), epithelial tumours of anal canal (p=0.03), epithelial tumours of rectum (p<0.01), tumours of central nervous system (CNS) (p<0.01), epithelial tumours of eye and adnexa (p=0.37), epithelial tumours of oral cavity and lip (p=0.02).

The third group consists of the remaining categories, *i.e.* for which the percentage ratio is in favor of the IOIC. From these 30 categories 18 have significant differences: testicular and paratesticular cancers, epithelial tumours of vulva and vagina, epithelial tumours of major salivary glands and salivary-gland type tumours, epithelial tumours of hypopharynx and larynx, epithelial tumours of nasal cavity and sinuses, malignant skin melanoma, epithelial tumours of breast, epithelial tumours of oropharynx, epithelial tumours of ovary and fallopian tube, soft tissue sarcoma, epithelial tumours of corpus uteri, bone sarcoma, embryonal tumors of CNS, neuroblastoma and ganglioneuroblastoma, gastrointestinal stromal sarcoma, carcinomas of thyroid gland, epithelial tumours of nasopharynx.

The other 12 categories do not reach the significance threshold:neuroendocrine tumours, Kaposi's sarcoma, epithelial tumours of penis, epithelial tumours of thymus, epithelial tumour of trachea, adnexal carcinoma of skin, non epithelial tumours of ovary, nephroblastoma, extragonadal germ cell tumours, epithelial tumours of middle ear, retinoblastoma, and carcinomas of parathyroid gland.

In total, 39 out of 65 categories (60%) provide a statistical significance.

The 65 categories can be stratified also in several groups by the rare common attributes and presence in the IOIC. The first group is same as before, consisting of entities which by RARECARENet definition are rare and they are absent in IOIC.

Next we have a group consisting of categories malignant skin melanoma and epithelial tumours of skin which by definition are common.

The following group consists of categories for which at level 1 are common tumors and by definition at the level 2 the components contain both rare and common tumors and the "Other" component is also present: epithelial tumors of colon, of lung, of breast, of prostate, of rectum, of stomach, of corpus uteri, of bladder, of pancreas, of kidney and lyphoid diseases.

In this group, when IOIC versus RARECARENet comparison is made only on rare and common categories, 4 from 11 categories have significant p value: epithelial tumors of colon (p<0.01), of lung (p<0.01), of breast (p<0.01) and lymphoid diseases (p<0.01) . If we add the "Other" category, we have statistical significance for all tumor categories except for epithelial tumors of bladder, but even here the p value of 0.02 is close to the statistical significance threshold of 0.01.

The next group is composed of common level 1 tumors, but level 2 components are all rare and the "Other" component is present: epithelial tumors of ovary and fallopian tube, of liver and intrahepaticbile duct (IBT), of hypopharynx and larynx, of esophagus, of cervix uteri and of central nervous system (CNS). Comparison with IOIC this time is done on "rare"/"Other" components. For all categories, p value is under 0.01. Likewise, the "rare" /"Other" percentage ratio is in favor of IOIC from 0 for epithelial tumours of oesophagus to 0.7 for epithelial tumours of cervix uteri.

It follows the fifth group of rare tumors at level 1 for which there is the "Other" component in RARECARENet.

From this set of categories of level 1 we highlight a subset for which the "Other" component does not exist in IOIC.

It is further noted for this group that only epithelial tumors of nasopharynx, soft tissue sarcoma and epithelial tumors of gallbladder and extrahepatic billiary tract (EBT) have significant differences, *i.e.* IOIC has a different distribution of cases from RARECARENet. It is highlighted the proportion of "Other" cases in favor IOIC excepting extragonadal germ cell tumors, acute myeloid leukemia and related precursor neoplasms, and epithelial tumor of trachea.

The remaining last group is without "Other" category.

This group can only be analyzed on level 2 where the number of cases permits.

For age, the statistical analysis of the average is correctly set only for the tumors where both commom and rare categories exist. Only 4 categories fullfil the condition: lung with an average of 60.3 years for common forms versus 62.5 years for rare forms (p=0.006); breast with an average of 56.3

years versus 58.6 (p=0.024); corpus uteri with an average of 60.3 years versus 67.1 (p=0.022); lymphoid diseases with an average of 63.2 years versus 50.9 years (p=0.018).

As said above, stage distribution analysis is performed on the same categories: for lung common/rare ratio is 44/23 in stage I-II versus 542/126 in stage III-IV (p<0.01); for breast common/rare ratio is 1422/90 versus 1060/37 (p<0.01); for corpus uteri common/rare ratio is 483/22 versus 105/26 for (p<0.01); for lymphoid diseases common/rare ratio is 21/92 versus 30/108 with p=0.54.

Further we were interested in seeing what is happening at level 2. Tumors that were not present in IOIC as well as those that have only one division of level 2 were left aside remaining 42 categories only.

It is first noted that p-Monte Carlo (MC) without the "Other" category indicates a significant difference for 15 categories.

Adding the "Other" category does not change the statistical significance.

Furthermore, these 88 categories correspond to 3657 rare cases and 4030 common cases, *i.e.* 48% versus 52%.

In rural areas there is higher rate for rare tumors. Common/rare ratio is 2067/2035 in rural areas versus 4916/3801 in urban areas (p<0.01). Adding the "Other" category, (191 cases in rural and 347 in urban) p value is also less than 0.01.

Discussion

The evaluation of statistical significance should be done mainly in the combination of rare versus common, leaving aside the "Other" category. The addition of "Other" makes no significant changes in our inferences. However, we have to note that in IOIC "Other" has only 4% comparing with 14% in RARECARENet (p<0.01) but should not be forgotten that in RARECARENet there are large varieties of health care units of different levels of comprehension which can bias the result.

Surely the definition of rare tumors according to the RARECARE methodology is not yet closed at a final edition and will be updated. At this moment the difference between RARECARE and RARECARENet is also reflected in IOIC cases. Thus, after RARECARE in the "Other" category we had 975 cases and after the last RARECARENet edition only 275 *i.e.* a decrease from 7% to 2%.

As can be seen from the above, the cases registered in IOIC come from all over Romania. The county of Cluj, which is the location for IOIC, accounts for only 21.6% (2888/13357) of the total IOIC cases, meaning statistical inferences give a good indication for Romania.

From the point of view of rare tumors, the percentage relative to the percentage of rare tumors in Cluj county is higher for 31 of the 41 counties (76%), which means that for the cases in these counties the percentage of rare tumors is higher. However, the difference is significant for only 9 of the 31 counties (22%).

For the other remaining 10 counties where the relative percentage is subunitary we did not find significant difference.

Globally, there is a difference from 42% (1172/2778) for Cluj county versus 46% (4664/10041) with p <0.01. This clearly suggests that patients with rare tumors in the outer counties have a tendency to come to IOIC.

Further, the fact that for carcinomas of pituitary gland, epithelial tumours of urethra, hepatoblastoma, histiocytic and dendritic cell neoplasms, odontogenic malignant tumors, olfactory neuroblastoma, pancreatoblastoma, pleuropulmonary blastoma and trophoblastic tumour of placenta we have no observations in IOIC deriving from the extreme rarity in Romania deduced from the very low incidence of 0.04, 0.13, 0.02, 0.05, 0.004, 0.03, 0.002, 0.001, 0.02 at 100,000 in RARECARENet.

The "Other" category collects cases that carry a load of errors and omissions so that the p value for data in this category turns into a cancer registry quality indicator and should be used with caution to compare the case structure. The quality of the registry is better as the percentage of "Other" cases is lower. Therefore, the "Other " category should always be reported to see data quality from the start. As shown above, calculating the p value with the "Other" category results in a lower value because the IOIC generally has a lower percentage of the "Other" category. The use of the "Other" category in statistical inferences should be made only if there is a reference to the quality of the data.

It is well known that cancer treatment in Romania is largely covered by national cancer institutes. However, there is a network of private clinics of varying sizes and forces that take up some of the task, especially in the common tumors. This, together with the higher intake of rare tumors from outside Cluj county, partly explains the relatively high percentage of rare tumors in IOIC: 44.7% versus 22% in RARECARENet (p<0.01).

Furthermore, the large percentage of rare tumors recommend *de facto* inclusion of IOIC in "European Reference Networks" complying with criteria from [2] and [25].

Rare tumors are thought to occur in older patients [9,12]. The analysis should be done on the level 1 categories in RARECARENet. Our data only partially confirms this for the lung, breast,

and uterine body, where older patients are more frequently in rare tumors and the p value is significant. Still, for lymphoma, things are the other way round. We have an average of 63.9 years for common tumors and only 50.9 for rare tumors with a tendency towards statistical significance (p=0.02, NS). This result can be partially explained by the existence in IOIC of a specialized departement in pediatric oncology, which attracts many cases outside the traditional IOIC area and changes the statistics. Unfortunately, we do not have information about age, sex, and staging in RARECARENet for comparison.

In terms of staging, in IOIC, we expected to have more advanced stages for rare tumors. Analysis of data can only be done in four categories: lung, breast, uterine body and lymphoma, and the idea is confirmed only for the lung, breast, and uterine body where the p value is significant. For lymphomas, the p value is not significant. Although the results are contradictory in this case, remembering that the percentage of unstaged cases for lymphomas is very high (48%) compared to 4%, 5% and 7% for the other sites.

Tumors with an occurrence of less than 50 cases in the IOIC over the study period should be given increased attention and/or directed to a specialized center if such a center is found. The total number of these cases is 308 (2.3%). The list of these 26 categories is as follows: epithelial tumours of eye and adnexa, epithelial tumours of middle ear, malignant melanoma of mucosa and extracutaneous, carcinomas of parathyroid gland, epithelial tumour of trachea, retinoblastoma, carcinoma of adrenal cortex, epithelial tumours of small intestine, epithelial tumours of thymus, nephroblastoma, extragonadal germ cell tumours, kaposi's sarcoma, malignant melanoma of uvea, neuroblastoma and ganglioneuroblastoma, epithelial tumours of pelvis and ureter, non epithelial tumours of ovary, adnexal carcinoma of skin, malignant mesothelioma, embryonal tumors of cns, epithelial tumours of nasal cavity and sinuses, epithelial tumours of penis, epithelial tumours of anal canal, gastrointestinal stromal sarcoma, myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases, myeloproliferative neoplasms, epithelial tumours of gallbladder and extrahepatic biliary tract.

We must add the categories for which IOIC did not have any observations in the analyzed period, *i.e.*: trophoblastic tumour of placenta, epithelial tumours of urethra, hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma, olfactory neuroblastoma, odontogenic malignant tumors, carcinomas of pituitary gland, histiocytic and dendritic cell neoplasms.

A balanced policy for the remaining categories could be to recommend IOIC as a specialized center for the categories where the percentage is favorable to IOIC and the significance threshold is reached.

The following 14 categories are highlighted in this manner: malignant skin melanoma, testicular and paratesticular cancers, epithelial tumours of vulva and vagina, epithelial tumours of major salivary glands and salivary-gland type tumours, epithelial tumours of hypopharynx and larynx, epithelial tumours of breast, epithelial tumours of oropharynx, epithelial tumours of ovary and fallopian tube, soft tissue sarcoma, epithelial tumours of corpus uteri, bone sarcoma, carcinomas of thyroid gland, epithelial tumours of cervix uteri, epithelial tumours of nasopharynx.

They account for 8370 cases, *i.e.* almost 63% of the total number of cases.

Next, there is a median group for which the IOIC/RARECARENet percentage ratio is unfavorable to IOIC, but the number of cases is important and thus strongly supports the idea of belonging to IOIC as a specialized center. These are: acute myeloid leukemia and related precursor neoplasms, epithelial tumours of liver and intraepatic bile tract, epithelial tumours of oesophagus, epithelial tumours of pancreas, tumours of central nervous system, epithelial tumours of bladder, epitelial tumours of kidney, epithelial tumours of skin, epithelial tumours of stomach, epithelial tumours of rectum, lymphoid diseases, epithelial tumours of prostate, epithelial tumours of colon, epithelial tumour of lung with significant p value comparing with RARECARENet and epithelial tumours of oral cavity and lip, neuroendocrine tumours with not significant p value.

Summarizing the above for level 1,34 out of the 65 (53%) categories should benefit from special treatment but they represent only 2.3% of the IOIC cases.

Concerning the level 1 categories structured by the level 2 categories, it was noticed significant differences in only 14 categories (14/64; 34%), but they represent 81% of the IOIC cases. However, we must look cautiously at this difference because it is also influenced by the high addressability of rare tumors to IOIC as we have seen above.

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Conflict of interests

The authors declare no conflict of interests.

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