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Testicular germ-cell tumours and penile squamous cell carcinoma: Appropriate management makes the difference

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ABSTRACT

Germ-cell tumours (GCT) of the testis and penile squamous cell carcinoma (PeSCC) are a rare and a very rare uro-genital cancers, respectively. Both tumours are well defined entities in terms of management, where specific recommendations - in the form of continuously up-to-dated guide lines-are provided.

Impact of these tumour is relevant. Testicular GCT affects young, healthy men at the beginning of their adult life. PeSCC affects older men, but a proportion of these patients are young and the personal consequences of the disease may be devastating.

Deviation from recommended management may be a reason of a significant prognostic worsening, as proper treatment favourably impacts on these tumours, dramatically on GCT and significantly on PeSCC.

RARECAREnet data may permit to analyse how survivals may vary according to geographical areas, histology and age, leading to assume that non-homogeneous health-care resources may impact the cure and definitive outcomes. In support of this hypothesis, some epidemiologic datasets and clinical findings would indicate that survival may improve when appropriate treatments are delivered, linked to a different accessibility to the best health institutions, as a consequence of geographical, cultural and economic barriers.

Finally, strong clues based on epidemiological and clinical data support the hypothesis that treatment delivered at reference centres or under the aegis of a qualified multi-institutional network is associated with a better prognosis of patients with these malignancies.

The ERN EURACAN represents the best current European effort to answer this clinical need.

Introduction

Among rare solid tumour of the male genital tract, testicular and penile cancers deserve a special interest due to their particular characteristics, although they show significant epidemiological differences.

Testicular tumours basically affect young men between 20 and 40 year-old, at the beginning or in full employment, social and affective life [1–5]. The annual incidence of testicular and paratesticular tumours is 3.29 (95% CI 3.27–3.32) cases per 10^5 individuals, corresponding to 16,061 new cases in 2013 in EU28 [6]. The vast majority of these tumours are germ-cell tumours (GCT), as para-testicular adenocarcinoma and sex stromal tumours, display a crude incidence of only 0.001 and 0.02 $\times$ 10^5 individuals [6], respectively. Following histological diagnosis, clinical decisions are crucial. Prognosis of GCT dramatically changed in the eighties of the past century, following the introduction of extremely effective drugs as cisplatin and etoposide, which allowed a cure for more advanced cases. Surgery evolved accordingly, and the most important and crucial intervention remains retroperitoneal lymph-node dissection (RPLND), which is usually indicated after completion of chemotherapy in non-seminoma, in very selected cases in seminoma and in some patients before chemotherapy in non-seminoma [1–4].

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Penile cancer usually affects men between the 5th and the 8th decades, associates with local chronic inflammation or with human papillomaviruses (HPV) infection of some subtypes (mainly HPV 16, 18, 30 and 33) [7,8]. In Europe, the annual crude incidence rate of penile cancer is 0.66 (95% CI 0.65–0.67) cases per 10^5 individuals, and equals to 3887 new cases in 2013 in EU28 [6]. Almost all penile cancers are penile squamous cell cancer (PeSCC), as adenocarcinoma had a crude incidence rate of 0.01. The prognosis of this disease is favourable in early stages, the most frequent, while it remains dismal in advanced disease, as no highly effective medical treatment is available. Surgery (i.e. inguinal and pelvic lymph-node dissection) remains crucial for the staging and the cure, as early detected small nodal metastases may be cured in more than 60% of cases at 5 years [7–10].

In common, GCT of the testis [1–4] and PeSCC [7,8] have defined recommendations, summarized by different and consistent guidelines, both in the diagnosis and in the treatment. The hypothesis is that a treatment not delivered according to the guidelines and by untrained professionals, may dramatically worsen the prognosis of these diseases.

This review discusses the burden of these two rare cancers, in term of frequency and outcome, focuses on the crucial points for diagnosis and treatments and sustains ongoing European efforts to standardize management.

Diagnosis

Clinical presentation

a GCT of the testis. Usual presentation is a tenderless intrascrotal mass, with no or just moderate pain. Many patients currently present with a small lesion identified by scrotal ultrasound. Although an increasing information pressure disseminates the importance of auto-palpation in the young men, many patients still present with very large testicular masses, which may associate with a greater risk of an advanced disease.

b PeSCC. Initial lesions are usually painless. Cultural heritage may impact on the individual attitude to access visit for a genital lesion. Diagnosis is often delayed due to patient modesty or due to wrong clinical diagnosis.

Histological diagnosis

a GCT of the testis

i Recently, the International Society of Urological Pathology (ISUP) held the *Testicular Cancer Consultation Conference* and produced recommendations to be followed for standardize pathology [10]. The most critical issues received a recommendation, and often the question of a central review is called in. An Italian study showed that up to the early 2000's, half of the reports regarding stage I non-seminoma patients did not contain the information about vascular invasion [11]. Moreover, 27% of cases on review at a central pathology laboratory were reclassified as having vascular invasion, while 19% were reclassified as not having vascular invasion [11]. Since then, an extensive informative campaign conducted by the Italian Germ Cell Testicular Tumour Study Group [12], was able to reduce the number of reports with lacking information on vascular invasion.

ii Intra-operative diagnosis through frozen sections examination. Most diagnoses occur following ultrasound examination that reveals a small testicular hypoechoic lesion (<10 mm). The diagnostic pathway often includes surgical exploration and open biopsy [13]. This pathway may spare a useless orchidectomy in case of benign lesions. An experienced pathologist can provide better performance in terms of accordance with definitive pathology [14]. Wrong intra-operative diagnoses may lead to useless orchiectomy or to a re-operation.

iii An emerging interest concerns malignant transformation of teratoma (TMT). Cellular atypia of epithelial and mesenchymal elements in teratomatous metastases of patients treated with cisplatin-based chemotherapy for non-seminoma have been frequently found, which does not necessarily imply a different clinical outcome. Presence of only the expansive growth of the somatic malignant proliferation is a significant feature for the diagnosis of a TMT [15]. Although we have not an evidence supporting the need of an expert pathologist to assure the diagnosis of TMT, the complex evaluation criteria are intuitively a reason to recommend a second opinion review, in order to reduce misdiagnoses (including over-diagnoses).

TMT is rare, but associates with a worse prognosis than usual GCT. Moreover, the role of surgery both as post-chemotherapy option and as primary treatment (RPLND) in early stages of disease is commonly recommended, as it is associated with a better outcome [16].

b PeSCC. The recent 2016 WHO classification on penile cancer deeply changed [17]. Most previous classifications were morphology-based. The current one presents a new classification based on clinic-pathologic distinctiveness and relation to HPV infection, which may be suspected by the analysis of p16 [18]. Some histological PeSCC variants associate with different clinical behaviour. Some have more favourable course than usual type, and deserve a more conservative treatment. Other, as sarcomatoid, basaloid and acantholytic SCC may have a rapid spread, sometime skipping inguinal nodes, and must require more aggressive treatment since the first diagnosis.

A UK experience [19] showed that after histology review, pathology diagnoses significantly changed, with 31% of cases receiving a reclassification. The changes were deemed to be critical in 60.4% cases: some patients required more extensive and invasive treatment for local penile cancer management, while a change to a more conservative treatment approach in the pathologically downgraded group was provided in some cases.

Although no proof supports a different survival according to central review Vs initial report, it is intuitive that an adequate sampling and expert examination may give more detailed information about variants, invasion and extent of invasion beyond *lamina propria*, which play a prognostic role and may permit organ preservation and better quality of life in many patients.

Treatment of primary tumour

1 GCT of the testis

a Radical orchiectomy is the standard surgery for testicular GCT. Actually, about 90% of these simple surgeries are performed in primary care hospitals. We have no evidence that centralization of orchiectomy may produce any impact on the outcome of these patients.

b Partial orchiectomy. This procedure is called in for mono-orchid patients, where maintaining a sufficient amount of testicular parenchyma ensures the preservation of patient's own body image and of endocrine function. This procedure needs precise surgical steps, although it is not considered technically difficult. It requires a cautious evaluation of the preoperative functional

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aspects, the patient expectations in terms of paternity and residual function; as a consequence dedicated endocrinologists and/or andrologists are advised [20].

2 PeSCC. Most early PeSCC may require conservative treatments. Laser excisions or surgical excision followed by glans resurfacing and - in some cases - Mohs surgery, represent documented effective alternatives with different indications and chances [21]. In a large mono-institutional series, patients treated with penile preservation showed no significant difference in survival compared to patients treated with partial amputation after adjusting for relevant co-variables [22]. Due to the rarity of disease, such procedures usually require dedicated surgeons, with a specific expertise.
Patients with recurrent disease or more advanced stage, need glansectomy or amputation. As the primary treatment of high-risk primary tumours temporally coincides with the management of inguinal nodes, which is the key treatment in PeSCC management (see next paragraph on staging), it is advisable to plan the initial surgery in experienced centres.

Staging following initial surgery

1) GCT of the testis. Following orchiectomy, staging of testicular GCT includes chest and abdominal CT scans with contrast medium and serial determination of serum tumour markers AFP and beta unit of human chorionic gonadotropin (β-hCG) [1–4,13]. Interpretation of imaging is crucial. Smallenlarged lymph-nodes may be wrongly interpreted as negative, and may determine an incorrect staging and thus inappropriate treatment. Although these imprecisions may hardly be a reason of prognostic variations in the short to medium term, they may induce further re-do treatments, which associate with a higher risk of late toxicity and late relapses. A multidisciplinary team of radiologists and clinicians must accurately evaluate imaging of the retroperitoneal space.
2) PeSCC. Staging includes palpation of inguinal nodes contextually or soon after surgery of the primary tumour. In case of non-palpable nodes, following an abdominal and pelvic CT/MRI scans with contrast medium, referral institutions have adopted the dynamic sentinel node biopsy (DSNB) [23,24]. This is a multistep procedure, which needs a dedicated team of urologists, radiologists, nuclear physicians and pathologists. The best results are achieved when each single step is correctly performed. A clinical data-set from the Dutch Cancer Institute, reported that patients with cN0 disease treated after 1994 showed improved cancer specific survival compared to those treated before 1994, when adjusting for pT category and grade [25,26]. Authors attributed this finding to the early detection of microscopic disease by DSNB, resulting in early lymph-node dissection in patients with a tumour positive sentinel node. Some evidences showing a trend towards a better survival in northern European countries have been reported [26]. These findings may support to refer patients with initial disease to high-volume experienced centres.

Surgical treatment of metastatic disease

The role of surgery remains crucial both in GCT and in PeSCC. The key surgery is lymph-node dissection, which takes places as prophylactic intervention, primary treatment or post-chemotherapy option according to stage.

1 GCT of the testis

a Prophylactic RPLND. Primary RPLND has been used in early stage non-seminomatous (NS) GCT of the testis for many years, but it has gradually lost its role [27]. In clinical stage I NS-GCT, the extremely favourable prognosis as well as the different therapeutic strategies with unaltered efficacy - even when they are delayed - led to a progressive reduction of the intensity of treatment and to an increasing role of tailored options. Currently, the recommended policies in these patients are active surveillance or adjuvant chemotherapy, consisting in one course of Bleomycin, Etoposide, Cisplatin (BEP), while RPLND is no longer suggested as first choice [1–4,13]. The reasons behind are the morbidity of surgery and, mostly, its low reproducibility on a large scale [28]. Mini-invasive RPLND (pure laparoscopic or robot assisted) has been introduced in order to reduce morbidity of open surgery [29]. Currently, the available evidences are consistent with a non-inferiority of mini-invasive RPLND in respect of open surgery [30–33]. However, RPLND – open or mini-invasive - remains a highly technical demanding procedure that requires experienced hands in referral centres, in order to achieve standardized levels of efficiency.
b Primary RPLND in early stage NS-GCT (stage II). RPLND represented the only effective therapeutic tool up to the introduction of effective chemotherapy, when the disease was limited to the retroperitoneum [32,34]). The chance of definitive cure depended on the burden of disease, which could vary from small volume (Stage IIA: < 2 cm), to very large disease (Stage II D: > 5 cm), where the chance of definitive cure was low [34]. Currently, indication of primary RPLND in stage II disease reduced, and currently is an option in small volume (Stage II A) disease with normal markers after orchiectomy. Other indications, as stage IIB non-seminoma or IIA/B seminoma, should be considered within clinical trials [1–4,13]. Expert opinions summarized by current guide-lines, recommend this surgery in experienced hands [1–4,13].
c Post-chemotherapy RPLND. Surgery is strongly indicated in case of a residual mass ≥1 cm and normalised markers following completion of primary chemotherapy in NSGCT [1–4,13]. Post-chemotherapy RPLND may be modulated, according to extent, volume, laterality and adhesion to other organs. A limited dissection in small and unilateral masses reduces the risk of retrograde ejaculation; a mini-invasive RPLND (pure laparoscopic or, with smaller experiences, robot-assisted) reduces the general morbidity of laparotomy [35]. On the other hand a maximal RPLND with contextual removal of organs involved by the disease and possible reconstructive surgery (e.g. vascular prosthesis or grafts) may increase the chance of cure in patients with gross masses infiltrating viscera or gross vessels [36]. This surgery is recommended in high-volume centres and should be performed by experienced hands. A better outcome following centralization of cure has been documented as far as in 1993 [37]. Considering 454 patients treated in West Scotland, year of diagnosis, extent of disease and treatment unit (the higher in volume Vs other 4), were all significant at regression analysis in predicting survival ($p < 0.001$). In a population-based study including 27,948 patients from 17 SEER registries (1998–2006), the 10-year testicular cancer mortality was derived according to different variables. Among 6192 patients with NSGCT, those who underwent RPLND had a 7-fold greater chance of survival than patients who had no RPLND ($p < 0.001$) at multivariable analysis [38]. A population study including 882 patients from (SEER database: 1988–1997), showed that the post-operative mortality increased as age and stage increased: 0.0%, 0.8% for regional, and 6.0% for metastatic disease (p .001) [39]. Authors

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drew attention about the need of referring advanced cases to high-volume centres, where the reported mortality was lower (0% for primary and 0.8% for post-chemotherapy RPLND.

2 PeSCC

a Prophylactic inguinal lymph-node dissection (ILND). Prophylactic ILND in case of clinically not palpable nodes (cN0) associates with a better disease control than ILND at relapse [40]. Nonetheless, ILND in stage N0, finds no more than 20% of patients with nodal disease, and associates with a significant morbidity, including lymphoedema and wound infections. Modified approaches, including template dissection, selection through individuation of risk category or DSNB, have been introduced, but require a specifically expertise, as already described for DSNB.

b Primary inguino-iliac lymph-node dissection (IILND). This intervention is the key treatment in PeSCC, as nodal metastases represent the landmark of curability for metastatic disease. Actually, early small nodal metastases associate with a 5-year cure rate of 60%, while advanced or pelvic node metastases associate with not more than 30%, at the best [6–9]. Extent of inguinal dissection is formalised [7–9]. Pelvic dissection is generally recommended, and could be omitted in a subset of patients with a particularly favourable condition, according to studies performed in high-volume centres [41–43].

c Post-chemotherapy IILND. These patients had undergone chemotherapy due to extent of disease or in the context of a clinical trial. Efficacy of chemotherapy prior to surgery has not definitively demonstrated [43]. The special set of application and the greater difficulties due to desmoplastic reaction due to chemotherapy advocate the need of expert surgeons in high-volume centres.

Population data in testicular and penile cancers

1 Survival analysis, time trends in population-based studies

a GCT of the testis

The EUROCARE-5 study included 56,397 patients recorded from 86 cancer registries (CRs), in the period 2000–2007, and followed up through 2008 in 29 countries [5]. Survival remained stable, and was high in most of the countries (around 90%). Nonetheless, the 5-year survival was low (<80%) in some Eastearn countries. Older patients bearing a non-seminoma had the worse prognosis. A previous EUROCARE study [44] focusing on 10-yr survival and relapse pattern, evaluated 1.350 testicular cancer cases from 13 population-based CRs (1987-92) in 9 countries. According to stage distribution, three Eastern European countries had the lowest proportion of organ-confined disease at presentation. The 10-yr survival was statistically lower for seminoma in Estonia (63%) and in Poland (68%) than in referral CRs (two Northern Italian provinces: 90%), and for non-seminoma in Estonia (47% Vs 85%). Of interest, although relapses associated with survival, French CRs showed the highest relapse rates, but the 10-yr survival remained high (85% for seminoma and 83% for non-seminoma). These findings induced authors to hypothesize that in eastern European populations the lower survival was not due entirely to advanced stage at diagnosis, but also to inadequate treatment. The unfavourable effect of inadequate treatment on the outcome in testicular cancer, due to disparity in accessing cure, may be derived also by population studies over-sea. The aforementioned study from Fossa et al. [38] found that both ethnicity (white Vs non-white) and educational level (a proxy of economic status) were associated with prognosis in patients with non-seminoma. The positive effect of accessing adequate health facilities can be derived from an English study, which evaluated data of patients aged 13–24 years treated during the period 1979–2001 by the National Cancer Intelligence Centre [45]. The relative survival for patients with testicular GCT increased from 84% to 96% between the first and last time period ($p < 0.001$), with a geographical variability that did not change after adjusting for deprivation index, used to mitigate the effect of economic income.

b PeSCC

Few datasets are available for penile cancer. The EUROCARE-5 study, analysing 10,935 patients from CRs, reported a stable survival during the study period from 1999 to 2007 [46]. Similarly, data from the US, confirmed no substantial time trend survival variation since 1990 in 450 patients from 9 SEER CRs [47]. Geographic differences of outcome, repeatedly reported by EUROCARE, was confirmed for epithelial tumours of penis also by the RARECAREnet project with the highest 5-year survival for the Northern (77%) and the lowest in the Eastern European countries (60%) [6]. The survival rate in northern Europe was assumed to depend on the introduction of early detection of inguinal lymph-node metastases through the introduction of DSNB, as reported above [25,26,41].

2 Conditional survival: a proxy of effective diagnosis and treatment?

The conditional survival is the probability to survive at five years being alive 1 or 3 years after diagnosis. This indicator may be a proxy of timely diagnosis and adequate treatment.

a GCT of the testis

Conditional survivals at 5 years, having survived the 1st year after diagnosis, were assessed from the EUROCARE dataset [5]. The 5 to 1-yr conditional relative survivals ranged between 95% and 97% in almost all areas and 92% in eastern European countries. As previously reported, we showed that in some Eastern countries initial stage was more advanced than in others. This observation may also imply that performance in treating patients in the first year could be suboptimal, probably due to more difficult accessibility to experienced centres.

PeSCC

From the EUROCARE-5 dataset a 5-yr survival of 68%, with a 1-year conditional survival of 80% are derived [5]. Considering conditional survivals figures, geographical differences markedly reduced. The greater increase between 5-year survival and conditional survival was however recognised for the Eastern European countries, indicating that many advanced and complex cases died during the first year after diagnosis.

3 Centralization and networking

a GCT of the testis

Dutch researchers, evaluating data between 1989 and 2009 from the Eindhoven Cancer Registry (ECR), reported an improvement of 5-yr relative survival in all the age-categories except for patients older than 60 years [48]. According to stage, a significant survival improvement was observed for seminoma with regional metastases: the 5-yr relative survival shifted from 93% in 1989–93 to 100% in 2004–9 ($p = 0.01$). Relevant improvement trends in 5-yr relative survival were recorded for metastatic non-seminoma and for metastatic seminoma, as they improved from 78% to 85% ($p = 0.05$), and from 73 to 88% ($p = 0.07$), respectively. The authors assumed that this was probably due to improved chemotherapy and to

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the referral of patients with metastasized cancer to specialized centres as well as to the improvements of the post-chemotherapy RPLND, reasonably associated with centralization of more complex cases.

In 2006, the German Testicular Cancer Study Group started an evidence-based national second-opinion network in order to improve the care of testicular cancer patients: 1284 requests were submitted by 350 primary care physicians to the 31 s-opinion centres from November 2006 to October 2011 [49]. The first-opinion therapy suggested by the advice seeker was concordant with the second-opinion therapy recommended by the centres in 58% of the cases. Discordance between first and second opinions was found in 39.5%. Metastatic cases were those at lower concordance. The second-opinion treatment was less extensive in 28.1% and more extensive in 15.6% of the discordant cases than that originally planned. In another 56.3% of the cases, there was no substantial difference. Actual delivered treatment did not adhere with any opinion in as many as 30% of patients; 85% of the remaining underwent a treatment more adherent to second opinion. No data are available regarding outcomes.

The Italian Germ Cell Study Group (IGG) was founded in 2005 with the aims of spreading information regarding testis cancer, through a series of divulgation events, and improving the prognosis of patients, by sharing complex cases, addressing patients to high volume centres for highly specialized treatment [12]. Moreover, IGG promoted both patients lobbying in order to facilitate information and patients advocacy, in order to warrant patients rights in their work activities. A measurable effect was that of having improved the quality of histological reports of germ-cell tumours.

Recently, a position paper supporting the need of centralization has been released [50]. Authors recognize that it is impossible to find the highest evidence supporting improved outcomes on the basis of institutional volume alone, but indirect available data and expert consensus support improved outcomes in testicular cancer being achieved at high-volume centres and through collaborative groups. A call upon six interventions by all the stake-holders including clinicians, researchers, health-providers, payers, media operators and patients is proposed [50]. Hospital volume analysis was performed from the RARECAREnet in 7 European countries covered by registration [6]. Centralization of patients with testicular tumours was in general low during the period 2000–2007. Bulgarian registry showed that 75% of patients were treated in 19 different hospitals with a mean annual admission volume (MAV) for testicular tumour of 12 cases. Nonetheless, in Belgium and in the Netherlands, more centres (40 and 42, respectively) treated the 75% of patients with a MAV of 8 and 18, respectively. In these countries survival of testis cancer was high, regardless of the decentralisation and low MAV. This may depend on the presence of an effective network which permits to share patients according to a national management guide-lines and by the country public health investment for cancer.

b PeSCC

The Dutch experience probably offered the best example of how a leading centre (the National Cancer Institute in Amsterdam in this country), may favourably impact in a medium size country through its long experience in clinical practice and research [51]. Mortality gradually decreased from 1959 to 2006, and the percentage of missing stages decreased significantly from 15% in 1989–1994 to 9% in 2001–2006 ($p < 0.001$). These findings may be due to diagnostic anticipation and to the diffusion of effective staging procedures, mainly DSNB, which may favourably impact the prognosis of PeSCC. Actually, according to the hospital volume analysis from the RARECAREnet data [6], centralization of PeSCC was very low in all the countries with the exception of the Netherlands and Slovenia.

Another positive example of networking is offered by the creation of networks specialized in penile cancer in UK. The experience of the supra-network multidisciplinary team in reviewing histology e redirecting treatment has been reported above [19]. In 2012, the first results of the network in the East Midlands in UK showed an increase in the number of cases discussed since its formation and a trend towards more conservative surgery [52].

Networking at EU level

As we argumented, the management of testis and penile cancers poses significant diagnostic challenges, sometimes with major consequences for patients' quality of life and outcome. Medical expertise can be difficult to find because of the rarity of the diseases, and many patients may migrate from country to country in search of appropriate care. Inappropriate management may result in an increased risk of relapse, and risk of death due to cancer or other causes which can be treatment-related.

In order to improve patients referral across EU countries, at EU level the European Reference Networks (ERNs) have been established. The ERNs, three of which are specifically devoted to rare cancers, have been conceived by the EU Commission as a means to provide “highly specialized healthcare for rare or low-prevalence complex diseases”. The ERN EURACAN covers all rare adult solid tumour cancers, grouping them into 10 domains corresponding to the RARECAREnet list. One of this domain is rare urological cancers and includes testicular cancer only.

The core business of ERNs is to provide multidisciplinary. In addition, the ERNs are meant to generate and disseminate knowledge on rare cancers, promote medical education and patient's information, produce clinical practice guidelines and foster research as well as epidemiological surveillance.

Conclusions

Population based studies showed survival differences across countries for these two rare cancers. It means that there is room for improvement thus for an European overall progress. The formal activation of ERNs is a cornerstone in the EU cooperation on rare cancers, and the Joint Action on rare Cancers (JARC) will be instrumental to make them grow up the best way possible. Actually, JARC aims at optimizing the process of creation of the ERNs, by providing them with operational solutions and professional guidance in the areas of quality of care, epidemiology, research and innovation, education and state of the art definition on prevention, diagnosis and treatment of rare cancers.

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Conflicts of interest statement

None.

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Appendix. RARECARENet Working Group

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Castilla-La Mancha Cancer Registry); Nerea Larrañaga, Arantza Lopez de Munain (Basque Country Cancer Registry); Ana Torrella-Ramos (Castellón-Valencia (breast); Cancer Registry); José María Díaz García (Cuenca Cancer Registry); Rafael Marcos-Gragera (Girona Cancer Registry); Maria Josè Sanchez (Granada Cancer Registry , CIBERESP, ibs.Granada); Carmen Navarro, Diego Salmeron(Murcia Cancer Registry, CIBERESP, IMIB-Arrixaca); Conchi Moreno-Iribas (Navarra Cancer Registry, CIBERESP); Jaume Galceran, Marià Carulla (Tarragona Cancer Registry); Mohsen Mousavi (Basel Cancer Registry); Christine Bouchardy (Geneva Cancer Registry); Silvia M. Ess (Grisons-Glarus, St. Gallen Cancer Registry); Andrea Bordoni (Ticino Cancer Registry); Isabelle Konzelmann (Valais Cancer Registry); Jem Rashbass (Public Health England); Anna Gavin (Northern Ireland Cancer Registry); David H Brewster (Scotland Cancer Registry); Dyfed Wyn Huws (Welsh Cancer Intelligence and Surveillance Unit); Otto Visser (The Netherlands Cancer Registry); Magdalena Bielska-Lasota (National Institute of Public Health-NIH, Warszawa); Maja Primic-Zakelj (Cancer Registry of Republic of Slovenia); Ian Kunkler (Edinburgh Cancer Centre, University of Edinburgh); Ellen Benhamou (Institut de Cancérologie Gustave Roussy, Villejuif, France).

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