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A web-based tumor registration system for a regional Canine Cancer Registry in Umbria, central Italy

Elisabetta Manuali[1], Raffaello Antonio Morgante[1], Carmen Maresca[1], Leonardo Leonardi[2], Ivana Purificato[4], Maria Donata Giaimo[3] and Gianni Giovannini[3]

[1]*Istituto Zooprofilattico Sperimentale dell'Umbria e delle Marche "Togo Rosati", Perugia, Italy*
[2]*Dipartimento di Medicina Veterinaria, Università degli Studi di Perugia, Perugia, Italy*
[3]*Prevenzione, Sanità Veterinaria e Sicurezza Alimentare, Regione Umbria, Perugia, Italy*
[4]*Dipartimento Sanità Pubblica Veterinaria e Sicurezza Alimentare, Istituto Superiore di Sanità, Rome, Italy*

Abstract

The Umbria Canine Cancer Registry (CCR) is a web-based platform for cancer registration set up in order to estimate the incidence of spontaneous tumors. It is an integral part of the regional canine demographic registry in which veterinary practitioners and pathologists interact. Veterinary pathologists perform double-blind comparisons and classify neoplasms in an automated classification process using the WHO criteria for canine neoplasms and the ICD-O tumor topographical and morphological keys. Here we describe the organization, on-line procedures and the methods used to assess canine demography, a pre-requisite for accurately estimating the incidence of cancer.

In its first 4 years the CCR recruited 4857 cases of suspected tumors, as diagnosed by practitioners, clinics and a veterinary hospital. After the first year the number of enrolled cases increased by 63%, suggesting growing interest from the regional veterinary community.

Key words

- Canine Cancer Registry
- web platform
- double-blind histopathology
- WHO
- ICD-O

INTRODUCTION

Neoplastic disease is one of the major causes of morbidity and mortality in dogs worldwide. As for humans, cancer registration provides information for estimating its incidence and relative risk factors and supplies data for epidemiological studies [1]. Moreover, as dogs share indoor and outdoor environments with humans, they can potentially act as bio-sentinels for environmental hazards [2, 3] and models for the study of human cancers [4].

Information from the Canine Cancer Registry (CCR) aids in assessing the incidence of different types of cancer. Consequently, the CCR must collect information on all cancer cases that are identified within a specific population in an established time-period. It must cover a defined geographical area, access a relevant number of sources within the area and provide a consolidated registration system to avoid duplicating case registrations. The CCR relies on close cooperation from the entire veterinary community (clinicians, pathologists, epidemiologists).

Although cancer registries in human medicine have evolved since the 1940s [5], veterinary cancer registration systems are much more recent even though several decades have passed since the first animal tumor registries were established [6-11]. A recent international workshop attempted to connect research groups working on the topic [12] so as to showcase their efforts to gather data and their different approaches to cancer information and registration. In Italy, the first Animal Tumor Registry (ATR) was established in the province of Genoa in 2008 [13] and the following year, the results of a cancer registration project in the provinces of Venice and Vicenza were published [14]. In 2017, incidence data were obtained in Piedmont, a well-delimited geographical area in northwest Italy [15]. *Table 1* summarizes the official Italian ATRs and their methodology.

In Italy and internationally, as a plethora of data collection methods, different approaches to cancer registration and diverse inclusion criteria preclude comparing information in existing ATRs, universal standardized procedures are required. Moreover, since the registries are based on histology records, possible diagnostic errors could be linked to pathologist subjectivity in interpreting samples. To prevent this bias, double-blind histology should be guaranteed. Furthermore, being aware that terminology may differ in the diverse neoplasm classification systems, pathologists must be per-

Address for correspondence: Elisabetta Manuali, Laboratorio di Istopatologia Veterinaria e Comparata, Istituto Zooprofilattico Sperimentale dell'Umbria e delle Marche "Togo Rosati", Via Gaetano Salvemini 1, 06126 Perugia, Italy. E-mail: e.manuali@izsum.it.

Table 1
Summary of the official animal tumor registries (ATR) in Italy (1985-2015) and their main characteristics

ATR	Start	Type of registry	Submission method	Species	N. of tumors (B and M)	Period	Inclusion criteria	Coding used
Genoa	1985	Provincial	paper	dog	6743[a]	1985-2002	histology	ICD-O-9
Piedmont	2001	Population-based	paper	dog	1172[b]	2001-2008	histology	ICD-O-9
Venice and Vicenza	2005	Provincial	paper	dog, cat	3003[c]	2005-2007	histology, IHC, diagnostic imaging	ICD-O-9
Palermo	2009	Population-based	on line	dog, cat	n.a.	2003-2016	histology, IHC	ICD-O-9
Rome	2009	ASL B and H	paper	dog, cat, other species	3237[d]	2009-2016	histology	ICD-O-9
Campania	2011	Population-based	on line	dog	633[d]	2009-2014	histology, IHC	ICD-O-9
Umbria	2013	Population-based	on line	dog	2559[d]	2014-2016	histology, IHC, cytology[e]	ICD-O-9
Sassari	2014	Provincial	n.a.	n.a.	n.a.	n.a.	n.a.	ICD-O-9
Marche	2015	Population-based	on line	dog	428[d]	2015-2016	histology, IHC	ICD-O-9
Abruzzo and Molise	2017	Population-based	paper	dog, cat	3953[d]	2013-2017	histology, IHC	ICD-O-9

a. Merlo et al. 2008 [13]
b. Baioni et al. 2017 [15]
c. Vascellari et al. 2009 [14]
d. Presented at the Italian Workshop "The animal tumor registries: at what point are we in Italy?" November 21, 2017 – Genoa
e. Only for lymphoma and leukemia
B: benign tumors; M: malignant tumors; ASL: local health authority; IHC: immunohistochemistry; n.a.= data not available.

suaded to opt for only one tumor codification system. The International Classification of Diseases for Oncology (ICD-O) is strongly recommended worldwide. It is also adopted for comparisons with human medicine in the universal concept of the One Medicine One Science which embraces common scientific approaches that unify health-related research at the intersection of humans, animals, and ecosystems [16].

Finally, the quality of cancer registry data depends first on the competence and experience of its staff and, then, on an active research program to maintain a good quality registry. All this can be ensured only if government institutions have the foresight to invest in this project.

The present paper describes a web-based cancer registration system which is set up as an integral part of the canine demographic registry and designed for exclusive electronic tumor registration. A platform that permits communication among veterinary practitioners and pathologists, it also serves pathologists with double-blind evaluations and classifies neoplasms in a complete and automated process using WHO criteria for canine neoplasms [17] and the topographical and morphological keys of the International Classification of Diseases for Oncology (ICD-O). It includes quality control and data access. Here we present the organization and procedures of this pilot web-based cancer registration system that is guaranteed by double-blind histopathology as well as validation of regional canine demography, as a pre-requisite for assessing prevalence data and accurately estimating the incidence of cancer.

MATERIALS AND METHODS

Study area and canine demography

This population-based registry was established to serve the Umbria region in central Italy which is divided into the two provinces of Perugia and Terni. Umbria is the only Italian region with neither a coastline nor an international border. As its municipalities are not strictly contiguous, the canine population is relatively concentrated. This "privileged" status is important because tumor occurrence and the estimated population at risk, can be attributed to a specific regional area.

Validation of the regional canine population demography is a pre-requisite for assessing prevalence data and – accurately estimating the incidence of cancer. The official canine demographic registry of Umbria was used as the primary source for estimating canine demography. To estimate the real size of the dog population, dogs living outside the region and crossbred dogs with age > of the 95th percentile of the age of deceased crossbred dogs in the registry were removed as were purebred dogs with age > to the maximum life expectancy of the specific breed (www.easypetmd.com; www.terrificpets.com). Data are updated every year. The QGIS 2.4.0 (Chugiak, free to download) was used to create the thematic maps.

89% of all veterinary clinics operating in Umbria are currently involved in this project.

Web-based technology and team organization

The departure point for developing this web-based cancer registration system was the Veterinary and Food

Information System (SIVA). A consolidated regional platform, which is a major strategic instrument for controlling and managing veterinary activities, SIVA guarantees the exchange of information between competent authorities. It permitted validation of a CCR prototype to be submitted to the scientific community. First, work teams were organized and a web-based system planned. This crucial phase involved integrating several technical skills (engineers, computer scientists, veterinary pathologists and epidemiologists) who worked together to build the web-based registry structure.

This expressly designed and developed software for tumor registration resides within the SIVA section dedicated to the Canine Demographic Registry/CCR, which registers microchipped/tattooed dogs living in Umbria region in an online database. The electronic system includes various components ranging from requests for tests (pre-acceptance of samples) to the laboratory report (diagnosis). The entire process is fully web-based. A Geographical Information System (GIS) was also planned as an integral part of this software so as to graphically display cancer patients throughout the region.

Following software validation and a trial period, the system was proposed to the regional veterinary community through training courses. All members were then contacted and invited to submit samples of suspected cancer cases, which had been obtained by surgery or necropsy, to the "Center of Veterinary Pathology for Animal Tumor Registry" (hereinafter named Centre) which had been established in Umbria in 2013 [18]. To encourage sample recruitment, histological examinations were offered free of charge. The free diagnostic service was also announced to veterinary clinics in bordering regions, which had been identified as a "buffer zone", in order to obtain data from dogs brought into them.

The registration form

Before typing the new record, each veterinary practitioner (hereinafter named VET) had to enter a password to access a reserved working area by linking to the Canine Demographic Registry, in which the demographic and health data of registered dogs are available. The system also provides a permanent data update (e.g. vaccinations, previous illnesses, cancer, date of death). The VET can then access the CCR section by clicking on the specific "box". There s/he can complete the form, with items focusing on animal and tumor data, (as a requirement for obtaining a histopathological diagnosis). To facilitate the procedure, dogs are sought by inserting their own microchip/tattoo, or name, or typing the last name of the owner or their Fiscal Code. The system automatically transfers all Canine Demographic Registry data to the CCR, thus avoiding manual errors. *Table 2* reports the data list. As shown, all these fields are mandatory for completing registration, thus ensuring database information quality. These data are indeed considered essential for comparative and epidemiological purposes. To ensure no duplication of case registrations, the software assigns each new case its own code (ID number) that identifies sample(s) which are submitted to the Centre.

Table 2
Mandatory data to be included in Canine Cancer Registry web registration form

Level	Data	Comments
The patients		
	Microchip/tattoo	Assigned by registry
	Name	
	Breed	
	Size	
	Sex	
	Age	
	Neutered/castrated	
	Case registration (ID number)	
Identification	General status (good/ preserved/poor/not known)	Assigned by VET by clicking in the specific boxes
	Habitat (urban/rural/not known)	
	Environment (apartment/garden/ mixed/kennel/not known)	
	Diet (wet/dry/mixed/ not known)	
	Data of surgical excision Margins of excision (if requested)	
	Stage of tumor (TNM)	
	Source (biopsy/surgery/ necropsy)	
	Topography (ICD-O codes)	
	Anamnesis	Assigned by VET in the specific space
The owner	Address	Assigned by registry
	GIS coordinates	
The tumor	Morphology (WHO)	Assigned by pathologists (P1 and P2)
	Coding system (ICD-O)	
	Immunohistochemistry	On line request by VET after the diagnosis was made
	Name of pathologist	Assigned by registry

P1: pathologist that firstly analyzes the HE stained section(s); P2: pathologist who provides the second opinion.

Double-blind histopathology

One of the key strengths of this population-based CCR is its double-blinded histological diagnosis. Emphasis is placed on Registry quality by obtaining consistent, uniform histological classification. At present, only tumors confirmed by Centre-affiliated pathologists are considered. In HE sections, cancers are classified according to the WHO's criteria for canine neoplasms [17] and coded according to the ICD-O system. A double-bind process with each Centre member conducting a histopathology evaluation without knowing the diagnosis from the other pathologist is guaranteed. Centre

Pathology staff includes 8 active pathologists working in the Togo Rosati Umbria and Marches Experimental Zooprophylactic Institute (Istituto Zooprofilattico Sperimentale dell'Umbria e delle Marche "Togo Rosati" (IZSUM) and the Department of Veterinary Medicine, University of Perugia (UNIPG). The consolidated double-blind histology implies systematic rotation of pathologists and in order to organize the diagnostic activity, a 12-month planning calendar/year is planned. All VETs are free to submit their collected sample(s) to IZSUM or UNIPG as they wish. This means that the first histological observation is performed by a pathologist who works at the institution that received the sample(s). Only a computerized linkage to the SIVA web is used. The flow chart is reported in *Figure 1*.

The pathologist that first analyzes the HE stained section(s) is named P1, while the other pathologist who provides the second opinion is named P2. Simplifying, P1 receives the formalin-fixed sample and, after tissue processing, slides are analyzed and a descriptive diagnosis is made. P1 logs-on to SIVA/CCR with their own password, identifies the case according to the ID number, clicks on the appropriate box, inserts the macroscopic and microscopic description of the tumor and selects the ICD-O code number. Slides are then delivered to P2 for blind evaluation of case(s). Importantly, P2 must insert only the WHO classification of tumor and its proper ICD-O code number into the web-based software system. In cases of agreement (the two pathologists use the same WHO and ICD-O tumor assigned code number) the web system automatically generates the final report that is e-mailed to the VET. In case of diagnostic discordance P1 and P2 re-evaluate the slide together, or a third pathologist (P3) reviews the case or there is a group discussion. When necessary, the VET can request immunohistochemical investigations using the same on-line procedure but this diagnostic service is not free of charge.

Statistical analysis

The degree of concordance of histological diagnosis among pathologists was calculated using the Cohen's kappa coefficient (CI 95%).

RESULTS

After fine-tuning and validation the CDR provided an accurate estimate of the size and the demographic structure (stratified by age, breed and sex) of the regional canine population.

The estimated dog population was 220.340 in 2014, 220.580 in 2015, 226.844 in 2016 and 228.267 in 2017. Canine demographics and municipalities are shown in *Figure 2*. Pure breeds accounted for 62% of dogs (source: Fédération Cynologique Internationale) and mixed breed for 38%. The largest purebred groups were group 7 (Pointing Dogs - 25.4%), group 6 (Scent hounds and related breeds - 21.8%) and group 8 (Retrievers - Flushing Dogs - Water Dogs - 15.8%). Females and males were

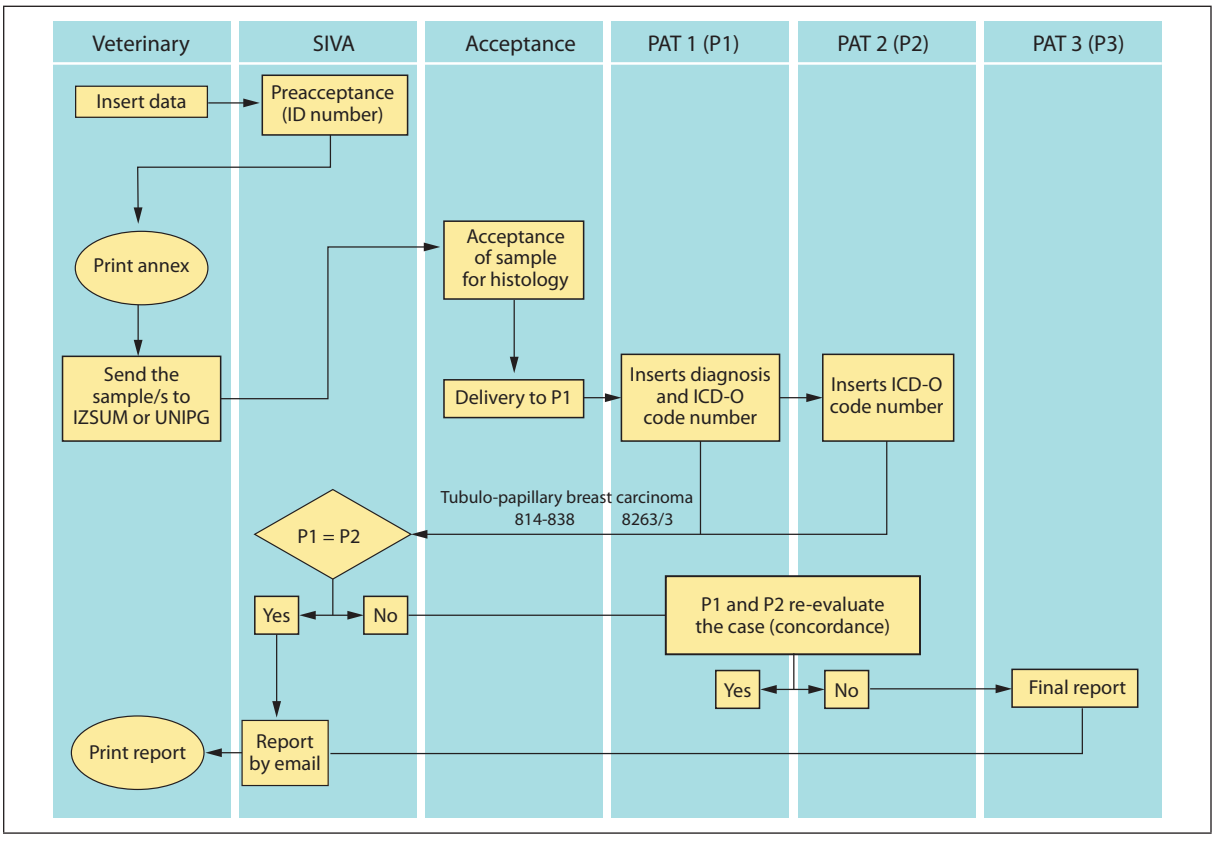

Figure 1
Flow chart that depicts the web-based organization of the Umbria Canine Cancer Registry (CCR).

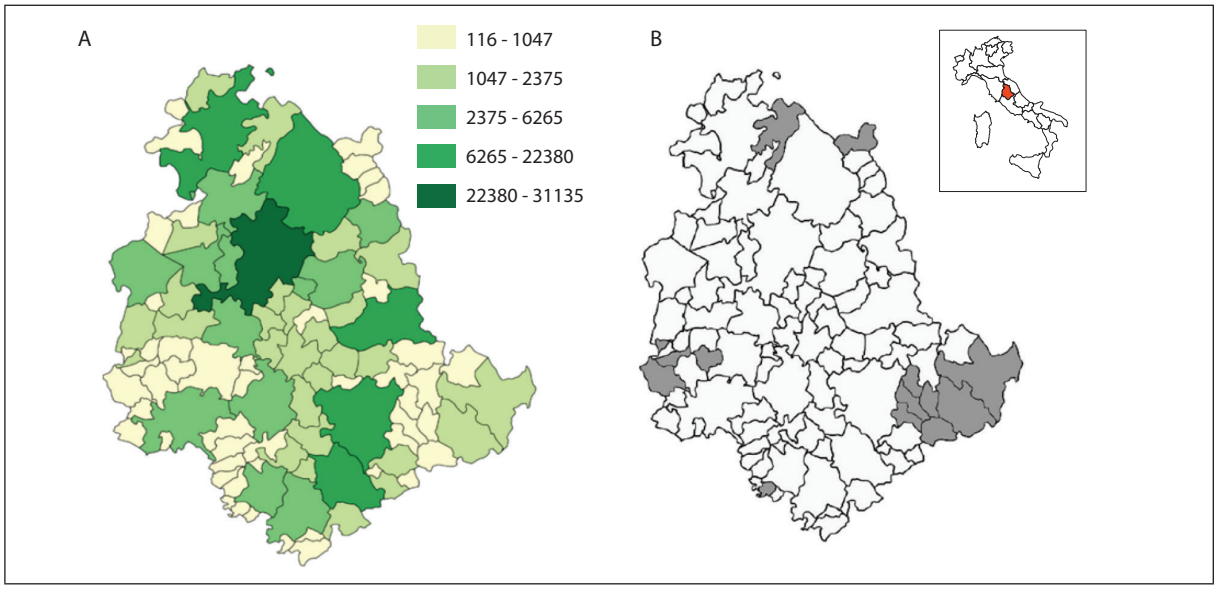

Figure 2
Consistence of dogs population for each municipality (A), in the Umbria region, Central Italy. All the municipalities involved (2014-2017) are spotted in white (B).

equally distributed, accounting for 44% and 56% respectively. The dogs' mean age was 8.1 years (SD = 4.8).

During the CCR's first 3 years of activity, 73% of veterinary clinics spontaneously adhered to it. They were distributed throughout Umbria and by 2017, 89% were involved (*Figure 2*).

Diagnostic agreement between pathologists (P1 and P2) was 0.77 (CI 95%: 0.73-0.81) in 2014 and 0.94% (CI 95%: 0.91-0.97) in 2017, demonstrating high level concordance.

In the first 4 years of activity this ATR recruited a total of 4857 cases. Of these, 4345 (89.4%) were diagnosed as tumors and 55.4% of them were malignant. The most common tumor locations were the skin and soft tissue (47.9%), mammary glands (26.8%) and genital system (10.2%).

From the first year onwards the number of registered cases increased by 3.3%, suggesting a sometimes unexpected but growing interest from the regional veterinary community,

DISCUSSION

Cancer records are a major key for collecting information about neoplastic cases and every animal cancer registry is essential for guaranteeing epidemiological research, even if only for comparative purposes. The veterinary community is becoming aware that cancer registries are needed and that all active ATRs should operate in a similar manner so as to provide complete, reliable data. In Italy, ATRs are still works in progress and most act for provinces [14] or municipalities [13]. As already planned for the Swiss CCR [11], post-mortem cases are also included, increasing the validity of regional CCR.

In the Umbria CCR high-level agreement on diagnoses was reached thanks to standardized terminology to describe the neoplasm, as well as familiarity with ICD-O codes which was gained in their use. In our data-base, distribution of malignancies concurs with reports by Merlo [13], Vascellari [14] and Baioni [15]. The most common tumor location was the skin and soft tissue followed by mammary glands and genital system. Although preliminary, these findings from the first four years of registry activity are consistent with data available in other CCRs.

One limitation of this study is the number of cases escaping this registry. Areas from which no sample has arrived have a low concentration of dogs and some veterinarians perform few surgical operations. In fact, there are only 4 active structures in the south-east area depicted in *Figure 2*. After recent earthquakes, they refer cases to other veterinarians, who send samples to the regional CCR. Cases belonging to Umbria but diagnosed outside of it deserve special interest as they should be identified and retrieved. To achieve this goal we are collaborating with veterinarians who use other diagnostic services in order to recoup as many cancer cases as possible that currently escape this CCR.

To date, VET participation has steadily increased, generating constant records of new tumor cases. In still providing a valuable boost to this ATR, which is crucial for keeping an active registry, they hope to contribute to building up Italian national and international canine cancer data in the future. The present process, which is founded on web-based technology, blind histopathology diagnoses as well as full canine demographics, ensures the validity of this population-based CCR.

Since the diagnostic activity of IZSUM covers not only Umbria but also The Marches region, this web-based electronic cancer collection system was also fully adopted by the Marches region in 2015 [19].

CONCLUSIONS

The Umbria CCR is a web-based pilot project which aims at collecting all, or almost all, cases of cancer occurring in the region. It works as a real population

registry, like the regional human cancer registry which, when it was established in 1994, was one of the first population-based registries to be activated in Italy (Associazione Italiana Registro Tumori, AIRTUM, http://www.registri-tumori.it/cms/it/storia).

This CCR web-based platform is unique. It provides access to a software system using only its tools. Compilation is easy and cancer data are visualized by means of real-time GIS mapping. The original double-blind method of histological diagnoses, which no other current ATR has adopted, was designed to reduce bias but has become one of its key strengths, enhancing the overall quality of all histological data.

Comparative oncology has recently provided valuable insights into how the pet-dog is not only man's companion but also plays an integral role in improving human health. More importantly is the added value of One Health perspective. Pets have the potential to act as sentinels (early warning systems), represent a model for studying early diagnosis and treatment of human cancer and possibly other animal cancers as well [20]. To do so, all cancer patients need to be recruited, including those cared by veterinarians who work in other regions. Recognizing this present limitation, we are looking for alternative routes that will lead to the recruitment of cases that currently escape this registry.

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Conflict of interest statement

None.

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