A web–based clinical folder for a multicentre observational study of bone metastases radionuclide therapy

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***Abstract*— Bone metastases radionuclide therapy (*bmrt*) plays a major role in the treatment of malignant bone pain. However multicentre studies with large number of patients need to be done in order to define optimal disease settings and modalities to maximise the effects of *bmrt*. At present, an Italian observational study on *bmrt* involves 72 nuclear medicine centres. In order to facilitate data collection and communication between centres, we developed a web–based clinical folder which allows participating centres to insert data of new patients, update their own records and perform multi–parametric searches.**

I. Introduction

BONE metastases appear in a fraction up to 85% of patients affected by primitive malignant tumors (usually prostate, breast, lung) and the disease is considered incurable. In most cases the therapy becomes unsatisfactory and problematic, producing high morbidity and worsening of the quality of life [1].

The main goal of the bone metastases radionuclide therapy (*bmrt*) remains the pain palliation. The capability to positively modify a true end–point of a tumoural treatment, as the quality of life of the patients, gives to *bmrt* a fundamental clinical value.

Recently, however, a growing number of signals of the possibility that the *bmrt* can act on the other true end–point of the anti–tumoural therapy — the survival increase — emerges.

II. The observational study

The main role of an observational study is to see whether effectiveness of a therapy established under controlled conditions in specialist centres reflects into effective treatment in routine practice. The observational study must be, however, designed with the same rigorousness of a randomised controlled trial. Information technology provides the methodological bases to assure the quality of the observational studies.

The first italian multicentre observational study on *bmrt* was organised between 1996 and 1998: only patients with painful bone metastases from prostate cancer treated with traditional *bmrt* protocol were enrolled [2], [3].

From current literature, it seems that *bmrt* is expanding its role in the clinical treatment of patients with bone metastases. New radiopharmaceuticals and new therapeutic programmes have been proposed; the use of the therapy in the early phase of metastatic disease has also been suggested; the integration of radionuclide therapy with chemotherapy, external radiotherapy and finally, bifosfonates are new proposals.

To evaluate the effectiveness of these new approaches of *bmrt* in clinical practice, a second phase of a multicentre observational study was promoted in the early 2001. All radionuclide treatments, performed with traditional or new protocols, on patients with bone metastases coming from any tumor were put under observation.

Analysis of performance status, bone pain syndrome, quality of life, therapeutic schemes, bone metastatic involvement, bone marrow reserve, tumour and bone serological markers performed at baseline and at pre–defined follow–up examinations were adopted as instruments for the evaluation of the effectiveness of *bmrt*.

In order to minimise costs and to facilitate inter–communication of Centres, a web–based system for data collection via Internet was also developed. Participating Centres can freely access them using an Internet browser. The users can insert data of new patients, update records and perform multi–parametric searches. The study protocol, the instructions for use as well as blank forms for the database can be downloaded and printed from the web site.

III. Basic implementation

The data collection of the observational study is based on a relational database management system (rdbms) which takes care of the clinical data and on a custom web interface developed to facilitate the interaction between the participating centres and the clinical data repository.

Due to the past history of this observational study and the acquired know–how of medical personnel, we decided to maintain continuity, implementing the database structure using the commercial product FileMaker Pro (FMPro) [4]. Its easy usage, the limited number of expected records and the capability to publish data on the web in a simple way, supported our choice. The 'Unlimited' version was chosen in order to accomplish Internet usage with an unlimited number of users (centres). The web service has been developed using the FMPro proprietary tools and web language: CDML.

A. Data repository

Due to the fact that the major purpose of the study is collection of clinical informations, the database is structured as a clinical folder organized to satisfy not only the study requirements according to the study protocol [5] but also the routinary use in a medical department. The main entity is therefore the patient while related entities are each self–consistent examination, therapy or medical investigation, performed on the patient.

The main database structure consists of eleven related tables recording data as listed below:

- *Patient:* Personal data of patients enrolled in the study;
- *Anamnesis:* Past clinical data relevant for the study (e.g. type and stage of the tumor, past therapy, etc);
- *Visit:* Analysis of the performance status, pain syndrome and any other clinical relevant data;
- *Quality of life:* Analysis of the quality of life of patients during the study period assessed by a validated questionnaire (Therapy Impact Questionnaire);
- *Radionuclide:* The protocol of the bone metastasis radionuclide therapy: data of execution, type of radiopharmaceutical, dosage, side effects, dosimetric analysis;
- *Therapy:* The protocol of "non radionuclide" therapies performed during the observation period;
- *X–ray:* The structural characteristic of the bone metastasis and the effects of the therapy on the tumour by measurement of the lesions;
- *Scintigraphy:* The presence of bone metastasis and the degree of the skeletal involvement by recording number, site and extension of the metastasis;
- *Laboratory:* The side effects of the therapy on bone marrow by haemocromocytometric analysis, the effects of the therapy on bone tissue by specific serologic markers and the tumor mass reduction by specific neoplasm markers;
- *Patient withdrawal:* Abandonment of the observational study with specification of the cause;
- *Evaluation:* The response to the *bmrt* at predefined intervals.

The main table, *patient*, has an one to one, or one to many, relation with each other table, making possible to keep track of the complete clinical history of each patient. One more table, *centres*, provides the association between patients and centres. This last table also allows to manage the access and the privileges on a per–centre basis.

Data stored in the clinical folder are ready to be studied in order to extract valuable informations. Basic analysis procedure have been developed to help physicians in the evaluation of clinical history (e.g. calculation of grade of bone marrow toxicity according to the World Health Organisation scale, calculation of the quality of life scores, etc). An export function has also been considered in case of external statistical elaborations.

Besides this main tables, an utility data structure has been implemented to give centres additional services. It consists of a few atomic tables where informations about useful links, document download, news headline and guest tracking system are stored. Any user of the web portal can access the news section, where conferences, workshops, meetings and general events or communications are reported, the links section, and a moderated discussion board. Registered users (centres) can also access a download section where documents of interest for the study are listed.

Fig. 1. Main page of the web service (in Italian) developed to allow data collection by participating centres.

The database system is hosted and served on MS Windows 2000 platform.

B. Web service

The clinical folder is accessible by means of a web portal hosted at the University of Ferrara at the address `bmrt.unife.it`. The main page, as shown in Fig. 1, has no access restriction and is designed to easily navigate across the content: on the left frame the most significant sections of the portal are listed. The web service is up to now only in Italian; a future release will implement an English version.

Access to clinical informations is straightforward following the "database" link and providing the username and password which identify the registered centre. Interested centres can register and participate to the observational study by filling an application form which is found following the "adesioni" (applications) menu option. Application is notified to the web service administrator, who can approve it and send instructions and password back to centre.

The web service allows navigation into the medical records in a hierarchical manner: the centre is the top of the tree constituted by its patients; each medical activity performed on patient is a secondary branch of the patient. This is done so that our electronic service reproduces the paper filing procedure.

Soon after the login procedure, the web service executes a search in the data repository and presents a list of the patients belonging to the centre (see Fig. 2). For each patient in this list is given a summary of its clinical folder and users can access it and see details. At this level the active centre can examine its own patients, search them on the basis of clinical criteria, or insert a new entry.

For the observational study purposes, the clinical folder of the patient is the core element. As shown in Fig. 3, it consists in a summary of general informations about the patient and the causes of its participation to the study, and in the list of the activities already carried out. In fact it is divided in many sections, each one devoted to a particular examination, where appointments and their most relevant data are listed in reverse chronological order. In this way, the clinical situation and history of

Fig. 2. The list of patients belonging to the logged centre. This page follows a successful login and permits to browse all data created by the centre.

the patient is available at a glance and the centre can select a particular activity of interest to see detailed informations. Any modification of the patient data and its appointments is possible; of course it is also possible to add a new clinical activity or delete an existing one, if necessary. Moreover, a printer–friendly version of the clinical folder is available.

The creation of new patients or a new activities is guided in a steps procedure in order to maintain integrity through the data repository. Moreover, on-line form validation procedure for mandatory fields have been developed to ensure data consistency and validity.

Navigation into the data repository is structured in three different processes. As discussed above, a centre can create, modify and view (and in some circumstances also delete) its own records. In addition, a centre can also view the records of other centres. This feature will be discussed in the next section. A third way to look at records is given by a public access that allows any user to partially view selected records. This process is part of the e–learning (ecm) section of the web service in which centres can select relevant clinical cases to be published in an anonymous format.

IV. Analysis and Data Sharing

As soon as data are entered in the database, they are ready to be analysed and shared among centres. Each centre can search its own records by means of a searching form in order to extract informations about particular aspects of the study. At this level, the result of the search is a list of patients which match the requested query. The searching form allows inquiries about clinical data related to the patient and the activities performed, making possible the generation of complex queries.

The most interesting feature is the possibility to perform searches through all patients in a centre–independent manner. Again, the result of the search is a list of patients but presented in an anonymous format to accomplish the privacy rules, allowing simple statistical analysis to be carried out. Moreover, centres can view the entire clinical folder of a patient belonging to another centre where only identity is hidden.

Basic analysis of collected data is automatically performed by the system. As an example, the laboratory data are processed and an evaluation of the toxicity grade is reported in the

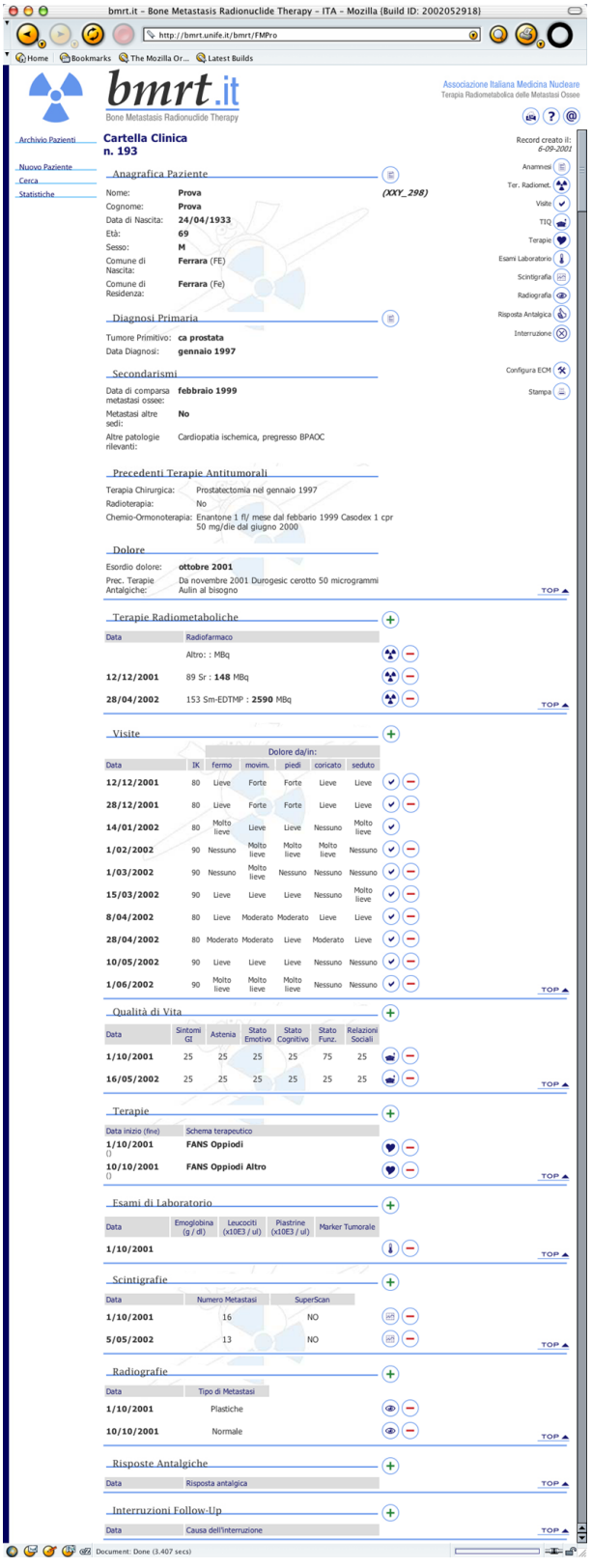

Fig. 3. The clinical folder of a patient. The summary and all clinical sections are visible. The navigation bar on the right allows to reach the desired section. New, edit, and delete buttons are on the side of each section or entry.

clinical folder. A procedure has been also implemented to analyse the answers to the quality of life questionnaire, resulting in the evaluation of common clinical parameters in this field.

Moreover, a basic data export function has been developed to allow advanced statistical analysis. Centres can download stand–alone backup of the data repository with their own records, or a backup with all records without informations about identity of the patients, in FMPro database format. Data can be then imported in the favourite analysis tool. An export function which will allow different formats is under development.

V. e–Learning

A section of the web portal has been devoted to an e–learning (ecm) service. To share the new methods and keep physicians up to date in this field, an access to selected clinical folder has been granted to everybody in the medical field.

Participating centres can decide the inclusion of a clinical folder to the ecm section on a per–patient basis. Once selected, the clinical folder is listed in anonymous format and data can be viewed by guest users. It is important to note that all clinical data of the patient are then available, excluding the identity, in the same way as the clinical folder of a centre is visible to other centres. This makes the service very useful and interesting.

In addition, an ensemble of lectures prepared by famous physicians and covering the multidisciplinary approach to the patient with bone metastasis, have been selected and are available in the ecm section.

In order to monitor the access and evaluate the contents quality in respect to the user typology, a guest tracking system has been developed. To grant access, users have to fill, only at the first connection, a simple form and leave informations about their activity, specialisation and affiliation.

VI. Conclusions

In 1996 the Italian Association of Nuclear Medicine organised the first observational study on bone metastases radionuclide therapy. 32 nuclear medicine centres participated. All information was collected by nuclear medicine physicians on pre-printed forms, which were jointly analysed by a central data-bank. The results of the study have been recently published [2], [3]. In the post-collection period and during the data analysis and manuscripts elaboration the organisers of the study observed that both the collection and data elaboration phases were time consuming and in some cases not able to provide accurate data. Moreover due to the delay in the data processing the participating centres could benefit from the results of the study only after a long period of time.

In the meantime, during the period of study and in the years immediately after, many authors suggested a new and wider role of bone metastases radionuclide therapy [6].

Even if the standard for the evaluation of the efficacy of any new therapy remains the randomised studies, recent papers published on high impact factor journals [7], [8] suggested that a well organised observational study allows not only to reach in a clinical setting the same results of a randomised study but, also, to expand and increase the collection of the informations.

Under the light of the literature, a second phase of observational study was started in 2001. The data collection will finish at the end of 2003. To overcome the limits of the previous observational study and to allow communication between the participating centres a web based clinical folder was created.

Up to now, 72 nuclear medicine centres participated and more than 300 patients were enrolled. The database was organised with strict insertion controls. The centres can perform research both on their patients archive and, in an anonymous form, on all the recruited records. In this way the preliminary results of the study can be available to all the participating centres and a real–time communication among the centres has been developed.

Because the observational study has the purpose to evaluate the effectiveness of a therapy in a clinical and routinary setting we decided to allow that the most interesting records, in an anonymous form, could be used as teaching cases for continuing medical educational purposes in a specific section of the web site.

The works are still in progress but it is our opinion that:

1) the information technology of the database has allowed to organise an observational study with the same rigourness criteria of a randomised study;
2) at the end of the study, having recruited and analysed cohorts of patients with bone metastases that have different clinical presentation and therapeutic protocols, we will be able to assess the effectiveness of the new directions of *bmrt*;
3) the web site and the clinical folder will be not only the data collection tools of the study but they could become a hub for the exchange of data among all physicians involved in the care of patients with bone metastases.

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