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Abstract

Cancer is a complex disease and unfortunately understanding how the components of the cancer system work does not help understand the behavior of the system as a whole. In the words of the Greek philosopher Aristotle “the whole is greater than the sum of parts.” To date, thanks to improved information technology infrastructures, it is possible to store data from each single cancer patient, including clinical data, medical images, laboratory tests, and pathological and genomic information. Indeed, medical archive storage constitutes approximately one-third of total global storage demand and a large part of the data are in the form of medical images. The opportunity is now to draw insight on the whole to the benefit of each individual patient. In the oncologic patient, big data analysis is at the beginning but several useful applications can be envisaged including development of imaging biomarkers to predict disease outcome, assessing the risk of X-ray dose exposure or of renal damage following the administration of contrast agents, and tracking and optimizing patient workflow. The aim of this review is to present current evidence of how big data derived from medical images may impact on the diagnostic pathway of the oncologic patient.

Keywords (separated by '-'): Oncologic imaging - Big data - Quantitative imaging biomarkers - X-ray dose - Renal damage - Imaging databases

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ONCOLOGY IMAGING

Big data in oncologic imaging

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Abstract Cancer is a complex disease and unfortunately understanding how the components of the cancer system work does not help understand the behavior of the system as a whole. In the words of the Greek philosopher Aristotle "the whole is greater than the sum of parts." To date, thanks to improved information technology infrastructures, it is possible to store data from each single cancer patient, including clinical data, medical images, laboratory tests, and pathological and genomic information. Indeed, medical archive storage constitutes approximately one-third of total global storage demand and a large part of the data are in the form of medical images. The opportunity is now to draw insight on the whole to the benefit of each individual patient. In the oncologic patient, big data analysis is at the beginning but several useful applications can be envisaged including development of imaging biomarkers to predict disease outcome, assessing the risk of X-ray dose exposure or of renal damage following the administration of contrast agents, and tracking and optimizing patient workflow. The aim of this review is to present current evidence of how big data derived from medical images may impact on the diagnostic pathway of the oncologic patient.

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Keywords Oncologic imaging · Big data · Quantitative imaging biomarkers · X-ray dose · Renal damage · Imaging databases

Introduction

Big Data initiatives are aimed at drawing inferences from large datasets that are not derived from carefully controlled information [1]. In medicine, the basic idea behind using big data is to learn new knowledge from every patient we have ever treated and apply this knowledge to the next patient [2]. This concept will give future generations the opportunity to bring into existence a "fast learning health system" to the benefit of each individual patient. In the era of precision medicine, this evolutionary concept may lead to a comprehensive and individual approach to treatment [3]. In oncology, where information collected from the single patient is extremely variegated, big data analysis could allow definition of specific and efficient diagnostic and therapeutic pathways, improving patient workflow and quality of life. The aim of this review is to collect current evidence and to envisage how in the future big data may impact on the diagnostic pathway of the oncologic patient.

Big data in oncologic imaging: the rationale

The following key concepts related to big data should be considered when approaching oncologic imaging issues:

1. Opposite to traditional hypothesis-driven cancer research [4], big data research may be launched regardless of whether important questions are identified.

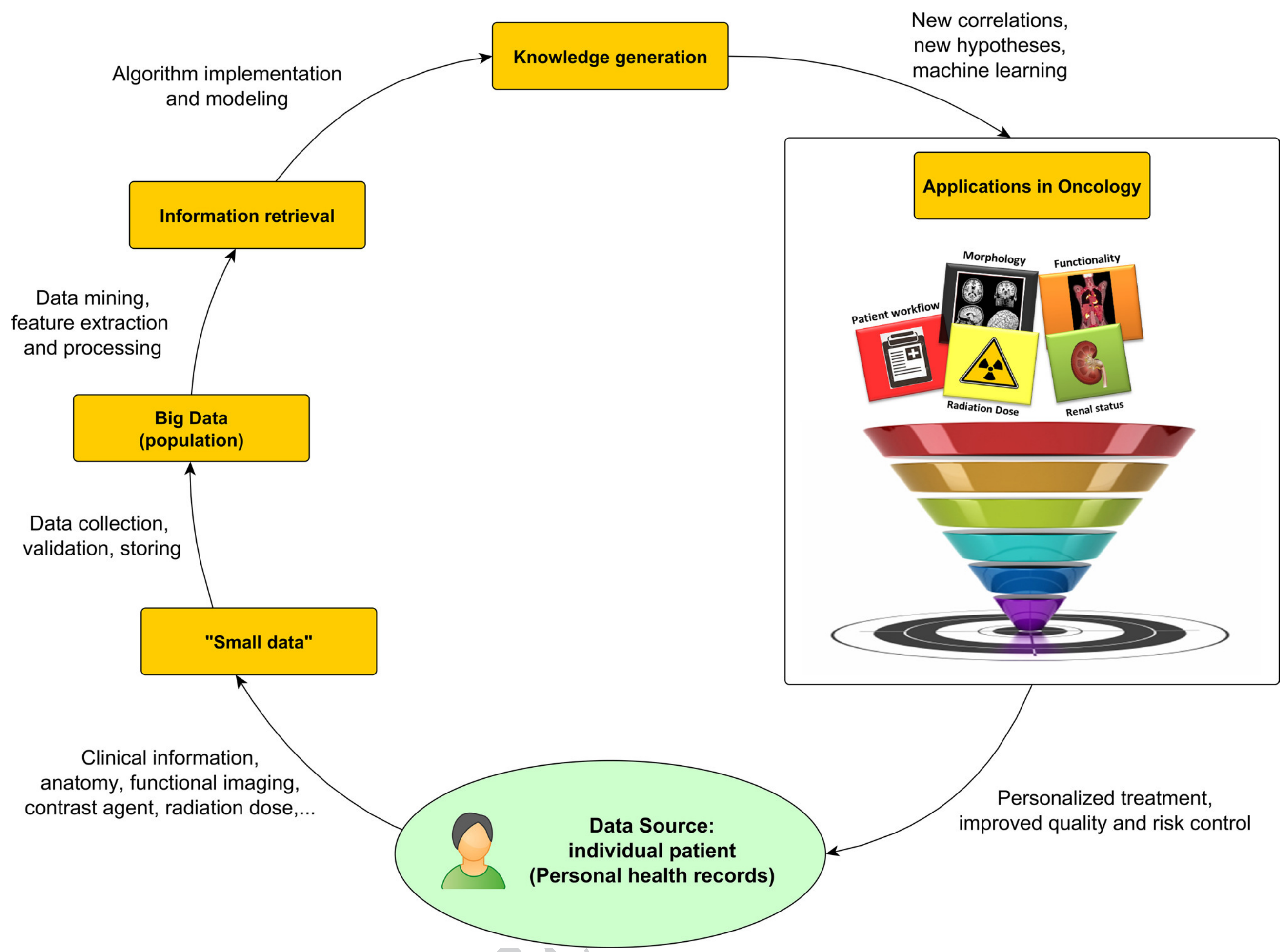

Fig. 1 Circle of medical knowledge in oncology. The individual patient is the source of information and the target of care delivery

2. Big data in health consists in datasets that are too big, too inhomogeneous, and too complex for healthcare providers to process and interpret with existing tools [5].
3. Big data is not about implementing one piece of technology, it also includes data mining and machine learning and offers potential alternative approaches to leveraging large data resources [6, 7].

Cancer fits well into these concepts, as it is a complex disease that changes, evolves, and adapts to the surrounding environment. Its evolution could be better understood by collecting information from different sources—e.g., demographic, genetic, imaging, treatment, and outcomes—that could then be processed as big data. In the last two decades, the development of efficient information technology (IT) infrastructures has allowed digitalization and electronic integration of healthcare information [8]. In 2012, AT&T estimated that the storage requirements for medical archives were increasing by 20–40 % each year, with medical images constituting one-third of total global storage demand [9, 10]. Today, an average size hospital manages approximately 665 TB of patient data, corresponding to approximately 140.000 DVDs [11].

Big data has the potential to dramatically reshape cancer care landscape, improving quality and efficiency in every cancer setting [12] (Fig. 1). In the field of oncologic imaging, big data may allow the development of tools for baseline assessment and for quantification of anatomic and functional changes over time. Quantitative imaging biomarkers will contribute to tailoring treatment to each individual patient. Extraction of data from radiation and contrast agent dose registries will allow to explore dose effects on subjects with cumulative X-rays, computed tomography (CT) scans, radiation therapy treatments, or nuclear medicine examinations and minimize contrast-induced nephrotoxicity by stratifying cancer patients into risk categories. Finally, processing of big data could support the development of optimized clinical workflows and in the end increase the management efficiency of comprehensive

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cancer centers and of tertiary health facilities in general [13].

Big data in oncologic imaging: current developments

Today, most of what we know about cancer comes from a tiny subset of patients, i.e., the 3 % who are enrolled in clinical trials; hence, those data are non-representative of the entire cancer population [14]. The remaining 97 % generate potentially useful information that is lost, due to the fact that data collection is mostly non-structured. In recent years, publicly accessible medical repositories are being implemented with the aim of collecting data from different imaging modalities. The cancer imaging archive (TCIA), for example, provides a public repository of cancer images and related clinical data [15]. The repository was created with the support of the National Cancer Institute with the aim of collecting, curating, and managing a rich collection of oncologic imaging data to enable open-science research. [16]. At present, more than 26 million radiologic images contributed by 28 institutions and several thousand pathology images are stored in this repository that is constantly increasing in size and variety [15]. In this chapter, we will review how the analysis of all this information benefits each individual patient.

Extracting the “dark matter” from medical images

AQ2 In medical images, data are usually provided as an orderly set of gray scale pixel values; however, in this form data are not synonymous of information or knowledge. Indeed, of the estimated 80 % of hospital data that are represented by unstructured imaging data [11], very little are currently being used for diagnosis. Eliot Siegel from the University of Maryland compared the data hidden in a clinical image, i.e., data that cannot be directly observed with current technology, as the “dark matter in space” [17]. The main challenge for future generations will be to extract important and meaningful information from this dark matter. Improvements in image analysis will reasonably bridge the gap between the visual content and its numeric representation, which includes encoded color and texture properties of an image, the spatial layout of objects, and geometric shape characteristics of anatomical structures. More and more diagnostic techniques are providing multi-modality imaging, with challenging big data management issues. A magnetic resonance (MR) examination, for example, includes high-resolution morphological images and information on tissue perfusion and diffusion capturing complex in vivo flow patterns; similarly, CT dual-energy acquisitions include information on material decomposition and spectral imaging [18]. Furthermore, combining different imaging modalities at the hardware level (MR/PET, PET/CT) will open up a range of new opportunities for image analysis [5].

Pattern recognition software and tools for high-throughput extraction of quantitative features have been implemented in parallel to the increase in dataset size and information. Conversion of images into mineable data and subsequent analysis for clinical decision support has paved the way to *radiomics* [1]. *Radiomic* data typically contain first-, second-, and higher-order statistics that can be combined with other patient data to develop models with improved diagnostic, prognostic, and predictive accuracy.

Diagnostic X-ray dose exposure

During the past 30 years, radiologic procedures involving ionizing radiation have been increasingly used in clinical routine leading to a dramatic increase in individual patient dose exposure. Today, medical radiation comprises almost 50 % of per capita radiation dose, compared with 15 % in the early 1980s [19]. Individual risk of developing radiation-related cancer from any single imaging procedure is extremely low; however, repeated examinations may lead to a substantial increase in such risk [20]. Unfortunately, epidemiologic literature on low-dose effects of ionizing radiations is limited by statistical power. In the future, the opportunity to exploit large databases will help clarify the relationship between cancer-induced pathologies and low-dose radiation levels [21, 22]. In particular, the introduction of radiation dose registries could be a valuable tool for patient monitoring and optimization of dose delivery. Collected information should include (1) radiation dose distributions and dose–volume metrics from treatment planning in radiotherapy (i.e., dose–volume histograms, the volume receiving a certain dose, minimum dose to a given volume, mean, maximum, and minimum dose); (2) X-ray doses from radiological imaging (i.e., volumetric CT dose index, dose-length product, dose-area product); and (3) gamma-ray and other radioisotopes radiation doses from nuclear medicine imaging and treatment. A radiation dose registry may allow clinicians to compare dose levels to the averages of other national and international centers, in order to successfully implement low-dose protocols. On the side, this AQ3 will favor standardization, create higher patient confidence in radiation safety, and offer the opportunity for better quality assessment.

Regulations and guidelines, such as the European directive Euratom 97/43, 2013/59/EURATOM, and the American College of Radiology dose Whitepaper, express the need for facilities to track radiation dose for patient and population, and support the implementation for dose registries. In particular, the European directive 2013/59/

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EURATOM points out that health authorities will be more pervasive on inspecting the dosimetry applied to patients. Integrating the Healthcare Enterprise (IHE—www.ihe.net) is an initiative of professional societies aimed at collaborating with the industry in order to coordinate standards-based solutions to problems that span multiple vendors systems. The new IHE radiation exposure monitoring (REM) Profile facilitates the collection and distribution of the estimated patient radiation exposure information resulting from imaging procedures and provides an implementation guide for vendors. By following this guide and participating in IHE Connectathon, vendors can release products that will interoperate to provide an exposure monitoring pipeline (http://www.aapm.org/meetings/amos2/pdf/42-12234-94897-404.pdf).

Some healthcare companies have already developed web-based dose management software to track and analyze patient radiation and iodine exposure across multi-facility, multi-modality, and multi-vendor imaging environments. These systems enable healthcare professionals to monitor radiation exposure and contrast media injection dose to their patients. In addition, these devices allow optimization of acquisition protocols in order to find the right balance between image quality and dose, minimizing the risk of radiation-induced cancers (http://www.dicardiology.com/article/software-help-manage-medical-imaging-radiation-dose). On the technical side, there are several crucial aspects of dose tracking that deserve to be remembered. The first is dose capture: non-DICOM-SR compatible CT scanners store dose information as images rather than in numerical form, requiring an optical character recognition algorithm to capture the data. Second, information has to be associated with the patient to be exportable to dose registries such as the American College of Radiology (ACR) Dose Index Registry (DIR). This database, opened in 2011, represents the most substantial effort to standardize radiation dose across the United States. Information related to dose indices to regional and national values is collected, anonymized, and stored across different care services. In 2013, the registry achieved dose index information on 5.5 million CT examinations across 750 registered facilities [23]. DIR is a data registry that allows facilities to compare their CT dose indices to regional and national values. Institutions are provided with periodic feedback reports comparing their results by body part and exam type to aggregate results (http://www.acr.org/Quality-Safety/National-Radiology-Data-Registry/Dose-Index-Registry).

Big data and radiation oncology

Big data repositories include detailed 3-dimensional dosimetric and imaging data, and their changes over time. Of these, the National Radiation Oncology Registry was designed to collect information on cancer care delivery among patients treated with radiation therapy [24, 25]. Predictive models can be applied to the collected treatment variables to assess patient outcome. In a pilot project, prostate cancer was selected as the initial disease site, and information was collected on clinical features, toxicity, and spatial and temporal dose distribution. Thanks to this pilot study, researchers may now identify best strategy options that allow patients to safely choose to do nothing or opt for mild treatments or surgery [26]. In the era of genomics, one may envision leveraging large repositories with detailed radiation therapy data, imaging data, and genomic profiles of tumor and normal tissue samples in order to better understand predictors of tumor control and risk of normal tissue injury, providing radiation oncologists the opportunity to potentially offer personalized dose prescriptions improving tumor control and reducing toxicity [7, 27].

Predicting renal damage

In recent years, the study of acute kidney injury has been facilitated by the increasing availability of stored demographic and clinical patient data [28, 29]. The Chronic Database of Kidney Diseases (CDKD), for example, is a database system designed to hold personal and laboratory investigatory details of patients with renal disease (http://www.cdkd.org/). Its goal is to make kidney-related physiological data easily available to the scientific community. CDKD currently contains more than 10,000 public data entries, available upon free registration [30]. Unfortunately, most datasets do not provide standardized information, and do not allow differentiation between acute and chronic disease. This heterogeneity may hinder comparisons and underestimate disease burden, limiting its application in a clinical setting [28].

Collecting information on kidney functional status could be particularly useful in cancer patients. These patients frequently repeat CT examinations for staging or assessment of response to treatment, in which administration of intravenous iodine contrast agent is generally required. It is well known that iodinated contrast agents are associated with an increased risk of contrast-induced nephrotoxicity; the risk is particularly high in patients that have impaired renal function and diabetes [31]. Furthermore, renal failure in oncological patients is often multifactorial and more common than in the general population [32]. The risk of complications from contrast medium administration is compounded by advanced age, dehydration, the number of times CT is repeated, and co-administration of nephrotoxic chemotherapeutic drugs. Thus, identification of factors predicting contrast-induced nephrotoxicity is important to avoid potentially serious complications, related to acute deterioration of kidney function [31].

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Tracking patient workflow

Oncological patient management is more and more a complex matter requiring constant monitoring throughout chemotherapy lines, radiation therapy sessions, scheduled follow-up assessments, etc. Thus, information collected from the very first diagnosis to outcome of every single patient is growing fast. To date, most of this information is passively accumulated by hospitals within PACS and RIS facilities. Conversely, in an integrated healthcare system, where interdisciplinary teams of specialists act together, all information should be linked with the aim of optimizing individual patient care, paving the way to truly personalized medicine.

To optimize current oncological workflows, it will be necessary to develop event-tracking systems in which monitoring points based on checklists are implemented. A good system should be able to identify workflow issues and technical errors in every step of patient management, advancing department quality control and improving existing processes or implementing new workflows [33]. Each patient in the processing chain will thus contribute to help clinicians and technicians to detect workflow inefficiencies, as incorrectly transmitted images or information during disease assessment, or delays in scheduled follow-ups. A patient tracking system would also simplify pinpointing the sources of error or mismatching within processes, producing as a result an honest picture of the current events, and enhance the ability to respond in real time. The opportunity at hand using big data is the ability to scan and connect massive repositories with the aim of providing new insights on patient workflow. Correlating clinical data with costs, outcomes, and performances will also support the development of evidence-based guidelines and clinical best practices. In the end, again, all of this will improve patient's access to treatment, reduce therapy side effects, and contribute to improve his quality of life and, on a population scale, allow healthcare systems to save more lives and contain costs.

Conclusions

The possibility to extract new knowledge from the huge amount of increasingly available unstructured data is crucial for advances in cancer diagnosis and treatment. Indeed, the strength of big data lies in its volume and variety. However, this process is not without challenges as big data analysis also has several intrinsic limitations, which limit its use. First, big data is usually extremely heterogeneous, can be missing, non-interpretable, conflicting, inaccurate, or stored in different locations. Second, it may be beyond human capabilities to analyze. Indeed, the very point of looking to big data is "to identify patterns that create answers to questions you didn't even know to ask" [34]. Finally, big data analysis may breach patient privacy. Therefore, the success of big data in creating healthcare value may require some changes in the current polices, to balance the potential societal benefits of big data approaches and the protection of patients' confidentiality [35].

In conclusion, the benefits of large-scale data mining to the oncologic patient are slowly emerging. Big data initiatives could be instrumental in improving the management and the quality of life of each individual cancer patient based on the results of imaging biomarker analysis or on the implementation of event-tracking systems. On a macroeconomics level, big data could support the implementation of evidence-based guidelines and of quality control measures, in the end reducing system inefficiencies. Because of their intrinsic heterogeneity, it will be very challenging to fully exploit big data.

Compliance with ethical standards

No funding was received for this work.

Conflict of interest Daniele Regge declares that he has no conflict of interest. Simone Mazzetti declares that he has no conflict of interest. Valentina Giannini declares that she has no conflict of interest. Christian Bracco declares that he has no conflict of interest. Michele Stasi declares that he has no conflict of interest.

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During the process of typesetting your article, the following queries have arisen. Please check your typeset proof carefully against the queries listed below and mark the necessary changes either directly on the proof/online grid or in the 'Author's response' area provided below

Query	Details Required	Author's Response
AQ1	Please check and confirm whether the affliations are processed correctly. Please amend if necessary.	
AQ2	Please confirm the section headings are correctly identified.	
AQ3	Please check the given sentence 'On the side, this will favor standardization...' for clarity and amend if necessary].	
AQ4	Please provide complete detailas for Ref. [9].	