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Current and future trends in imaging informatics for oncology

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Abstract

Clinical imaging plays an essential role in cancer care and research for diagnosis, prognosis and treatment response assessment. Major advances have been made over the last several decades in imaging informatics to support medical imaging. More recent informatics advances focus on the special needs of oncologic imaging, yet gaps still remain. We review the current state, limitations, and future trends in imaging informatics for oncology care including clinical and clinical research systems. We review information systems to support cancer clinical workflows including oncologist ordering of radiology studies, radiologist review and reporting of image findings, and oncologist review and integration of imaging information for clinical decision making. We discuss informatics approaches to oncologic imaging including but not limited to controlled terminologies, image annotation, and image processing algorithms. With the ongoing development of novel imaging modalities and imaging biomarkers, we expect these systems will continue to evolve and mature.

Keywords

Imaging Informatics; Oncologic Imaging; Cancer Imaging; Image Annotation; Electronic Order Entry; Image Repository; Image Meta-data Repository; Treatment Decision Support; Cancer Treatment Response Assessment; Response Criteria

1. Introduction

Clinical imaging plays an essential role in the continuum of cancer care and research including diagnosis, prognosis, and treatment response assessment. Imaging studies are used to identify the location, extent, and features of tumor lesions. These imaging features may be qualitative (e.g. lesion density) or quantitative (e.g. lesion dimension), and form the basis for an image-based interpretation of the disease state that likewise may be qualitative (e.g. partial response to treatment) or quantitative (e.g. %50 decrease in sum of diameters of target lesions). Oncologists use imaging studies to determine clinical stage and inform initial

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treatment decisions such as the appropriateness of upfront surgery versus systemic therapy. Imaging studies are also used to monitor response to treatment including defining the events of tumor remission, recurrence, and progression. These assessments inform clinical decision-making with respect to the duration of therapy and changes in therapy with disease recurrence or progression. In addition, research is ongoing to develop novel imaging features for cancer diagnosis, prognosis, prediction of response to treatment, and early assessment of treatment response to enable adaptive therapy (1).

Over the past 3 decades, significant advances have been made in imaging informatics to support clinical imaging. Most radiology departments are now filmless and largely paperless, utilizing digital image acquisition modalities, digital image storage media, and electronic text reporting systems. Picture archiving and communication systems (PACS) (2) are now the predominant systems for storing, querying and retrieving digital images. The universal format for PACS image storage and transfer is DICOM (Digital Imaging and Communications in Medicine) (3). DICOM viewers, previously only available at high cost in radiology departments are now available as web-based applications that can be integrated into electronic health records for review of images by referring providers as well. Radiology Information Systems (RIS) manage patient scheduling, reporting, and billing.

These advances have enabled distributed viewing of imaging studies by multiple providers outside of the physical constraints of the film library. Oncologists are now able to view the imaging studies in their clinic and make treatment decisions based on these findings at the point of care. Imaging studies may also be transmitted via digital media or electronically between institutions further enabling distributed cancer care across multiple locations. Yet these advances have also created a communication fissure between what previously was often a face-to-face consultation between the radiologist and oncologist regarding the indication for and interpretation of the findings for complex cases (4).

Despite these informatics advances, gaps remain in supporting the needs of oncologic imagers and oncologists in the interpretation of image findings for cancer care. In the current clinical workflow, oncologists and radiologists communicate through various forms of clinical documentation. Oncologists create radiology requisitions, either paper or electronic, which communicate the indication, timing, modality and body part to be evaluated by the requested imaging study. The radiologist reviews the images and creates a radiology report summarizing the findings. The oncologist then reviews the radiology report and images to inform their diagnostic and treatment decisions.

There are several limitations to this current workflow and communication approach between oncologists and radiologists. A recent survey by Jaffe examined the opinions and practice patterns of radiologists (5) and the opinions and expectations of oncologists (6) regarding reporting tumor measurements in radiology reports for cancer patients. They found a significant discordance between radiologist practice patterns and oncologist expectations on the types of imaging findings that should be reported in a radiology report for cancer patients. This included both expectations for standard of care and clinical trial studies. In another study, we evaluated radiology reports of patients enrolled in clinical trials and found that only 26% of follow-up studies had sufficient information recorded in the medical record

to perform quantitative RECIST measurements at follow-up (7). Current approaches for evaluating and reporting image findings for cancer patients are inconsistent and suboptimal.

In addition, there are several limitations to current approaches for quantitative assessment of tumor response in clinical trials that make it difficult to change this paradigm. Tumor response criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST) (8) for solid tumors and the International Harmonization Criteria (IHC) (9) for lymphoma have several advantages and limitations. In particular, RECIST and the IHC utilize imaging modalities that are widely available with reproducible image acquisition techniques. They also utilize anatomic estimates of tumor burden (e.g. the sum of diameters for RECIST) that are relatively easy to generate using standard caliper tools available in all digital image viewing workstations. However, despite the simplicity of this measurement technique, linear measurement of longest diameter is not consistently reproducible between reviewers (10). Nor is the selection of target and non-target lesions for inclusion in the sum of diameters calculation (10).

In addition, changes in the estimate of tumor burden with treatment do not always correlate with time to progression and overall survival, especially for non-cytotoxic therapies (11). These limitations diminish the utility of RECIST as an intermediate response biomarker in cancer clinical trials, and put into question the appropriate use of this criterion for standard of care practice (8). Yet RECIST has been evaluated with data from multiple clinical centers and multiple types solid tumor (12) and remains the sanctioned response criteria by regulatory agencies for cancer clinical trials (8). As new imaging modalities are introduced and new image biomarkers are validated, it is expected that cancer response criteria will continue to evolve (1,13).

The situation is further complicated by the rising utilization of imaging studies in cancer care with the resultant rising cost (14) balanced by growing concerns for increased medical radiation exposure, especially in young, long-term survivors (15,16). Clinical practice guidelines regarding appropriate and inappropriate utilization of imaging studies in oncology are maintained by both radiology (17) and oncology professional societies. Yet there is a relative lack of decision support tools to assist providers in selecting appropriate image based strategies for staging and response assessment.

More recent imaging informatics efforts have begun to focus on the needs of both radiologists and oncologists to better support cancer care and research. We review the current state, limitations, and future trends in imaging informatics that are oncology specific and those general trends which will secondarily impact the oncology community. We review these trends in the context of workflows for clinical care and clinical research. Clinical and clinical research workflows include a discussion of informatics tools to support 1) the oncologist ordering imaging studies, 2) the radiologist review and annotation of images and reporting of image findings, and 3) the oncologist review of the images and reports for clinical decision making. This framework enables a discussion of the people, process and technologies in these workflows, their limitations, and opportunities for improvement.

2. Current trends and limitations in workflows for oncologic imaging

2.1. Oncologist orders imaging study

Imaging studies are used for many clinical indications within oncology. The oncologist must first select the appropriate imaging modality, body part, and frequency with which the imaging study is performed based on the clinical indication. The oncologist then orders the study using either a paper or electronic radiology requisition form. Several factors are taken into account when selecting the appropriate imaging study. The imaging modality (e.g. CT, MRI, or PET) is selected depending upon the primary type of cancer (e.g. breast, prostate, brain), the location of any metastasis, and patient tolerance to the procedure (e.g. IV contrast allergy or poor renal function may be a contraindication for certain CT protocols). Imaging studies are often performed serially to assess disease response to treatment. In clinical trials, the frequency with which imaging studies should be acquired is well specified in the clinical trial protocol, as is the preferred imaging modality. In standard of care practice however, the guidelines for the appropriate frequency of imaging studies are not as well specified.

Professional societies in both radiology and oncology have developed clinical practice guidelines for appropriate utilization of imaging studies in oncology. The American College of Radiology (ACR) has developed the Appropriateness Criteria® (17,18), evidence based guidelines to assist referring providers make the most appropriate use of imaging studies for specific clinical conditions including cancer. ACR offers an online search tool to help providers find relevant sections of the Appropriateness Criteria® which are published as PDF documents (19). The Appropriateness Criteria have variable coverage of specific cancer imaging findings (e.g. liver mass) and specific cancer diagnoses (e.g. pretreatment staging of colorectal cancer). Likewise, the National Comprehensive Cancer Network (NCCN) clinical practice guidelines contain information on the appropriate use of imaging studies for particular cancer diagnosis (20) and are also published as PDF documents. However, despite the existence of these guidelines, there is a relative lack of decision support for oncologists at the point of order placement in selecting the appropriate imaging study for a particular indication. In addition, the PDF format for publishing these guidelines does not facilitate adoption at the point of care.

Once the oncologist has selected the imaging study to perform, they complete an order using either a paper or electronic radiology requisition form. At the time the order is placed, the oncologist must communicate sufficient information so that the correct study and image acquisition protocol is performed at the correct time, and provide sufficient clinical context to assist the radiologist in answering the clinical question posed by the imaging study. Radiology technicians typically determine the image acquisition protocol based on the ICD-9 billing code provided by the oncologist in the radiology requisition. The acquisition protocol includes details regarding the use of contrast, the image slice thickness, and the anatomic coverage of the imaging study for a particular modality. The inconsistent use of ICD-9 codes by the ordering provider can result in different image acquisition protocols being performed from baseline to follow-up. For example, the image acquisition protocol for “abdominal pain” which may be the indication for the baseline imaging study when the cancer is first diagnosed, may differ from the image acquisition protocol for “colon cancer”

used at the time of requesting the follow-up study. The use of different image acquisition techniques can make it difficult to compare the baseline and follow-up studies with respect to treatment response assessment.

In addition, the oncologist should communicate the clinical context for the imaging study to the radiologist so that they can best interpret the image findings in the context of the clinical question being asked. For example, in order for a radiologist to make a sufficient interpretation of tumor response to treatment in the advanced disease setting, they need information regarding the type of therapy the patient is currently receiving, when it started so they can compare to the baseline study, and any particular lesions of interest that the oncologist is tracking (e.g. target lesions). In addition, for clinical trial protocols, it is important to communicate to the radiologist which response criterion (e.g. RECIST 1.0 (21) or RECIST 1.1 (8)) is being used for response assessment in that particular clinical trial. However, radiology requisitions typically do not contain this level of detail, and the lesion flow sheets that track the target and non-target lesions of interest are not typically completed by the oncologist, are stored in the clinical trial management system, and are not shared with the radiologist. This communication gap is partially due to limitations of the current information artifacts used to communicate requests for imaging studies and partially due to lack of a shared view of clinical information between radiologists and oncologists.

Finally, little decision support exists for assisting providers in taking into account the patient's prior medical radiation exposure and the potential for additional radiation exposure with the planned study. There has been a great deal of media and scientific coverage related to potential adverse effects of medical radiation (15,16) including an increased risk of malignancies. Oncology care often involves repeat exposure to medical radiation in follow-up care. The long-term effects of radiation exposure are especially relevant for young long term survivors who continue to get regular follow-up imaging studies to screen for recurrence. The Radiologist Society of North American (RSNA) has launched the Image Wisely campaign (22) to increase awareness about adult radiation protection and to encourage radiology departments to optimize the effective radiation dose of their image acquisition protocols to balance image quality required for answering the clinical question with radiation exposure. Likewise, the Alliance for Radiation Safety in Pediatric Imaging has introduced the Image Gently campaign (23) with the goal of lowering radiation doses in imaging of children. Other initiatives are encouraging the collection of patient specific effective radiation dose information as part of the image acquisition process (24). Little decision support however is available to incorporate this information into a providers decision regarding which modality to choose or how frequent to image their patients in order to minimize lifetime radiation exposure. Complexity remains in the dimensions that must be taken into account when making a decision on if, when and how to use imaging studies in the care of cancer patients.

2.2. Radiologist reviews and reports image findings

Once the radiology requisition is received, the imaging study is scheduled, the radiology technician selects the image acquisition protocol according to departmental guidelines, and the images are acquired. The radiologist then reviews the images, identifies any tumor

lesions, and summarizes the findings in a text report. Imaging studies may contain hundreds of images, yet only a few images have significant findings. As such, much of radiology reports summarize the lack of findings or the presence of normal findings. Debate remains among radiologists and oncologists regarding the necessary level of detail sufficient to describe tumor lesions in radiology reports for oncology clinical decision-making in standard of care practice (5,6). Yet it remains clear that current standards for radiology reporting are insufficient for more rigorous application of formal oncology response criteria such as RECIST (7). Radiology reports sufficient to apply quantitative response criteria would need to contain detailed information on 1) the features of identified tumor lesions, 2) an estimate of the tumor burden, and if applicable, 3) an estimate of changes in tumor burden. While such detail is currently the standard only in cancer clinical trials, it presents a useful framework for discussing some of the current limitation in radiology reporting of cancer cases.

Tumor lesion features required for quantitative estimates of tumor burden include a lesion identifier, anatomic location, qualitative and quantitative attributes, and comparison of attributes over time. A lesion identifier is commonly used in lesion flow sheets, such as the one shown in Figure 1. A lesion identifier allows the lesion to be serially tracked over time, across overlapping series, and across modalities. However, lesion identifiers are not typically used in standard radiology reporting practices. Instead, the radiologist can use several methods for describing the location of the lesion including anatomic descriptions (e.g. 4th segment of the liver), series and image number (e.g. series 2 image 75) and/or image mark-up. While these methods can assist a reviewer of the radiology report in re-identifying the lesions, ambiguity remains especially in the situation when multiple tumor lesions are co-located on the same image and in the same organ, as is common with liver metastasis. Furthermore, the level of detail provided with respect to lesion identifiers and location varies considerably from radiologist to radiologist, and from lesion to lesion within the same report.

In addition to location, information is required regarding the qualitative and quantitative features of lesions. Qualitative features include visual observations such as lesion border or density, as well as lesion classifications such as target lesion or non-target lesion. Lesion classification according to response criteria is rarely included in the radiology report and limited to use in lesion flow sheets for clinical trials. Yet such classifications provide essential information to radiologists regarding the key lesions of interest for the oncologist who is tracking treatment response both on and off study. Communication of the target lesions is especially important when baseline and follow-up studies are reviewed and reported by different radiologists who may focus on different image findings when reporting lesion details.

Quantitative lesion features are typically attributes measured using tools for image feature extraction. Caliper tools in radiology workstations enable manual measurement of a lesion's linear dimension. SUV maximum and density measurement tool provide similar semi-automated feature extraction. As with the reporting of qualitative features, there is a wide variability in radiologist measurement and reporting of these quantitative lesion features

within and across studies, making it difficult for oncologists to complete the details of the lesion flow sheet (7).

In addition, these approaches for tumor lesion feature extraction lack inter- and intra-reader precision and accuracy. Studies comparing inter-reader lesion measurements for RECIST show a high degree of discordance that can impact calculated estimates of tumor burden and classification of response (25,26). More sophisticated lesion image feature extraction methods (e.g. lesion segmentation algorithms) may provide an improvement in precision and accuracy across readers, and remain the focus of ongoing research (1).

Furthermore, the method of recording these quantitative features in free text reports makes it impossible to perform even simple calculations of changes in lesion dimension over time or aggregate calculations such as estimates of tumor burden. Calculations such as the RECIST sum of diameters are rarely included in radiology reports and are limited to the special circumstances of clinical trial lesion flow sheets (Figure 1). Likewise, radiologists typically do not report quantitative changes in tumor burden needed to perform formal classification of treatment response. Instead, they provide a qualitative impression of treatment response that typically only compares the tumor lesion features to those of the most recent study as opposed to the baseline study.

The method of reporting imaging features in free text reports and image mark-up contributes to the lack of reporting quantitative feature aggregation. Image mark-up refers to the graphical display of information describing an image or a region on an image. Image mark-up tools include caliper tools for linear measurement, arrows, and rectangles that identify the set of significant pixels on the image. However, image mark-up lack semantics, that is the meaning of the significant findings. Their primary function is to redisplay visual overlays on top of images to focus the viewer's attention to key image findings. Yet without semantics, the computer has no understanding of the significance of those findings. Furthermore, industry standards for the representation, storage and transfer of image mark-up are lacking. As such, image workstation vendors created their own unique representation and storage format for the image mark-up. This means image mark-up cannot be transmitted or shared between systems unlike the DICOM images themselves that conform to a standard.

Likewise, there is no industry standard for representing and storing aggregated information regarding tumor lesion finding such as would be required to store information on the sum of diameters estimate of tumor burden for RECIST. Radiologists rarely calculate or report aggregated quantitative tumor burden estimates in standard of care practice. In clinical trials with central reviews, radiologists will often calculate these types of estimates however, inter- and intra-reader discordance remains (10). Radiologists however, will typically provide a subjective, qualitative interpretation of tumor response to treatment in standard of care practice. However, radiologists will often interpret tumor response by comparing the new study to the previous study instead of the pre-treatment baseline study, in part because they are unaware of when the patient started the most recent therapy. In addition, they lack a consistent terminology and methodology for describing tumor response when not formal response criteria are not utilized.

As we have described above, there are significant limitations to current approaches for summarizing radiology image findings in free text reports. Free text reports lack a direct reference to the image findings to which they refer and are not machine computable. Most radiology reporting practices do not utilize a set of controlled terminology for describing the tumor lesion location and image features. In addition, there is high variability in the level of detail and diagnosis specific imaging features recorded by individual radiologists. The RSNA has developed a set of reporting templates that define the types of features that should be reported and a respective terminology to describe the features for a given image finding (27). This effort is similar to efforts by the College of American Pathologists cancer diagnosis checklists that describe the essential features required when reporting the pathology findings of a cancer case (28). However, the RSNA templates remain more focused on general image findings such as “lung mass” as opposed to specific cancer diagnosis such as “lung cancer”. Templates are still lacking that describe the set of relevant image features to report for a specific modality (e.g. CT), anatomic location (e.g. chest), and cancer specific diagnosis (e.g. Non-Small Cell Lung Cancer).

2.3. Oncologist reviews and integrates imaging data for clinical decision-making

The oncologist uses the report, image annotations, and raw imaging data to aid diagnosis and treatment decisions. However, there is no current technology to enable the ordering clinician to directly access those regions of the images corresponding to each abnormality described in the radiology report. The oncologist must use the textual descriptions and image number references in the report as a guide to re-identify the lesions of interest. Some image viewing systems allow all images with image markup to be viewed together as key images, decreasing the search space, but unfortunately, radiologists do not mark all the regions of interest. Like the radiologist, the oncologist uses a qualitative assessment of the data within the context of the larger clinical picture to make an impression of the disease state and subsequent treatment decisions.

In the context of clinical trials on the other hand, the oncologist will typically complete the lesion flow sheet (Figure 1), extracting the tumor lesion dimensions, calculating the tumor burden and changes in tumor burden, and classifying response according to the defined clinical trial protocol response criteria. The classified response drives treatment decisions with respect to continuing or discontinuing therapy according to the clinical trial protocol decision logic. However, the lesion feature information in the flow sheet does not directly reference a set of voxels in the image to enable auditing, and oncologists are often being asked to take screen captures or print the images with the measurement mark-up of the respective lesions.

3. Informatics to support oncologic imaging

As described above, several limitations remain in the current clinical workflow of oncologist imaging. Several ongoing efforts in imaging informatics are attempting to address some of these issues with respect to enhanced computerized order entry, and tumor lesion feature extraction, representation, storage and visualization.

3.1. Computerized order entry

As discussed above, several limitations remain with respect to assisting oncologists at the point of order entry select the appropriate imaging study and communicate sufficient information to the radiologist to answer the clinical question posed. Several informatics initiatives are working to address these limitations. In particular, work is also ongoing to transform the ACR Appropriateness Criteria into a computable format, so that this business logic can be integrated into order entry systems (29,30). This could allow sharing of computable business logic across institutions but requires mapping the computable interpretable guidelines data items with the institutions electronic health record.

A parallel but complimentary effort by the RSNA is the develop of the RadLex Playbook (31), an ontology to provide a standard, comprehensive lexicon of radiology orderables and imaging procedure step names. This could improve the consistency of imaging procedure names across institutions, a vital step for image data exchange across institutions both for clinical care and research. It could also assist efforts to encode the ACR Appropriateness Criteria with a standardized terminology for radiology procedures.

Opportunities also exist to improve the communication gap between oncologists and radiologists with respect to the oncologist specifying the relevant clinical history, key tumor lesions, and response criterion needed for the radiologist to adequately interpret an imaging study. As will be discussed in more detail below, new methods for annotating, recording, visualizing, and integrating the image meta-data of tumor lesions provide an opportunity to assist both the radiologist and oncologist in understanding the clinical context of a study.

3.2. Tumor lesion feature extraction, representation, and storage

The current approach for managing the feature information of cancer lesions is to record these image meta-data on paper or electronic case report forms. One of the key limitations of this approach is the inability to link the image meta-data to the voxels in the source image. This presents challenges for auditing and reasoning with image meta-data. The current digital image measurement tools only generate simple image mark-up that is viewable by humans but not directly machine-accessible. Recent informatics initiatives offer an opportunity to transform how image meta-data is recorded and stored such that the link to the primary image source is maintained. These initiatives include the development of 1) imaging ontologies and Common Data Elements, 2) image annotation standards, 3) image annotation tools, and 4) image meta-data databases.

Ontologies and Common Data Elements—Case report forms (CRFs) are used in clinical trials to standardize the acquisition of clinical research data. CRFs contain data elements—data collection items comprising a question and a set of allowed answers to that question. The allowed answers often are constrained values chosen from ontologies or controlled terminologies. For example, a RECIST CRF would include a data element for each image finding “RECIST lesion classification” with a possible set of answers including “Target Lesion, Non-Target Lesion, Suspicious Lesion, Normal Finding, and New Lesion” (controlled terms from the RECIST criteria). Ontologies provide a formal representation of concepts and relationships between concepts, enabling a shared semantics between systems.

CRFs created for many different clinical trials share data elements, referred to as Common Data Elements (CDEs). The CDEs are useful to identify since they can be re-used by multiple case report forms within and across organizations. The National Cancer Institute's Cancer Therapy Evaluation Program (CTEP) has created CDEs for use in RECIST 1.0 case report forms. The NCI's Cancer Data Standards Registry and Repository (caDSR) (32) maintains these CDEs for public use. The use of common data elements across clinical trials and institutions also enables data sharing.

Several ontologies exist or are under development that may assist in the creation of CDEs for imaging. The RSNA has developed the RadLex (33) ontology describing over 30,000 radiology related concepts and relationships. Early applications of RadLex include radiology decision support, reporting tools, and search applications for radiology research and education (33). The RSNA reporting templates use RadLex terms to encode the content of their image findings (27). RadLex contains a comprehensive set of terms that describe the features of cancer lesions, and contains several RECIST related concepts, but not a comprehensive set of concepts to represent all of the qualitative and quantitative imaging findings and aggregated data for RECIST. At this time, there is no existing ontology that describes the range of quantitative imaging biomarkers required to describe cancer lesions.

Image annotation standards—It is useful to distinguish between *image mark-up* and *image annotation*. Image mark-up refers to the graphical display of information describing an image or a region on an image. An image annotation refers to the information conveyed by the mark-up (image meta-data) that describes the content of the image or image region. DICOM Structured Reporting (SR) (34) is the industry standard for representing image meta-data generically. DICOM-SR specifies the classes used for transmission and storage of clinical documents including free text reports and structured information. Clunie in (35) proposes a DICOM-SR template structure that could be used to record quantitative and qualitative information related to RECIST measurements for patients enrolled in cancer clinical trials. He describes the use of DICOM-SR template that would store all of the key lesion meta-data information for a single patient over the course of multiple serial imaging studies and multiple image modalities. However, the DICOM-SR model on non-image information is report-centric, not an explicit model tailored to representing image content in terms of anatomic entities, radiology observations, and ROIs corresponding to those observations. DICOM-SR lacks a particular model focused on the image content per-se.

The Annotation and Image Markup (AIM) (36) standard has been developed as part of the NCI Cancer Biomedical Informatics Grid (caBIG) program (37). AIM provides an information model for storing the key information about lesions needed to describe cancer lesions and apply quantitative criteria of response assessment, such as lesion identification, location, size measurements, method of measurement, and other quantitative features. The AIM files also convey information about the image mark-up including the source image file, image coordinates, quantitative features such as measurements, and qualitative observations. The image observations are encoded utilizing an ontology such as RadLex (33) that contains radiology specific terms. The AIM project includes a module to serialize DICOM-SR for culpability.

Image annotation tools—Image annotation tools have been developed (38) that implement the AIM standard for creating image meta-data in a structured format. These tools are crucial to implement AIM since the latter is a complex data structure that is a transformation of the unstructured information collected during the image interpretation process.

Image annotation templates are incorporated into image annotation tools to facilitate structured capture of image annotation information. These annotation templates combine data elements for use in a specific context. For example, image annotation templates have been developed for annotation of liver lesions on abdominal CT scans that detail the pertinent qualitative descriptions for diagnostic evaluation of liver lesions. Annotation templates have also been developed for structured reporting of malignant glioma lesions on Brain MRI's as part of the VASARI project for the REMBRANDT (REpository of Molecular BRAin Neoplasia DaTa) (39).

Image meta-data databases—The image meta-data files need to be stored in a database to manage and retrieve this information. Image meta-data databases have been developed using relational (40,41) and XML-based models (42). Annotation of image findings enables queries regarding the visual observations in image data sets (40).

3.3. Visualization and integration of image meta-data and clinical data

Current approaches for organizing, aggregating and visualizing image meta-data consist of manual processes of transcribing lesion feature information onto case report forms or lesion flow sheets. However, these approaches do not maintain the link between the image meta-data and the respective set of voxels in the image. Image annotation offers an improvement over these manual approaches. Research systems have recently been developed that automatically populate lesion flow sheets, calculate estimates of tumor burden (43) and classify tumor response to treatment using rule-based interpretation of response criteria (44) much like those shown in Figure 1. The use of an image annotation tool to directly populate lesion flow sheets provides several advantages. First, the use of an information model and controlled terminology to encode cancer lesion image findings provides a consistent representation for storage and sharing of image meta-data needed for cancer clinical trials. The information model also provides a foundation to enable reasoning with and querying over image meta-data for response assessment (44). Image annotation provides lesion identifiers that link lesion meta-data directly to the source image and image mark-up. Image annotation tools also directly generate meta-data about image mark-up such as length calculations eliminating possible transcription errors for length measurements.

Furthermore, the development of structured image meta-data presents an opportunity to integrate image meta-data into electronic health records for use in tracking disease for treatment decision-making. From this perspective, it is important to consider how quantitative response data is visualized and presented within the workflow of the treating provider for treatment decision-making. The RECIST sum of diameters can be visualized along a temporal axis as shown in the bottom graph of Figure 2. Placed in the context of treatment data (top of Figure 2), such information very quickly communicates the disease

status of a patient over time. Methods that exploit image annotation offer the possibility to utilize the quantitative and qualitative features in images to improve the quality of information presented to oncologists in such patient information summaries. It also presents an opportunity to share these same integrated views of the information with the radiologist who is interpreting the images to better understand the clinical context for the study. Such visualizations provide the essential link between the abstracted features within images and the respective source image, and not merely summarize changes in disease over time, but enable navigation to the source image files. Integration and visualization of image annotation data offers a unique opportunity to transform image data from the traditional text report format to a flexible computable format.

4. Future Directions

Over the past thirty years, image based cancer response criteria have been iteratively refined based on estimates of tumor burden that rely upon human measurement of cancer lesion dimensions and qualitative evaluations of the presence or absence of lesions. As noted above, this approach has several advantages and limitations. Ongoing research initiatives strive to develop accurate and reproducible quantitative estimates of tumor burden that correlate with clinical outcomes (1). In particular, changes in the quantitative estimate of tumor burden should correlate with time to progression and overall survival in order to be a useful response biomarker and intermediate endpoint for cancer clinical trials and treatment decision-making. Development, validation, and qualification of novel quantitative image response biomarkers require both retrospective and prospective testing with large data sets. Ideally, image-processing algorithms will enable automated or semi-automated cancer lesion detection and feature extraction for quantitative and reproducible estimates of tumor burden.

5. Conclusions

We have described the current and future trends in imaging informatics to support oncologic imaging. Significant limitations exist with the current workflows for ordering imaging studies, and for extracting, reporting, reasoning about, and visualizing cancer lesion imaging features sufficient for clinical decision-making. People, process and information technology initiatives are addressing some of these issues. Image annotation in particular represents a key innovation by introducing a machine-readable and semantically explicit form for recording tumor lesion features. Much work however remains in evaluating these approaches for radiologist acceptance and integration with vendor imaging workstations and PACS. However, the needs of the oncology community for improved annotation and reporting of tumor lesion findings is one of the driving use cases for this new approach.

Limitations also remain with the currently available oncologic imaging features as biomarkers for diagnosis, prognosis, prediction and response assessment in oncology. The development of novel cancer imaging biomarkers may present an opportunity to improve the consistency of patient care and the predictive value of imaging biomarkers as intermediate clinical trial endpoints. The ongoing development of quantitative imaging algorithms to extract quantitative features of disease presents a promising prospect for improved reproducibility and consistency for estimates of tumor burden. Much of this science remains

in the early phases of development, and much work remains to validate and qualify these biomarkers for use in standard of care practice. Much work will also need to be done to integrate these novel image-processing tools into clinical imaging systems for use in everyday practice. Imaging informatics methods to support oncologic imaging will continue to evolve as new imaging modalities and image biomarkers evolve for cancer care.

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	Lesion ID	Anatomic Location/Lesion Type	B 7/8/06	F1 9/15/06	F2 11/22/06	F3 1/29/07
Target Lesions	1	liver mass	1.8	1.0	0.9	1.3
	2	liver mass	3.7	2.0	1.9	2.4
Non-target Lesions	3	liver mass	1.1	0.5	-	-
	4	T4 bone lesion	+	+	NE	++
	5	Right 8th rib bone lesion	+	+	NE	+
	6	Left pleural space effusion	+	+	-	-
New Lesions	7	liver mass				+
Response Analysis	Sum of Diameters (SD)		5.5	3.0	2.8	3.7
	% Change SD from Baseline			-45%	-49%	-33%
	% Change SD from Nadir			0	0	+32%
	Target Lesion Response			PR	PR	PD
	Non-target Lesion Response			Non-CR/ Non-PD	Not all Evaluated	PD
	Response			PR	PR	PD
	Overall Best Response		Partial Response (RR=-49%)			

Figure 1.

Lesion flow sheet: Example RECIST flow sheet for patient LL. MR# = Medical Record Number, B=Baseline, F1= First Follow-up, F2 = Second Follow-up, F3 = Third Follow-up, NA=Not Applicable, (+) = present, (-) = absent, SD = Sum of Diameters, PR = Partial Response, PD = Progressive Disease, non-PD/non-CR = Not-Progressive Disease/Not-Complete Response.

Figure 2.

Visualization of response data and clinical data along a time-line. The top section visualizes specific medication administration events. The middle graph visualizes a serum response biomarker CEA in relation to the treatment events. The bottom graph visualizes the RECIST sum of diameters with each colored bar representing the longest diameter of a respective target lesion.