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Utilization of a Novel Thoracic Oncology Database in Evaluation of Response to Chemotherapy, Radiology, and Pathology in Malignant Pleural Mesothelioma

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Abstract

Objective An area of need in cancer informatics is the ability to store images in a comprehensive database as part of translational cancer research. To meet this need, we have implemented a novel tandem database infrastructure that facilitates image storage and utilization.

Background We had previously implemented the Thoracic Oncology Program Database Project (TOPDP) database for our translational cancer research needs. While useful for many research endeavors, it is unable to store images, hence our need to implement an imaging database which could communicate easily with the TOPDP database.

Methods The Thoracic Oncology Research Program (TORP) imaging database was designed using the Research Electronic Data Capture (REDCap) platform, which was developed by Vanderbilt University. To demonstrate proof of principle, we performed an investigation into tumor response for malignant pleural mesothelioma (MPM) patients treated with either of two analogous chemotherapy regimens.

Results A cohort of 22 MPM patients was identified using clinical data in the TOPDP database. After measurements were acquired, images were successfully stored in the TORP database, along with clinical and demographic data.

Discussion We implemented the TORP imaging database to be used in conjunction with our comprehensive TOPDP database. While it requires additional effort to use two databases, our database infrastructure facilitates more comprehensive translational research.

Conclusion The investigation described herein demonstrates the successful implementation and ease of use of this novel tandem imaging database infrastructure, as well as the potential utility of investigations enabled by it.

Introduction

Imaging is an integral tool in oncology, aiding clinicians in such tasks as diagnosing a patient's malignancy, determining appropriate therapies, and assessing treatment response. In order to maximize the utility of cancer imaging, the oncology and imaging communities have devoted significant resources to developing informatics tools that allow both clinicians and researchers to store, utilize, and share cancer images in more effective ways.[1-3] Efforts to date have yielded many benefits, especially for clinicians and imaging specialists; however, they have yet to address some areas of need in cancer imaging. One of these deficit areas is the ability to efficiently store and utilize images as a part of collaborative translational cancer research.

The Thoracic Oncology Research Program at the University of Chicago Medical Center (UCMC) have used the Thoracic Oncology Program Database Project (TOPDP) database for our translational research efforts.[4] The TOPDP database was developed to serve as a comprehensive translational database that interfaces with the UCMC online tissue bank and integrates patient clinical information with proteomic and genomic information obtained from tumor tissue samples. Because the TOPDP database uses Microsoft Access as its underlying technology, it is technically capable of storing images. However, Access databases can only store up to 2 GB of data, so the TOPDP database does not meet our imaging storage demands. To meet this need, we have designed and implemented the Thoracic Oncology Research Program (TORP) imaging database using the Research Electronic Data Capture (REDCap) database platform, which was developed by researchers at Vanderbilt University and made available to UCMC by the University of Chicago Center for Research Informatics (CRI). Our TORP imaging database is not meant to replace our TOPDP database; rather, it is meant to be utilized in conjunction with the TOPDP database.

In the following paper, we demonstrate the potential of utilizing the TORP imaging database alongside our TOPDP relational database. To do this, we show proof of principle using a retrospective study investigating malignant pleural mesothelioma (MPM) patient tumor measurements in patients treated with either of two analogous chemotherapy regimens (carboplatin with pemetrexed and cisplatin with pemetrexed). While this paper will exclusively discuss MPM, it is our hope that this paper will be of general interest to oncology-related informatics as a whole, as it highlights the types of investigations made possible by our tandem informatics infrastructure.

Background: Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is a deadly disease that affects nearly 3000 new patients annually in the United States.[5] In at least 70% of cases, the disease develops secondary to asbestos exposure, with a median latency period of 20 to 40 years.[5] MPM is an extremely difficult disease to treat, and median overall survival (OS) ranges between 6 and 17 months, depending on histologic subtype.[6] Currently, the standard chemotherapy agents for MPM are the antifolates, pemetrexed and raltitrexed.[7] While pemetrexed was shown to induce moderate response (14.1%) as a single agent, it demonstrated considerably higher activity (41.3% response) when used in conjunction with cisplatin.[8, 9] Cisplatin is sometimes poorly tolerated, especially in older patients, but it can be substituted with

carboplatin, a cisplatin analog which has a reduced toxicity profile.[7] Similar activity has been observed between cisplatin-pemetrexed and carboplatin-pemetrexed (26.3% response vs. 21.7%, respectively).[10] Imaging is critical in MPM cases because it is the primary means of assessing tumor response to treatment, which often correlates to such variables as patient quality of life and overall survival. Currently, computed tomography (CT) is the standard imaging modality used to assess tumor response; it can be supplemented with fluorodeoxyglucose-positron emission tomography (FDG-PET) or PET/CT, as well as magnetic resonance (MR) imaging.[11]

Materials and Methods

Subject Enrollment

Subjects were included in this retrospective study if they met the following criteria: 1) they were diagnosed with MPM, 2) were subsequently treated at UCMC with two or more cycles of either carboplatin-pemetrexed or cisplatin-pemetrexed, and 3) had a baseline CT scan acquired before their first chemotherapy cycle and a follow-up scan acquired after their second cycle. Providers decided which regimen patients should receive. All subjects were over 18 years of age. No healthy controls were included in this study.

Human Subject Protection

All subjects signed a written consent for one of two UCMC Institutional Review Board (IRB) protocols. One is a prospective tissue-banking study that allows researchers to bank and analyze tissue from patients treated at UCMC for a thoracic malignancy. The other allows for the study of tissue which has already been collected. Although no tumor tissue analysis was performed for the present study, both protocols also allow for the abstraction of medical information and images from the patients' charts.

Database Security Measures

Both the TOPDP and TORP databases include the protective measures necessary to ensure that they meet or exceed regulatory requirements instituted by the Health Insurance Portability and Accountability Act (HIPAA) Security Rule and HIPAA Privacy Rule.[12, 13] Microsoft Access databases do not automatically have these protective measures in place, but the TOPDP database has been amended using optional Access security features and Visual Basic for Applications (VBA) scripts to meet HIPAA regulations for databases. In particular, access to the database is restricted to an approved list of users, username and passwords are required when opening the database, the database is encrypted, and an audit trail has been created to track changes and user access. Additionally, data can be automatically de-identified before export. REDCap has inherent security measures: only approved users are given access; different users are assigned different levels of access, depending on their research needs; username and password are required; an audit trail records the time, nature, and author of a change to the database; and fields marked as identifiers can automatically be excluded when data are exported. Lastly, embedded protected health information (PHI) within images was anonymized by the University of Chicago Human Imaging Research Office (HIRO).[14]

Informatics Infrastructure

The TOPDP database contains demographic, clinical, follow-up, proteomic, and genomic data for over 3000 patients with various thoracic malignancies. It is a relational database which is composed of a master Patients Table and subsidiary tables which are linked to the Patients Table via a common field, in this case, a field containing the patient's medical record number (MRN).Currently, most subsidiary tables contain genomic and proteomic data, but new tables can be designed as needed. Related tables can be queried to display desired variables in a new table.

For every patient, the Patients Table contains demographic and clinical data, as well as data regarding social, environmental, and family history. These variables follow the national standard for oncology databases, as set forth by the NCI Common Data Elements Committee, but they extend beyond standard variables to meet needs specific to the Thoracic Oncology Program.[15] Not all variables of interest are contained in the patients' medical charts; consequently, it is necessary to obtain data via a patient interview; following the patient interview, unknown or unreported variables are abstracted from the patient's medical chart, which is also used to crosscheck patient-reported data for quality assurance purposes. Data are subsequently imported into the TOPDP database.

The TOPDP database is used not only to give a comprehensive view of all consented patients and related research performed by the lab but also to identify smaller cohorts of patients for new research projects in the context of the currently-existing IRB protocol, as was done in this study and as will be described in further detail below. The Patients Table is designed to give general knowledge of each patient's demographics, history, and oncology care; it is not meant to be an exhaustive record. For example, the database captures whether or not a patient has received chemotherapy and the names of the chemotherapy agents the patient has received. However, it does not capture information regarding the number or timing of chemotherapy cycles. Such detailed information is time-consuming to collect and is generally of little utility for our research. When more detailed patient information is required for an investigation, it is abstracted from the patient's medical chart and imported into the TOPDP database in a subsidiary table.

In most cases, the TOPDP database also stores the data required for hypothesis validation after the data are generated or collected. However, in some instances, the TOPDP database is insufficient, as when large files must be stored as part of the study. In this case, the TORP database is used alongside the TOPDP database. Identical tables are created in both databases, data in the TOPDP database are transferred into the TORP database, and the TORP database is augmented with uploaded files (e.g., images). Figure 1 presents a chart detailing our informatics infrastructure.

Utilization of Databases for MPM Study

For the purposes of this study, the TOPDP database was used to identify a cohort of previously-consented qualifying MPM patients. Specifically, the Patients Table was filtered to display patients with MPM who had received chemotherapy and who had CT scans acquired at UCMC. However, additional data (number and dates of CT scans and chemotherapy cycles) were required to verify that patients met the selection criteria. These data were abstracted from the patients' medical charts and then entered into a subsidiary table created in the TOPDP database to capture desired variables. A similar table was

then created in the TORP imaging database. Both tables were identical, with the exception that the TORP database table also contained file upload fields, which were used to capture pre- and post-treatment CT section images and histological images. To ensure that data were transferred correctly and easily, fields were given the same names in both databases. Data were transferred from the TOPDP database to the TORP database using a Microsoft Excel comma-separated values (.csv) spreadsheet as an intermediary. Images were uploaded into the TORP database using REDCap's online file uploader. Data were exported to Microsoft Excel for analysis.

Data Elements and Imaging

For each patient, demographic, exposure (to known MPM risk factors), and clinical data relevant to MPM were captured. Many of these data (e.g. histology, stage, grade, treatments received, imaging acquired, vital status, Eastern Cooperative Oncology Group (ECOG) performance status at time of first visit, etc.) are routinely captured for all patients entered into the database. However, some variables of interest are not routinely collected (for example, number, date(s), and type(s) of surgeries and chemotherapy cycles; number and date(s) of CT scans; response to treatment), as they are not necessary for most of the investigations performed by the lab. These variables were collected for subjects included in this study via chart abstraction after an initial cohort of subjects was identified.

In addition, as histology is integral for prognosis in MPM,[6] histological images were selected and supplied to the research team by the UCMC pathology department. Three types of images were selected: low power images, medium power images, and images with immunohistochemistry (IHC) staining. Patients had between 0 and 35 IHC images. Example pathological images can be found in figure 2. Finally, two CT images for each patient were obtained and uploaded into the database: a representative section image from a baseline pre-treatment CT scan and an anatomically matched section image from a follow-up CT scan acquired according to clinical protocol. Follow-up images were selected from scans acquired immediately after the second cycle of treatment. If no scan was acquired immediately after cycle two, the next available scan after the second cycle of treatment was selected. While the Modified Response Evaluation Criteria in Solid Tumors (RECIST) dictates that tumor thickness be measured at two pleural lesions on three different slices at least 1 cm apart,[16] it was felt that since this study was performed as a demonstration, only one pre- and one post-treatment measurement were necessary to show proof of principle. Sample pre- and post-therapy CT section images are presented in figure 3.

Scans used for research purposes were obtained by UCMC's Human Imaging Research Office (HIRO) from the Department of Radiology's clinical image archive. After images were anonymized by the HIRO, a study investigator selected representative sections for pleural measurement. Measurement of pleural thickness was performed using a radiology software package called Abras, which was developed in-house. Abras is image-visualization interface software that offers tools for image annotation, measurement, and contouring and enables the extraction of a wide-range of image-based quantitative and statistical data. It provides users with a high degree of versatility in the interaction with, and manipulation of, medical images. Abras was developed to provide a cross-platform tool to rapidly access, view, and evaluate images in support of medical imaging research projects.

Results

Database Results

Using the TOPDP database, 129 consented patients with MPM were identified. 22 patients met the selection criteria. For these 22 patients, data were captured in the TOPDP database and subsequently transferred to the TORP database. Patient pre- and post-treatment CT scans were assessed, tumor measurements were recorded, and representative images were stored in the TORP database. Lastly, histological images were also captured for future research use.

Specific results from the study itself are detailed below. It is important to emphasize that tumor measurements were not acquired in accordance with Modified RECIST[16] and were only acquired at two time points. Consequently, these tumor measurements cannot be considered valid data from which to draw clinical conclusions. They are included here, nevertheless, as an example of the kind of results enabled by utilizing this informatics infrastructure.

Example Results Enabled by Utilization of the TOPDP and TORP Databases to Assess Tumor Response

Patient Characteristics

Patient characteristics are listed in Table 1. Of the 22 patients, 21 were male and 1 was female. 20 were Caucasian and 2 were African American. Ages ranged from 47 to 80 years, with a median age of 65 years. 18 patients endorsed prior occupational and/or para-occupational asbestos exposure; 2 patients reported unknown exposure; and 2 patients did not have data regarding asbestos exposure recorded in the TOPDP database or their electronic medical records (EMRs). 16 patients were diagnosed with epithelial mesothelioma, 2 with sarcomatoid mesothelioma, and 2 with mixed-type mesothelioma. 18 patients underwent one or more surgeries: 3 patients underwent extrapleural pneumonectomy, three underwent pleurodesis, 6 underwent pleurectomy/decortication, and a further 6 underwent pleurodesis followed by pleurectomy/decortication. 11 patients were assessed by the clinician as having an ECOG performance status of 0 at their initial appointments, 8 received a score of 1, and 3 patients were given a score of 2.

Chemotherapy Response

Table 2 summarizes chemotherapy details and patient outcome by chemotherapy regimen. Table 3 provides more detailed data regarding pleural measurements for each patient. 14 patients received two to four cycles of carboplatin-pemetrexed and 8 patients received four to six cycles of cisplatin-pemetrexed. Overall, 1 patient received two cycles, 5 patients received three cycles, 11 patients received four cycles, 2 patients received five cycles, and 3 patients received six cycles of chemotherapy. Based on the measurements generated for this study, the mean percentage change in pleural thickness for carboplatin-pemetrexed patients was -25%, indicating a 25% reduction in pleural thickness between the time points of the two CT scans, compared to -11% for cisplatin-pemetrexed patients. Of the 14 patients who received carboplatin-pemetrexed, 9 (41%) remain alive 6-28 months after commencing chemotherapy. Of the 8 patients who received cisplatin-pemetrexed, 4 (50%) remain alive at 16-27 months after commencing chemotherapy.

Discussion

Informatics has been an important part of cancer research efforts to develop more effective diagnostics and therapeutics. These initiatives have led to better clinical outcomes for many patients.[17, 18] However, prognosis for many patients, including those with MPM, remains poor.[17, 18] Consequently, it is imperative that we continue researching novel therapeutics to combat cancer as its incidence rises worldwide. To ensure that such research continues, we must develop informatics infrastructures that meet research needs.

Unfortunately, widely-available, readymade database platforms are often designed to meet a variety of research needs, but rarely ever do they meet all the needs of a specific researcher. Consequently, it is sometimes necessary, as in this case, to utilize tandem databases in order to undertake certain research projects. Microsoft Access has been a very useful platform for our translational research due to its relational nature, ease of querying, portability, ease of deployment, and low cost and ubiquity, which enable collaboration with institutions around the world. These features have allowed us to develop the TOPDP database, a comprehensive thoracic database containing patient demographic, clinical, proteomic, and genomic data in a centralized location.[4] However, Microsoft Access is not without its problems: in particular, Access databases are limited to a 2 GB footprint. Thus, Access is well-suited to capture text-based data, but it is limited when capturing images or other files with a large memory footprint.

For this reason, we developed the TORP database using the online REDCap database platform, which was developed at Vanderbilt University and made available to us by the University of Chicago CRI. Like Microsoft Access, the REDCap platform is well-suited to meet some of our research needs, but falls short in other areas. REDCap is not relational, so the decision was made to maintain our comprehensive database in Microsoft Access. However, REDCap allows up to 1 TB of storage space and so is ideal for research projects utilizing large files. This capability was especially important for this research project, as multiple representative images from CT scans and histological images for each patient were uploaded into the database. Moreover, REDCap interacts easily with Access, communicating via Microsoft Excel or an API call, and, like Access, REDCap encourages collaboration within and among institutions, as it is web-based and available freely.

In addition to facilitating more robust and novel analyses, this database structure also fosters intra- and inter-institutional collaboration. Microsoft Access is widely available for a minimal cost, and REDCap is available freely online to registered users. Moreover, researchers interested in adopting the Salgia Lab's TOPDP and TORP databases may access the lab's standard operating procedures (SOPs) for its Access[19] and REDCap[20] databases, which further detail the construction and utilization of the databases and are freely available on the iBridge network. Only by developing a common infrastructure will we be able to facilitate fast and easy collaboration in MPM research, which will be essential if the global biomedical research community is to overtake this increasingly global disease.

Limitations

Study Limitations

While the TOPDP database has information on over 3000 patients, the study was limited by sample size. Only 22 patients met the inclusion criteria requiring that patients were diagnosed with MPM, treated with at least two cycles of carboplatin-pemetrexed or cisplatin-pemetrexed, and had CT scans acquired prior to and following two cycles of chemotherapy treatment. As this study was retrospective, it was also limited by a lack of standardization: when possible, we selected a follow-up CT scan acquired immediately after the second cycle of chemotherapy, but for some patients, follow-up CT scans were only available after the third or fourth cycle. Additionally, patients received different numbers of chemotherapy cycles. Furthermore, due to the study's retrospective nature, some patient data remained unreported because it could not be found in physician notes during chart abstraction. Finally, tumor measurements were not acquired using Modified RECIST, so they cannot be said to be valid data from which we can draw clinical conclusions.

Informatics Limitations

Data were transferred easily from the Access to REDCap databases using Microsoft Excel as an intermediary and REDCap's data upload functionality. This method was sufficient for the purposes of the present study, but if necessary or desired, it is also possible to automate the data transfer process using the REDCap API. One limitation of the current informatics infrastructure is that data must be captured via either patient report or chart abstraction and then manually entered into the TOPDP database. This process is tedious, subject to error, and time-consuming. However, there are plans to automate this process by enabling data to be transferred immediately from the patient's EMR, which will reduce workload and the potential for error considerably.

Conclusion

Informatics must continue to enable more robust cancer research by meeting evolving research needs. One of these needs has been the ability to utilize and store imaging as a part of translational cancer research. To fill this deficit area, we have implemented a novel tandem database using our TOPDP and TORP databases. As proof of principle, we utilized these databases to investigate MPM tumor response to two standard chemotherapy regimens. While our focus has been thoracic malignancies, it is our hope that this example investigation has illustrated the potential of our informatics infrastructure for use in cancer research as a whole.

Tables and Figures

Table 1 Patient Characteristics

	Number of Cases (%)
Total Cases	22 (100)
Sex	
Male	21 (95)
Female	1 (5)
Race	
Caucasian	17 (77)
African American	2 (9)
Other	0 (0)
Unspecified	3 (14)
Histology	
Mesothelioma– Sarcomatoid Type	2 (9)
Mesothelioma– Epithelioid Type	16 (73)
Mesothelioma– Mixed Type	4 (18)
Surgery*	
Extrapleural Pneumenectomy	3 (14)
Pleurectomy/Decortication	12 (55)
Pleurodesis	9 (41)
Asbestos Exposure	
Occupational/Para-Occupational	18 (82)
Unknown	2 (9)
Not Reported	2 (9)
Age at Diagnosis (years)	
Median	65
Range	47-80

*Some patient underwent more than one procedure.

Table 2 Chemotherapy Details

	Number of Cases (%)* Entire Patient Pool	Carboplatin-pemetrexed	Cisplatin-pemetrexed
Total Patients	22	14 (64)	8 (36)
Cycles of Chemotherapy			
2	1 (5)	1 (7)	0 (0)
3	5 (23)	5 (36)	0 (0)
4	11 (50)	8 (57)	3 (38)
5	2 (9)	0 (0)	2 (25)
6	3 (14)	0 (0)	3 (38)
Pleural Thickness Percentage Change			
Mean	-20%	-25%	-11%
Median	-19%	-18%	-19%
Performance Status			
0	11 (50)	9 (41)	2 (9)
1	8 (36)	3 (14)	5 (23)
2	3 (14)	2 (9)	1(5)
Vital Status at Time of Study			
Alive	13 (59)	9 (64)	4 (50)
Deceased	9 (41)	5 (36)	4(50)

*Due to rounding, percentages may not sum to 100.

Table 3 Chemotherapy response details

Patient ID	Chemo-therapy Regimen*	Chemo-therapy Total Cycles	Follow-Up CT Scan Post-Cycle	Pleural Thickness Pre-Cycle 1 (mm)	Pleural Thickness Follow-Up CT Scan (mm)	Difference in Pleural Thickness (mm)
1	Cis/Pem	4	4	6.96	4.39	-2.57
2	Cis/Pem	4	2	19.67	17.06	-2.61
3	Cis/Pem	6	2	10.83	8.61	-2.22
4	Cis/Pem	4	2	34.53	28.29	-6.24
5	Cis/Pem	5	2	16.06	12.75	-3.31
6	Cis/Pem	6	2	25.28	17.01	-8.27
7	Cis/Pem	5	2	24.00	33.47	9.47
8	Cis/Pem	6	2	10.50	12.10	1.60
9	Carbo/Pem	4	2	16.75	14.21	-2.54
10	Carbo/Pem	4	2	18.94	12.52	-6.42
11	Carbo/Pem	3	2	13.30	9.19	-4.11
12	Carbo/Pem	3	3	41.82	44.29	2.47
13	Carbo/Pem	4	4	13.44	7.16	-6.28
14	Carbo/Pem	4	3	41.04	30.94	-10.10
15	Carbo/Pem	2	2	48.65	9.47	-39.18
16	Carbo/Pem	4	4	5.59	5.12	-0.47
17	Carbo/Pem	4	2	21.89	19.68	-2.21
18	Carbo/Pem	4	4	28.59	22.70	-5.89
19	Carbo/Pem	3	3	23.61	21.87	-1.74
20	Carbo/Pem	3	3	13.46	12.12	-1.34
21	Carbo/Pem	3	3	20.35	19.30	-1.05
22	Carbo/Pem	4	4	6.30	2.65	-3.65
Average	Cis/Pem	5	2.25	18.48	16.71	-1.77
Average	Carbo/Pem	3.5	2.93	22.41	16.52	-5.89

*Abbreviations: Carbo, carboplatin; Cis, cisplatin; Pem, pemetrexed

Figure 1. Mind map illustrating the relationships between the databases utilized for this project.

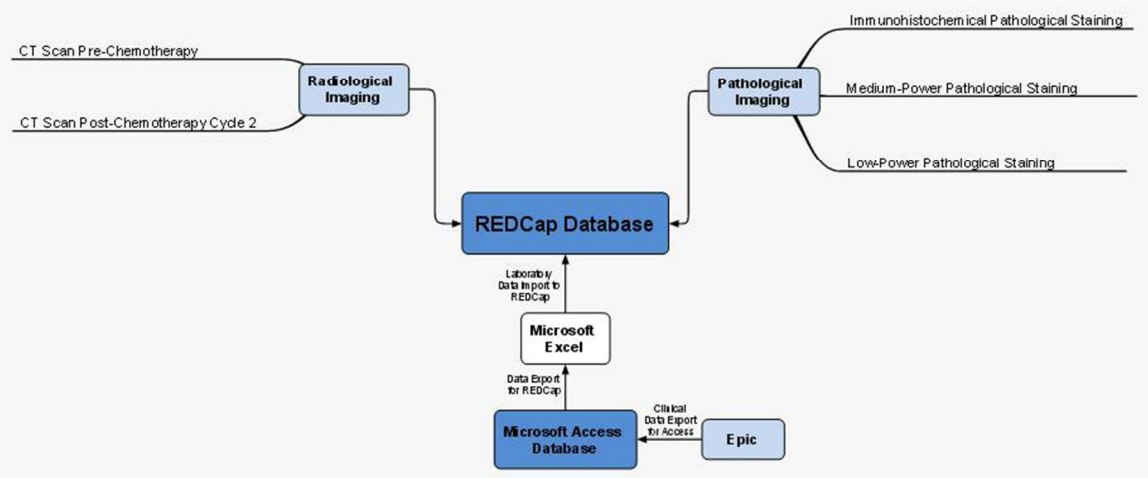
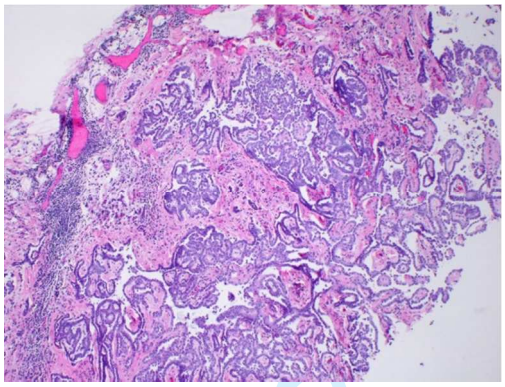
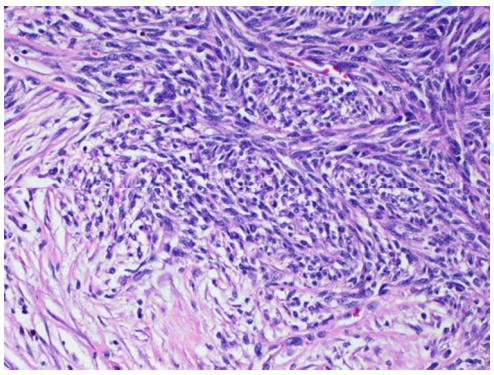


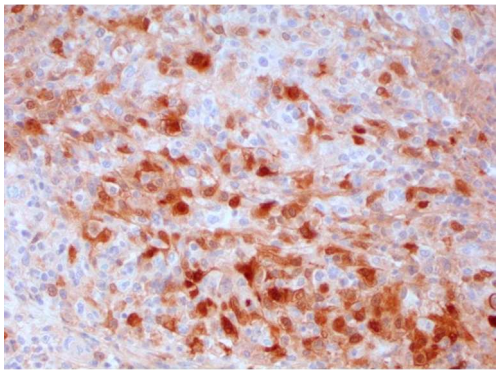
Figure 2. Representative histological images.



2a. Low power photomicrograph of pleural biopsy showing malignant mesothelioma, epithelioid type, tubulo-papillary pattern



2b. Medium power photomicrograph of pleural resection showing malignant mesothelioma, sarcomatoid type



2c. Medium power photomicrograph of malignant mesothelioma, epithelioid type, staining positive for calretinin (both nuclear and cytoplasmic staining)

Figure 3 Example of measurement of CT scan images from a single patient. (A) CT scan image pre-cycle 1 of chemotherapy. Pleural thickness pre-treatment was 13.3 mm. (B) CT scan image post-cycle 2 of chemotherapy. Pleural thickness post-2 cycles of treatment was 9.19 mm.

A **B**

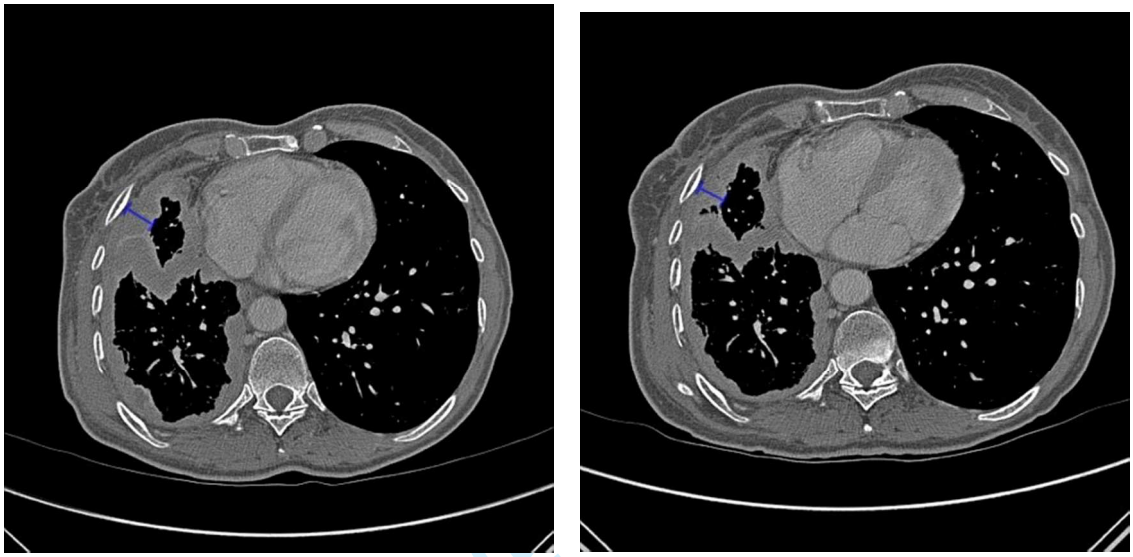


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Figure 1. Mind map illustrating the relationships between the databases utilized for this project.

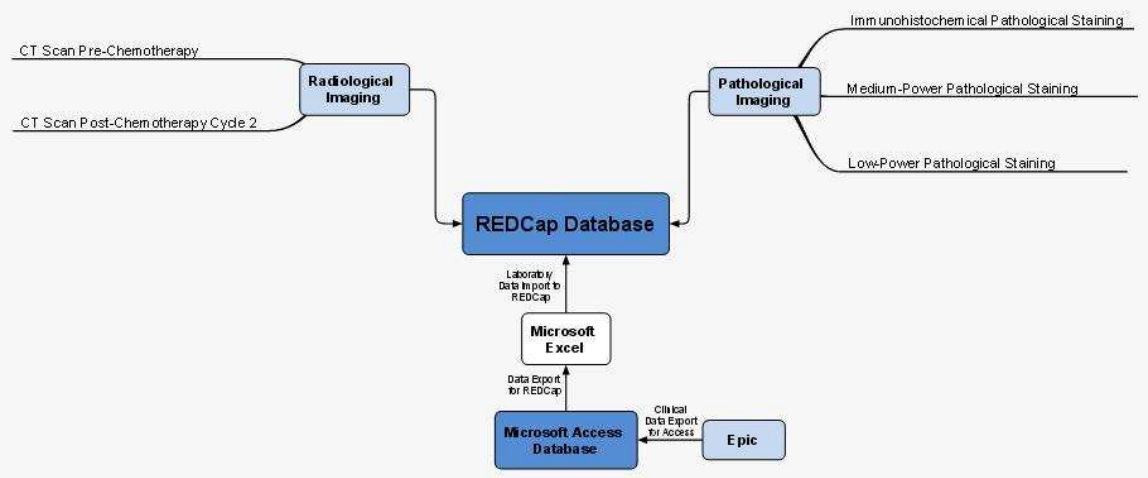
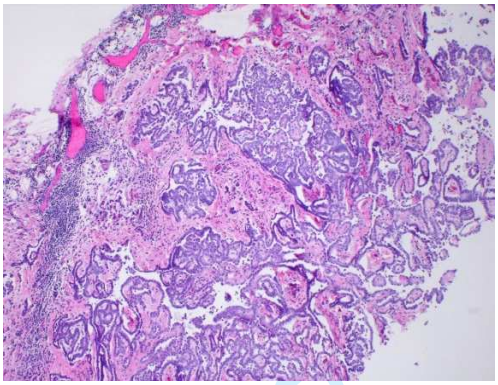
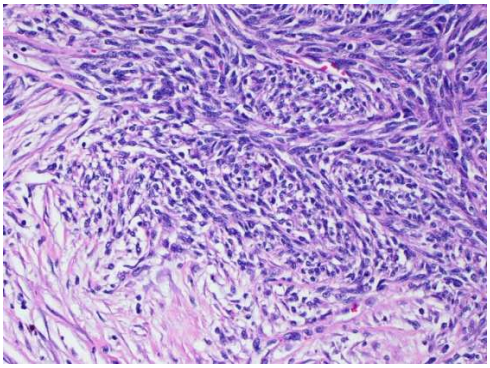


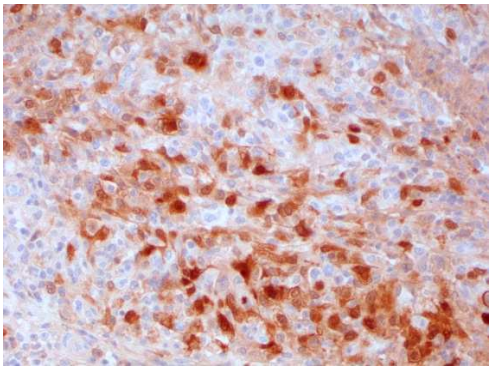
Figure 2. Representative histological images.



2a. Low power photomicrograph of pleural biopsy showing malignant mesothelioma, epithelioid type, tubulo-papillary pattern



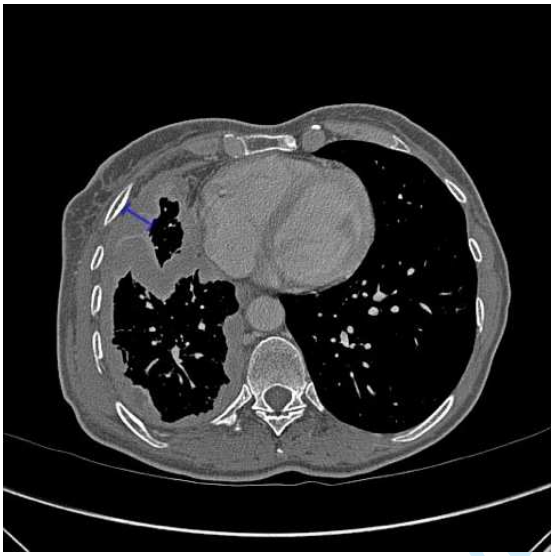
2b. Medium power photomicrograph of pleural resection showing malignant mesothelioma, sarcomatoid type



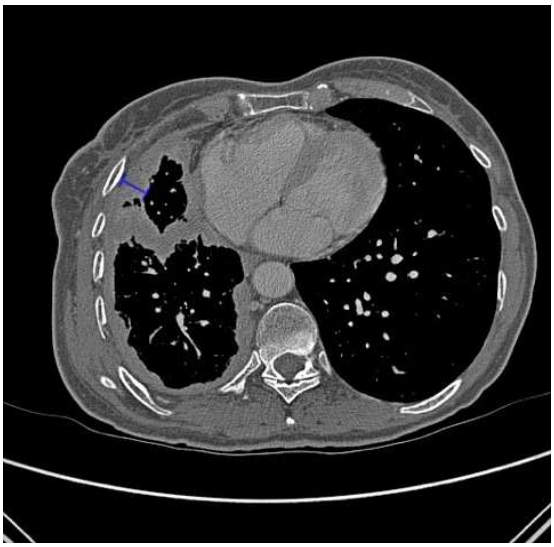
2c. Medium power photomicrograph of malignant mesothelioma, epithelioid type, staining positive for calretinin (both nuclear and cytoplasmic staining)

Figure 3 Example of measurement of CT scan images from a single patient. (A) CT scan image pre-cycle 1 of chemotherapy. Pleural thickness pre-treatment was 13.3 mm. (B) CT scan image post-cycle 2 of chemotherapy. Pleural thickness post-2 cycles of treatment was 9.19 mm.

A



B



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Utilization of a Thoracic Oncology Database to Capture Radiological and Pathological Images for Evaluation of Response to Chemotherapy in Patients with Malignant Pleural Mesothelioma

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Utilization of a Thoracic Oncology Database to Capture Radiological and Pathological Images for Evaluation of Response to Chemotherapy in Patients with Malignant Pleural Mesothelioma

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Abstract

Objective An area of need in cancer informatics is the ability to store images in a comprehensive database as part of translational cancer research. To meet this need, we have implemented a novel tandem database infrastructure that facilitates image storage and utilization.

Background We had previously implemented the Thoracic Oncology Program Database Project (TOPDP) database for our translational cancer research needs. While useful for many research endeavors, it is unable to store images, hence our need to implement an imaging database which could communicate easily with the TOPDP database.

Methods The Thoracic Oncology Research Program (TORP) imaging database was designed using the Research Electronic Data Capture (REDCap) platform, which was developed by Vanderbilt University. To demonstrate proof of principle and evaluate utility, we performed a retrospective investigation into tumor response for malignant pleural mesothelioma (MPM) patients treated at the University of Chicago Medical Center (UCMC) with either of two analogous chemotherapy regimens and consented to at least one of two UCMC IRB protocols, 9571 and 13473A.

Results A cohort of 22 MPM patients was identified using clinical data in the TOPDP database. After measurements were acquired, 2 representative CT images and 0-35 histological images per patient were successfully stored in the TORP database, along with clinical and demographic data.

Discussion We implemented the TORP imaging database to be used in conjunction with our comprehensive TOPDP database. While it requires additional effort to use two databases, our database infrastructure facilitates more comprehensive translational research.

Conclusion The investigation described herein demonstrates the successful implementation of this novel tandem imaging database infrastructure, as well as the potential utility of investigations enabled by it.

The data model presented here can be utilized as the basis for further development of other larger, more streamlined databases in the future.

Article Summary

Article focus

- This article highlights a novel tandem thoracic oncology database infrastructure that is designed to capture radiological and histological images for translational research purposes.
- To evaluate the utility of this database infrastructure, this article discusses a retrospective investigation into tumor response rates in patients with malignant pleural mesothelioma treated with one of two similar chemotherapy regimens.

Key messages

- This tandem database infrastructure requires some additional effort to maintain and utilize compared with a single database platform.
- The extra effort required for smaller-scale studies is minimal, as demonstrated by our investigation. Moreover, this infrastructure enables more comprehensive translational research.
- This data model can serve as a potential example for the development of databases that unify and streamline workflow, enabling larger-scale studies.

Strengths and limitations of this study

- The study was limited by a small sample size (n=22).
- The study suffered from a lack of standardization: patients received a varying number of chemotherapy cycles and post-treatment CT scans were not always acquired at the same time point.
- Tumor response measurements were not acquired according to Modified RECIST.

Introduction

Imaging is an integral tool in oncology, aiding clinicians in diagnosing malignancies, determining appropriate therapies, and assessing treatment response. In order to maximize the utility of cancer imaging, the oncology and imaging communities have devoted significant resources to developing informatics tools that allow both clinicians and researchers to store, utilize, and share cancer images in more effective ways.[1-5] Despite these efforts, there remain areas of need in cancer imaging. One of these deficit areas is the ability to efficiently store and utilize images as a part of collaborative translational cancer research. Consequently, we sought to develop a relational database infrastructure that 1) integrated proteomic, genomic, and imaging data; 2) was easily and efficiently created, used, and adapted with little to no need for coding; and 3) could be acquired by collaborators at negligible cost.

Prior to the initiation of this effort, The Thoracic Oncology Research Program at the University of Chicago Medical Center (UCMC) had implemented the Thoracic Oncology Program Database Project (TOPDP) database for our translational research efforts.[6] Because the TOPDP database uses Microsoft Access as its underlying technology, it is technically capable of storing images. However, Access databases can only store up to 2 GB of data, so the TOPDP database does not meet our imaging storage demands. To meet this need, we designed and implemented the Thoracic Oncology Research Program (TORP) imaging database using the Research Electronic Data Capture (REDCap) database platform, which was developed by researchers at Vanderbilt University and made available to UCMC by the University of Chicago Center for Research Informatics (CRI). Due to limitations of REDCap discussed below, our TORP imaging database was not meant to replace our TOPDP database; rather, it was meant to be utilized in conjunction with the TOPDP database.

In the following paper, we evaluate the potential of utilizing the TORP imaging database alongside our TOPDP relational database. We demonstrate proof of principle using a retrospective study investigating

malignant pleural mesothelioma (MPM) patient tumor measurements in patients treated with either of two analogous chemotherapy regimens. While this paper will exclusively discuss MPM, it is our hope that this paper will be of general interest to oncology-related informatics as a whole.

Background: Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is a deadly disease that affects nearly 3000 new patients annually in the United States.[7] In at least 70% of cases, the disease develops secondary to asbestos exposure, with a median latency period of 20 to 40 years.[7] MPM is an extremely difficult disease to treat, and median overall survival (OS) ranges between 6 and 17 months, depending on histologic subtype.[8] Currently, the standard chemotherapy agents for MPM are the antifolates, pemetrexed and raltitrexed.[9] While pemetrexed was shown to induce moderate response (14.1%) as a single agent, it demonstrated considerably higher activity (41.3% response) when used in conjunction with cisplatin.[10, 11] Cisplatin is sometimes poorly tolerated, especially in older patients, but it can be substituted with carboplatin, a cisplatin analog which has a reduced toxicity profile.[9] Similar activity has been observed between cisplatin-pemetrexed and carboplatin-pemetrexed (26.3% response vs. 21.7%, respectively).[12] Imaging is critical in MPM cases because it is the primary means of assessing tumor response to treatment, which often correlates to such variables as patient quality of life and overall survival. Currently, computed tomography (CT) is the standard imaging modality used to assess tumor response; it can be supplemented with fluorodeoxyglucose-positron emission tomography (FDG-PET) or PET/CT, as well as magnetic resonance (MR) imaging.[13]

Materials and Methods

Human Subject Protection

All subjects signed a written consent for at least one of two UCMC Institutional Review Board (IRB) protocols. One is a prospective tissue-banking study that allows researchers to bank and analyze tissue from patients treated at UCMC for a thoracic malignancy. The other allows for the study of tissue which has already been collected. Although no tumor tissue analysis was performed for the present study, both protocols also allow for the abstraction of medical information and images from the patients' charts.

Database Security Measures

Both the TOPDP and TORP databases include the protective measures necessary to ensure that they meet regulatory requirements instituted by the Health Insurance Portability and Accountability Act (HIPAA) Security Rule and HIPAA Privacy Rule.[14, 15] Microsoft Access databases do not automatically have these protective measures in place, but the TOPDP database has been amended using optional Access security features and Visual Basic for Applications (VBA) scripts to meet HIPAA regulations for databases. In particular, access to the database is restricted to an approved list of users, username and passwords are required when opening the database, the database is encrypted, and an audit trail has been created to track changes and user access. Additionally, data can be automatically de-identified before export. REDCap has inherent security measures: only approved users are given access; different users are assigned different levels of access, depending on their research needs; username and password are required; an audit trail records the time, nature, and author of a change to the database; and fields marked as identifiers can automatically be excluded when data are exported. Lastly, embedded protected health information (PHI) within images was anonymized by the University of Chicago Human Imaging Research Office (HIRO).[16]

Informatics Infrastructure

The TOPDP database contains demographic, clinical, follow-up, proteomic, and genomic data for over 3000 patients with various thoracic malignancies. It is a relational database composed of a master Patients Table and subsidiary tables linked to the Patients Table via a field containing the patient's medical record number (MRN). Currently, subsidiary tables contain genomic and proteomic data, but new tables can be designed as needed. Related tables can be queried to display desired variables in a new table.

The Patients Table contains demographic and clinical data, as well as data regarding social, environmental, and family history. These variables follow the national standard for oncology databases established by the NCI Common Data Elements Committee, but they extend beyond standard variables to meet needs specific to the Thoracic Oncology Program.[17] Not all variables of interest are contained in the patients' medical charts; consequently, it is necessary to obtain data via a patient interview. Following the patient interview, unknown or unreported variables are abstracted from the patient's medical chart, which is also used to crosscheck patient-reported data for quality assurance purposes. Data are subsequently imported into the TOPDP database.

The TOPDP database is used not only to give a comprehensive view of all consented patients and related research performed by the lab but also to identify smaller cohorts of patients for new research projects in the context of the currently-existing IRB protocol. The Patients Table is designed to give general knowledge of patient demographics, history, and oncology care. For example, the database captures whether or not a patient has received chemotherapy and the names of the chemotherapy agents the patient has received. However, it does not capture information regarding the number or timing of chemotherapy cycles. When more detailed patient information is required for an investigation, it is abstracted from the patient's medical chart and imported into the TOPDP database in a subsidiary table.

In most cases, the TOPDP database also stores the data required for hypothesis validation after the data are generated or collected. However, in some instances, the TOPDP database is insufficient, as when large files must be stored as part of the study. In this case, the TORP database can be used alongside the TOPDP database. Identical tables are created in both databases, data in the TOPDP database are transferred into the TORP database, and the TORP database is augmented with uploaded files (e.g., images). Figure 1 presents a chart detailing this informatics infrastructure.

Utilization of Databases for MPM Study

Subjects were included in this retrospective study if they met the following criteria: 1) they were diagnosed with MPM, 2) were subsequently treated at UCMC with two or more cycles of either carboplatin-pemetrexed or cisplatin-pemetrexed, and 3) had a baseline CT scan acquired before their first chemotherapy cycle and a follow-up scan acquired after their second cycle. The TOPDP database was used to identify a cohort of previously-consented qualifying MPM patients. Specifically, the Patients Table was filtered to display patients with MPM who had received chemotherapy and who had CT scans acquired at UCMC. However, additional data (number and dates of CT scans and chemotherapy cycles) were required to verify that patients met the selection criteria. These data were abstracted from the patients' medical charts and then entered into a subsidiary table in the TOPDP database. A similar table was then created in the TORP imaging database. Both tables were identical, with the exception that the TORP database table also contained file upload fields, which were used to capture pre- and post-treatment CT section images and histological images. To ensure that data were transferred correctly and easily, fields were given the same names in both databases. Data were transferred from the TOPDP database to the TORP database using a Microsoft Excel comma-separated values (.csv) spreadsheet as an intermediary. Images were uploaded into the TORP database using REDCap's online file uploader. Data were exported to Microsoft Excel for analysis.

Data Elements and Imaging

For each patient, demographic, exposure (to known MPM risk factors), and clinical data relevant to MPM were captured. Many of these data (e.g., histology, stage, treatments received, imaging acquired, vital status, etc.) are routinely captured. Variables of interest not routinely collected (for example, number, date(s), and type(s) of surgeries and chemotherapy cycles; number and date(s) of CT scans; response to treatment) were abstracted from patient charts.

As histology is integral for prognosis in MPM,[8] histological images were selected and supplied to the research team by the UCMC pathology department. Three types of images were selected: low power images, medium power images, and images with immunohistochemistry (IHC) staining. Patients had between 0 and 35 IHC images. Finally, two CT images for each patient were obtained and uploaded into the database: a representative section image from a baseline pre-treatment CT scan and an anatomically matched section image from a follow-up CT scan acquired according to clinical protocol. Follow-up images were selected from scans acquired immediately after the second cycle of treatment. If no scan was acquired immediately after cycle two, the next available scan after the second cycle of treatment was selected. While the Modified Response Evaluation Criteria in Solid Tumors (RECIST) dictates that tumor thickness be measured at two pleural lesions on three different slices at least 1 cm apart,[18] it was felt that since this study was performed as a demonstration, only one pre- and one post-treatment measurement were necessary to show proof of principle. Sample pre- and post-therapy CT section images are presented in figure 2.

Scans used for research purposes were obtained by UCMC's Human Imaging Research Office (HIRO) from the Department of Radiology's clinical image archive. After images were anonymized by the HIRO, a study investigator selected representative sections for pleural measurement. Measurement of pleural thickness was performed using a radiology software package called Abras, which was developed in-

house. Abras is image-visualization interface software that offers tools for image annotation, measurement, and contouring and enables the extraction of a wide-range of image-based quantitative and statistical data. It provides users with a high degree of versatility in the interaction with, and manipulation of, medical images. Abras was developed to provide a cross-platform tool to rapidly access, view, and evaluate images in support of medical imaging research projects.

Results

Database Results

Using the TOPDP database, 129 consented patients with MPM were identified. 22 patients met the selection criteria. For these 22 patients, data were captured in the TOPDP database and subsequently transferred to the TORP database. Patient pre- and post-treatment CT scans were assessed, tumor measurements were recorded, and representative images were stored in the TORP database. Histological images were also captured.

Specific results from the study itself are detailed below. It is important to emphasize that tumor measurements were not acquired in accordance with Modified RECIST[18] and were only acquired at two time points. Consequently, these tumor measurements cannot be considered valid data from which to draw clinical conclusions. They are included here, nevertheless, as an example of the kind of results enabled by utilizing this informatics infrastructure.

Example Results Enabled by Utilization of the TOPDP and TORP Databases to Assess Tumor Response

Patient Characteristics

Of the 22 patients, 21 were male and 1 was female. 20 were Caucasian and 2 were African American. Ages ranged from 47 to 80 years, with a median age of 65 years. 18 patients endorsed prior occupational and/or para-occupational asbestos exposure; 2 patients reported unknown exposure; and 2 patients did not have data regarding asbestos exposure recorded in the TOPDP database or their electronic medical records (EMRs). 16 patients were diagnosed with epithelial mesothelioma, 2 with sarcomatoid mesothelioma, and 2 with mixed-type mesothelioma. 18 patients underwent one or more surgeries: 3 patients underwent extrapleural pneumonectomy, three underwent pleurodesis, 6 underwent pleurectomy/decortication, and a further 6 underwent pleurodesis followed by pleurectomy/decortication. 11 patients were assessed by the clinician as having an ECOG performance status of 0 at their initial appointments, 8 received a score of 1, and 3 patients were given a score of 2.

Chemotherapy Response

14 patients received two to four cycles of carboplatin-pemetrexed and 8 patients received four to six cycles of cisplatin-pemetrexed. Overall, 1 patient received two cycles, 5 patients received three cycles, 11 patients received four cycles, 2 patients received five cycles, and 3 patients received six cycles of chemotherapy. Based on the measurements generated for this study, the mean percentage change in pleural thickness for carboplatin-pemetrexed patients was -25%, indicating a 25% reduction in pleural thickness between the time points of the two CT scans, compared to -11% for cisplatin-pemetrexed patients. Of the 14 patients who received carboplatin-pemetrexed, 9 (41%) remain alive 6-28 months after commencing chemotherapy. Of the 8 patients who received cisplatin-pemetrexed, 4 (50%) remain

alive at 16-27 months after commencing chemotherapy. A brief summary of patient characteristics and tumor measurements is presented in table 1.

Discussion

Informatics has been an important part of cancer research efforts to develop more effective diagnostics and therapeutics. These initiatives have led to better clinical outcomes for many patients.[19, 20] However, prognosis for many patients, including those with MPM, remains poor.[19, 20] Consequently, it is imperative that we continue researching novel therapeutics to combat cancer as its incidence rises worldwide. To ensure that such research continues, we must develop informatics infrastructures that meet research needs, one of which is an easily implementable comprehensive translational research database capable of handling imaging.

Relational databases that incorporate imaging have been developed by other groups,[3-5] but they differ from ours in a fundamental way: ease of implementation. For example, the eDiaMoND database is designed to aid clinicians and researchers by compiling mammography and related clinical data;[3] the Biomedical Image Metadata Manager (BIMM) allows researchers to access and query images and associated metadata;[4] and the Pathology Analytic Imaging Standards (PAIS) data model database enables the storage and analysis of large TMA datasets.[5] All three of these databases are developed based on published data models that can be replicated by outside groups. While implementing one of these databases might be beneficial for some, they are sophisticated enough that we feel it would require a dedicated informatics specialist to replicate them. Consequently, we felt the need to design a simpler informatics infrastructure that incorporated imaging but did not focus on it and that would be more easily implemented by translational research groups without special informatics expertise.

To do so, we decided to use a ready-made database platform that required little to no coding. Unfortunately, widely-available, readymade database platforms are often designed to meet a variety of research needs, but rarely ever do they meet all the needs of a specific researcher. Consequently, it was necessary to utilize a tandem database infrastructure in order to incorporate imaging. Microsoft Access has been a very useful platform for our translational research due to its relational nature, ease of querying, portability, ease of deployment, and low cost and ubiquity, which enable collaboration with institutions around the world. These features have allowed us to develop the TOPDP database, a comprehensive thoracic database containing patient demographic, clinical, proteomic, and genomic data in a centralized location.[6] However, Microsoft Access is not without its problems: in particular, Access databases are limited to a 2 GB footprint. Thus, Access is well-suited to capture text-based data, but it is limited when capturing images or other files with a large memory footprint.

For this reason, we developed the TORP database using the online REDCap database platform, which was developed at Vanderbilt University and made available to us by the University of Chicago CRI. Like Microsoft Access, the REDCap platform is well-suited to meet some of our research needs, but falls short in other areas. REDCap is not relational, so the decision was made to maintain our comprehensive database in Microsoft Access. However, REDCap allows up to 1 TB of storage space and so is ideal for research projects utilizing large files. This capability was especially important for this research project, as multiple representative images from CT scans and histological images for each patient were uploaded into the database. Moreover, REDCap interacts easily with Access, communicating via Microsoft Excel or an API call, and, like Access, REDCap encourages collaboration within and among institutions, as it is web-based and available freely.

In addition to facilitating more robust and novel analyses, this database structure also fosters intra- and inter-institutional collaboration. Microsoft Access is widely available for a minimal cost, and REDCap is

available freely online to registered users. Moreover, researchers interested in adopting the Salgia Lab's TOPDP and TORP databases may access the lab's standard operating procedures (SOPs) for its Access[21] and REDCap[22] databases, which further detail the construction and utilization of the databases and are freely available on the iBridge network. Only by developing a common infrastructure will we be able to facilitate fast and easy collaboration in MPM research, which will be essential if the global biomedical research community is to overtake this increasingly global disease.

This informatics infrastructure is not without its limitations, however, one of which is that data must be captured via patient report or chart abstraction and then manually entered into the TOPDP database. This process is tedious, subject to error, and time-consuming. However, there are plans to automate this process by enabling data to be transferred immediately from the patient's electronic medical record (EMR), which will reduce workload and the potential for error considerably. In this investigation, data were transferred easily from the Access database to REDCap using Microsoft Excel as an intermediary and REDCap's data upload functionality. This method was sufficient for the purposes of the present study, but if necessary or desired, it is also possible to automate the data transfer process using the REDCap API. However, images must be uploaded manually using REDCap's online file upload field. The time required to upload images for this investigation was negligible. However, having to upload images manually would most likely be prohibitive of studies involving hundreds or thousands of patients.

Our proof of principle investigation was also limited in various ways, for one by sample size (n=22). As this study was retrospective, it was also limited by a lack of standardization: when possible, we selected a follow-up CT scan acquired immediately after the second cycle of chemotherapy, but for some patients, follow-up CT scans were only available after the third or fourth cycle. Furthermore, some patient data remained unreported because it could not be found in physician notes during chart

abstraction. Finally, tumor measurements were not acquired using Modified RECIST, so they cannot be said to be valid data from which we can draw clinical conclusions.

Conclusion

We sought to develop a relational database infrastructure that 1) efficiently incorporated images with proteomic, genomic, or other laboratory data; 2) could be implemented, used, and altered easily with little knowledge of coding; 3) and was available to collaborators at minimal cost;. At first it seemed ideal to capture all our imaging and laboratory data exclusively in REDCap. However, moving entirely into REDCap would require giving up the relational component of our database infrastructure. Consequently, we developed the TORP REDCap database to be used in tandem with our TOPDP Microsoft Access database. In order to evaluate this informatics infrastructure, we performed an investigation into MPM tumor response to two standard chemotherapy regimens. In large part, our investigation was a success: as intended, we were able to implement a relational database that housed both laboratory and imaging data using database platforms that are available at negligible cost and are easily developed and utilized. However, in the course of the investigation, a limitation to our informatics model became apparent: while the time required to upload images in this investigation was negligible, the fact that images must be uploaded manually would most likely preclude large-scale studies. Consequently, we are now working to implement an SQL database, which will be slightly more complex to develop but will enable us to automate workflow and store imaging and laboratory data in a single relational database. In conclusion, it is to be appreciated that this tandem database infrastructure is a very useful tool for small datasets for both informaticians and non-informaticians. Moreover, one can ultimately envision utilizing the data model for this infrastructure as a basis for developing a larger, more-streamlined database.

Table 1 Patient Characteristics and Tumor Measurements

	Number of Cases (%)* Entire Patient Pool	Carboplatin-pemetrexed	Cisplatin-pemetrexed
Total Cases	22 (100)	14 (100)	8 (100)
Sex			
Male	21 (95)	14 (100)	7 (88)
Female	1 (5)	0 (0)	1 (13)
Race			
Caucasian	17 (77)	11 (79)	6 (75)
African American	2 (9)	0 (0)	2 (25)
Unspecified	3 (14)	3 (21)	0 (0)
Histology			
Sarcomatoid Type	2 (9)	2 (14)	0 (0)
Epithelioid Type	16 (73)	11 (79)	5 (63)
Mixed Type	4 (18)	1 (7)	3 (38)
Age at Diagnosis (years)			
Median	65	68.5	58.5
Range	47-80	49-80	47-75
Performance Status			
0	11 (50)	9 (41)	2 (9)
1	8 (36)	3 (14)	5 (23)
2	3 (14)	2 (9)	1 (5)
Vital Status at Time of Study			
Alive	13 (59)	9 (64)	4 (50)
Deceased	9 (41)	5 (36)	4 (50)
Pleural Thickness Percentage Change			
Mean	-20%	-25%	-11%
Median	-19%	-18%	-19%

*Due to rounding, percentages may not sum to 100.

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Contributions

GBC, SK, and MS drafted the manuscript. GBC, SK, MS, AK, and CER were responsible for the design, implementation, and maintenance of the TOPDP and TORP databases. ASadiq, TH, EEV, WV, HLK, and RS provided clinical knowledge and support. NB, BR, RM, and PD provided REDCap support. SGA and AStarkey created the Abras imaging software. SGA acquired radiological measurements and selected representative CT images. AH reviewed pathology slides for each patient and provided the histological images. RS oversaw the development of the databases, as well as the drafting of the manuscript.

Competing interests

The authors have no competing interests.

Data sharing statement

No additional data available.

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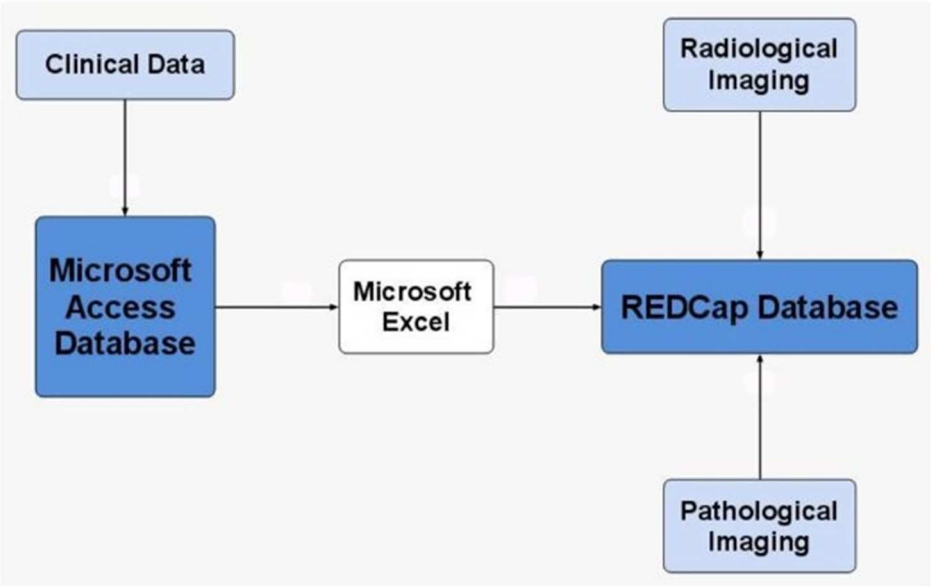
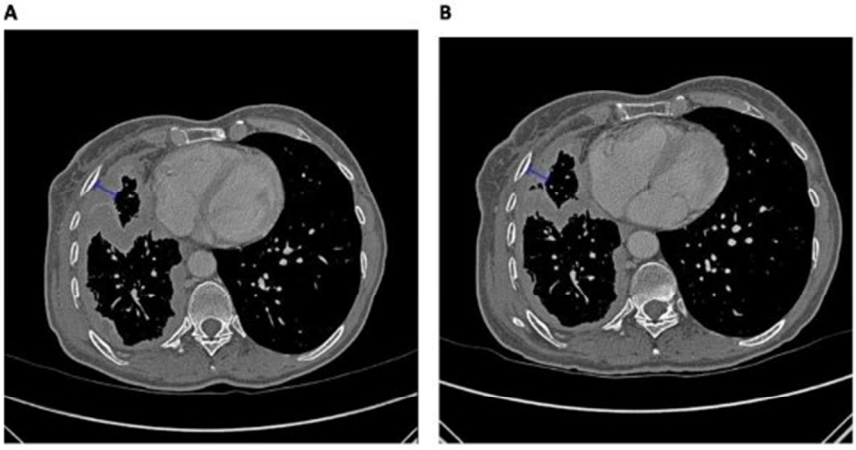
Figure 1. Mind map illustrating the relationships between the databases utilized for this project.



56x47mm (300 x 300 DPI)

Figure 2 Example of measurement of CT scan images from a single patient. (A) CT scan image pre-cycle 1 of chemotherapy. Pleural thickness pre-treatment was 13.3 mm. (B) CT scan image post-cycle 2 of chemotherapy. Pleural thickness post-2 cycles of treatment was 9.19 mm.



Utilization of a Thoracic Oncology Database to Capture Radiological and Pathological Images for Evaluation of Response to Chemotherapy in Patients with Malignant Pleural Mesothelioma

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Abstract

Objective An area of need in cancer informatics is the ability to store images in a comprehensive database as part of translational cancer research. To meet this need, we have implemented a novel tandem database infrastructure that facilitates image storage and utilization.

Background We had previously implemented the Thoracic Oncology Program Database Project (TOPDP) database for our translational cancer research needs. While useful for many research endeavors, it is unable to store images, hence our need to implement an imaging database which could communicate easily with the TOPDP database.

Methods The Thoracic Oncology Research Program (TORP) imaging database was designed using the Research Electronic Data Capture (REDCap) platform, which was developed by Vanderbilt University. To demonstrate proof of principle and evaluate utility, we performed a retrospective investigation into tumor response for malignant pleural mesothelioma (MPM) patients treated at the University of Chicago Medical Center (UCMC) with either of two analogous chemotherapy regimens and consented to at least one of two UCMC IRB protocols, 9571 and 13473A.

Results A cohort of 22 MPM patients was identified using clinical data in the TOPDP database. After measurements were acquired, 2 representative CT images and 0-35 histological images per patient were successfully stored in the TORP database, along with clinical and demographic data.

Discussion We implemented the TORP imaging database to be used in conjunction with our comprehensive TOPDP database. While it requires additional effort to use two databases, our database infrastructure facilitates more comprehensive translational research.

Conclusion The investigation described herein demonstrates the successful implementation ~~and ease of use of~~ of this novel tandem imaging database infrastructure, as well as the potential utility of

investigations enabled by it. The data model presented here can be utilized as the basis for further development of other larger, more streamlined databases in the future.

Article Summary

Article focus

- This article highlights a novel tandem thoracic oncology database infrastructure that is designed to capture radiological and histological images for translational research purposes.
- To evaluate~~illustrate~~ the utility of this database infrastructure, this article discusses a retrospective investigation into tumor response rates in patients with malignant pleural mesothelioma treated with one of two similar chemotherapy regimens.

Key messages

- This tandem database infrastructure requires some additional effort to maintain and utilize compared with a single database platform.
- ~~However, t~~The extra effort required for smaller-scale studies is minimal, as demonstrated by our ~~proof of concept~~ investigation. Moreover, this infrastructure enables more comprehensive translational research.
- This data model can serve as a potential example for the development of databases that unify and streamline workflow, enabling larger-scale studies.~~This database infrastructure can also be of use to translational research programs outside thoracic oncology.~~

Strengths and limitations of this study

- The study was limited by a small sample size (n=22).
- The study suffered from a lack of standardization: patients received a varying number of chemotherapy cycles and post-treatment CT scans were not always acquired at the same time point.
- Tumor response measurements were not acquired according to Modified RECIST.

Introduction

Imaging is an integral tool in oncology, aiding clinicians in ~~such tasks as~~ diagnosing ~~a patient's~~ malignancies~~y~~, determining appropriate therapies, and assessing treatment response. In order to maximize the utility of cancer imaging, the oncology and imaging communities have devoted significant resources to developing informatics tools that allow both clinicians and researchers to store, utilize, and share cancer images in more effective ways.[1-5] Despite these efforts, there remain~~Efforts to date have yielded many benefits, especially for clinicians and imaging specialists; however, they have yet to address some~~ areas of need in cancer imaging. One of these deficit areas is the ability to efficiently store and utilize images as a part of collaborative translational cancer research. Consequently, we sought to develop a~~n~~ relational database infrastructure that 1)- integrated proteomic, genomic, and imaging data; 2) was easily and efficiently created, used, and adapted with little to no need for coding; and 3) could be acquired by collaborators at negligible cost.

Prior to the initiation of this effort, The Thoracic Oncology Research Program at the University of Chicago Medical Center (UCMC) had implemented~~ve used~~ the Thoracic Oncology Program Database Project (TOPDP) database for our translational research efforts.[6] ~~The TOPDP database was developed to serve as a comprehensive translational database that interfaces with the UCMC online tissue bank and integrates patient clinical information with proteomic and genomic information obtained from tumor tissue samples.~~ Because the TOPDP database uses Microsoft Access as its underlying technology, it is technically capable of storing images. However, Access databases can only store up to 2 GB of data, so the TOPDP database does not meet our imaging storage demands. To meet this need, we ~~have~~ designed and implemented the Thoracic Oncology Research Program (TORP) imaging database using the Research Electronic Data Capture (REDCap) database platform, which was developed by researchers at Vanderbilt University and made available to UCMC by the University of Chicago Center for Research

Informatics (CRI). Due to limitations of REDCap discussed below, o~~O~~ur TORP imaging database wa~~i~~s not meant to replace our TOPDP database; rather, it was~~is~~ meant to be utilized in conjunction with the TOPDP database.

In the following paper, we evaluate~~demonstrate~~ the potential of utilizing the TORP imaging database alongside our TOPDP relational database. ~~To do this, w~~We demonstrate~~show~~ proof of principle using a retrospective study investigating malignant pleural mesothelioma (MPM) patient tumor measurements in patients treated with either of two analogous chemotherapy regimens~~ (carboplatin with pemetrexed and cisplatin with pemetrexed)~~. While this paper will exclusively discuss MPM, it is our hope that this paper will be of general interest to oncology-related informatics as a whole~~, as it highlights the types of investigations made possible by our tandem informatics infrastructure.~~

Background: Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is a deadly disease that affects nearly 3000 new patients annually in the United States.[7] In at least 70% of cases, the disease develops secondary to asbestos exposure, with a median latency period of 20 to 40 years.[7] MPM is an extremely difficult disease to treat, and median overall survival (OS) ranges between 6 and 17 months, depending on histologic subtype.[8] Currently, the standard chemotherapy agents for MPM are the antifolates, pemetrexed and raltitrexed.[9] While pemetrexed was shown to induce moderate response (14.1%) as a single agent, it demonstrated considerably higher activity (41.3% response) when used in conjunction with cisplatin.[10, 11] Cisplatin is sometimes poorly tolerated, especially in older patients, but it can be substituted with carboplatin, a cisplatin analog which has a reduced toxicity profile.[9] Similar activity has been observed between cisplatin-pemetrexed and carboplatin-pemetrexed (26.3% response vs. 21.7%, respectively).[12] Imaging is critical in MPM cases because it is the primary means of assessing tumor response to treatment, which often correlates to such variables as patient quality of life and overall

survival. Currently, computed tomography (CT) is the standard imaging modality used to assess tumor response; it can be supplemented with fluorodeoxyglucose-positron emission tomography (FDG-PET) or PET/CT, as well as magnetic resonance (MR) imaging.[13]

Materials and Methods

~~Subject Enrollment~~

~~Subjects were included in this retrospective study if they met the following criteria: 1) they were diagnosed with MPM, 2) were subsequently treated at UCMC with two or more cycles of either carboplatin-pemetrexed or cisplatin-pemetrexed, and 3) had a baseline CT scan acquired before their first chemotherapy cycle and a follow-up scan acquired after their second cycle. Providers decided which regimen patients should receive. All subjects were over 18 years of age. No healthy controls were included in this study.~~

Human Subject Protection

All subjects signed a written consent for at least one of two UCMC Institutional Review Board (IRB) protocols. One is a prospective tissue-banking study that allows researchers to bank and analyze tissue from patients treated at UCMC for a thoracic malignancy. The other allows for the study of tissue which has already been collected. Although no tumor tissue analysis was performed for the present study, both protocols also allow for the abstraction of medical information and images from the patients' charts.

Database Security Measures

Both the TOPDP and TORP databases include the protective measures necessary to ensure that they meet ~~or exceed~~ regulatory requirements instituted by the Health Insurance Portability and

Accountability Act (HIPAA) Security Rule and HIPAA Privacy Rule.[14, 15] Microsoft Access databases do not automatically have these protective measures in place, but the TOPDP database has been amended using optional Access security features and Visual Basic for Applications (VBA) scripts to meet HIPAA regulations for databases. In particular, access to the database is restricted to an approved list of users, username and passwords are required when opening the database, the database is encrypted, and an audit trail has been created to track changes and user access. Additionally, data can be automatically de-identified before export. REDCap has inherent security measures: only approved users are given access; different users are assigned different levels of access, depending on their research needs; username and password are required; an audit trail records the time, nature, and author of a change to the database; and fields marked as identifiers can automatically be excluded when data are exported. Lastly, embedded protected health information (PHI) within images was anonymized by the University of Chicago Human Imaging Research Office (HIRO).[16]

Informatics Infrastructure

The TOPDP database contains demographic, clinical, follow-up, proteomic, and genomic data for over 3000 patients with various thoracic malignancies. It is a relational database ~~which is~~ composed of a master Patients Table and subsidiary tables ~~which are~~ linked to the Patients Table via ~~a common field, in this case,~~ a field containing the patient's medical record number (MRN). Currently, ~~most~~ subsidiary tables contain genomic and proteomic data, but new tables can be designed as needed. Related tables can be queried to display desired variables in a new table.

~~For every patient, t~~The Patients Table contains demographic and clinical data, as well as data regarding social, environmental, and family history. These variables follow the national standard for oncology databases established~~, as set forth~~ by the NCI Common Data Elements Committee, but they extend beyond standard variables to meet needs specific to the Thoracic Oncology Program.[17] Not all

variables of interest are contained in the patients' medical charts; consequently, it is necessary to obtain data via a patient interview.; fFollowing the patient interview, unknown or unreported variables are abstracted from the patient's medical chart, which is also used to crosscheck patient-reported data for quality assurance purposes. Data are subsequently imported into the TOPDP database.

The TOPDP database is used not only to give a comprehensive view of all consented patients and related research performed by the lab but also to identify smaller cohorts of patients for new research projects in the context of the currently-existing IRB protocol, as was done in this study and as will be described in further detail below. The Patients Table is designed to give general knowledge of each patient's demographics, history, and oncology care; it is not meant to be an exhaustive record. For example, the database captures whether or not a patient has received chemotherapy and the names of the chemotherapy agents the patient has received. However, it does not capture information regarding the number or timing of chemotherapy cycles. Such detailed information is time-consuming to collect and is generally of little utility for our research. When more detailed patient information is required for an investigation, it is abstracted from the patient's medical chart and imported into the TOPDP database in a subsidiary table.

In most cases, the TOPDP database also stores the data required for hypothesis validation after the data are generated or collected. However, in some instances, the TOPDP database is insufficient, as when large files must be stored as part of the study. In this case, the TORP database can beis used alongside the TOPDP database. Identical tables are created in both databases, data in the TOPDP database are transferred into the TORP database, and the TORP database is augmented with uploaded files (e.g., images). Figure 1 presents a chart detailing thisour informatics infrastructure.

Utilization of Databases for MPM Study

Subjects were included in this retrospective study if they met the following criteria: 1) they were diagnosed with MPM, 2) were subsequently treated at UCMC with two or more cycles of either carboplatin-pemetrexed or cisplatin-pemetrexed, and 3) had a baseline CT scan acquired before their first chemotherapy cycle and a follow-up scan acquired after their second cycle. ~~For the purposes of this study, t~~The TOPDP database was used to identify a cohort of previously-consented qualifying MPM patients. Specifically, the Patients Table was filtered to display patients with MPM who had received chemotherapy and who had CT scans acquired at UCMC. However, additional data (number and dates of CT scans and chemotherapy cycles) were required to verify that patients met the selection criteria. These data were abstracted from the patients' medical charts and then entered into a subsidiary table ~~created~~ in the TOPDP database ~~to capture desired variables~~. A similar table was then created in the TORP imaging database. Both tables were identical, with the exception that the TORP database table also contained file upload fields, which were used to capture pre- and post-treatment CT section images and histological images. To ensure that data were transferred correctly and easily, fields were given the same names in both databases. Data were transferred from the TOPDP database to the TORP database using a Microsoft Excel comma-separated values (.csv) spreadsheet as an intermediary. Images were uploaded into the TORP database using REDCap's online file uploader. Data were exported to Microsoft Excel for analysis.

Data Elements and Imaging

For each patient, demographic, exposure (to known MPM risk factors), and clinical data relevant to MPM were captured. Many of these data (e.g., histology, stage, ~~grade,~~ treatments received, imaging acquired, vital status~~, Eastern Cooperative Oncology Group (ECOG) performance status at time of first visit~~, etc.) are routinely captured ~~for all patients entered into the database~~. ~~However, some v~~Variables of

interest ~~are~~ not routinely collected (for example, number, date(s), and type(s) of surgeries and chemotherapy cycles; number and date(s) of CT scans; response to treatment)~~, as they are not necessary for most of the investigations performed by the lab. These variables~~ were abstracted from patient charts~~collected for subjects included in this study via chart abstraction after an initial cohort of subjects was identified.~~

~~In addition, a~~As histology is integral for prognosis in MPM,[8] histological images were selected and supplied to the research team by the UCMC pathology department. Three types of images were selected: low power images, medium power images, and images with immunohistochemistry (IHC) staining. Patients had between 0 and 35 IHC images. ~~Example pathological images can be found in figure 2.~~ Finally, two CT images for each patient were obtained and uploaded into the database: a representative section image from a baseline pre-treatment CT scan and an anatomically matched section image from a follow-up CT scan acquired according to clinical protocol. Follow-up images were selected from scans acquired immediately after the second cycle of treatment. If no scan was acquired immediately after cycle two, the next available scan after the second cycle of treatment was selected. While the Modified Response Evaluation Criteria in Solid Tumors (RECIST) dictates that tumor thickness be measured at two pleural lesions on three different slices at least 1 cm apart,[18] it was felt that since this study was performed as a demonstration, only one pre- and one post-treatment measurement were necessary to show proof of principle. Sample pre- and post-therapy CT section images are presented in figure 2~~3~~.

Scans used for research purposes were obtained by UCMC's Human Imaging Research Office (HIRO) from the Department of Radiology's clinical image archive. After images were anonymized by the HIRO, a study investigator selected representative sections for pleural measurement. Measurement of pleural thickness was performed using a radiology software package called Abras, which was developed in-

house. Abras is image-visualization interface software that offers tools for image annotation, measurement, and contouring and enables the extraction of a wide-range of image-based quantitative and statistical data. It provides users with a high degree of versatility in the interaction with, and manipulation of, medical images. Abras was developed to provide a cross-platform tool to rapidly access, view, and evaluate images in support of medical imaging research projects.

Results

Database Results

Using the TOPDP database, 129 consented patients with MPM were identified. 22 patients met the selection criteria. For these 22 patients, data were captured in the TOPDP database and subsequently transferred to the TORP database. Patient pre- and post-treatment CT scans were assessed, tumor measurements were recorded, and representative images were stored in the TORP database. ~~Lastly,~~ ~~h~~Histological images were also captured ~~for future research use~~.

Specific results from the study itself are detailed below. It is important to emphasize that tumor measurements were not acquired in accordance with Modified RECIST[18] and were only acquired at two time points. Consequently, these tumor measurements cannot be considered valid data from which to draw clinical conclusions. They are included here, nevertheless, as an example of the kind of results enabled by utilizing this informatics infrastructure.

Example Results Enabled by Utilization of the TOPDP and TORP Databases to Assess Tumor Response

Patient Characteristics

~~Patient characteristics are listed in Table 1.~~ Of the 22 patients, 21 were male and 1 was female. 20 were Caucasian and 2 were African American. Ages ranged from 47 to 80 years, with a median age of 65 years. 18 patients endorsed prior occupational and/or para-occupational asbestos exposure; 2 patients reported unknown exposure; and 2 patients did not have data regarding asbestos exposure recorded in the TOPDP database or their electronic medical records (EMRs). 16 patients were diagnosed with epithelial mesothelioma, 2 with sarcomatoid mesothelioma, and 2 with mixed-type mesothelioma. 18 patients underwent one or more surgeries: 3 patients underwent extrapleural pneumonectomy, three underwent pleurodesis, 6 underwent pleurectomy/decortication, and a further 6 underwent pleurodesis followed by pleurectomy/decortication. 11 patients were assessed by the clinician as having an ECOG performance status of 0 at their initial appointments, 8 received a score of 1, and 3 patients were given a score of 2.

Chemotherapy Response

~~Table 2 summarizes chemotherapy details and patient outcome by chemotherapy regimen. Table 3 provides more detailed data regarding pleural measurements for each patient.~~ 14 patients received two to four cycles of carboplatin-pemetrexed and 8 patients received four to six cycles of cisplatin-pemetrexed. Overall, 1 patient received two cycles, 5 patients received three cycles, 11 patients received four cycles, 2 patients received five cycles, and 3 patients received six cycles of chemotherapy. Based on the measurements generated for this study, the mean percentage change in pleural thickness for carboplatin-pemetrexed patients was -25%, indicating a 25% reduction in pleural thickness between the time points of the two CT scans, compared to -11% for cisplatin-pemetrexed patients. Of the 14

patients who received carboplatin-pemetrexed, 9 (41%) remain alive 6-28 months after commencing chemotherapy. Of the 8 patients who received cisplatin-pemetrexed, 4 (50%) remain alive at 16-27 months after commencing chemotherapy. A brief summary of patient characteristics and tumor measurements is presented in table 1.

Discussion

Informatics has been an important part of cancer research efforts to develop more effective diagnostics and therapeutics. These initiatives have led to better clinical outcomes for many patients.[19, 20] However, prognosis for many patients, including those with MPM, remains poor.[19, 20] Consequently, it is imperative that we continue researching novel therapeutics to combat cancer as its incidence rises worldwide. To ensure that such research continues, we must develop informatics infrastructures that meet research needs, one of which is an easily implementable comprehensive translational research database capable of handling imaging.

Relational databases that incorporate imaging have been developed by other groups,[3-5] but they differ from ours in a fundamental way: ease of implementation. For example, the eDiaMoND database is designed to aid clinicians and researchers by compiling mammography and related clinical data;[3] the Biomedical Image Metadata Manager (BIMM) allows researchers to access and query images and associated metadata;[4] and the Pathology Analytic Imaging Standards (PAIS) data model database enables the storage and analysis of large TMA datasets.[5] All three of these databases are developed based on published data models that can be replicated by outside groups. While implementing one of these databases might be beneficial for some, they are sophisticated enough that we feel it would require a dedicated informatics specialist to replicate them. Consequently, we felt the need to design a

simpler informatics infrastructure that incorporated imaging but did not focus on it and that would be more easily implemented by translational research groups without special informatics expertise.

To do so, we decided to use a ready-made database platform that required little to no coding.

Unfortunately, widely-available, readymade database platforms are often designed to meet a variety of research needs, but rarely ever do they meet all the needs of a specific researcher. Consequently, it ~~is sometimes necessary, as in this case,~~was necessary to utilize a tandem database infrastructure~~s~~ in order to incorporate imaging~~undertake certain research projects~~. Microsoft Access has been a very useful platform for our translational research due to its relational nature, ease of querying, portability, ease of deployment, and low cost and ubiquity, which enable collaboration with institutions around the world. These features have allowed us to develop the TOPDP database, a comprehensive thoracic database containing patient demographic, clinical, proteomic, and genomic data in a centralized location.[6] However, Microsoft Access is not without its problems: in particular, Access databases are limited to a 2 GB footprint. Thus, Access is well-suited to capture text-based data, but it is limited when capturing images or other files with a large memory footprint.

For this reason, we developed the TORP database using the online REDCap database platform, which was developed at Vanderbilt University and made available to us by the University of Chicago CRI. Like Microsoft Access, the REDCap platform is well-suited to meet some of our research needs, but falls short in other areas. REDCap is not relational, so the decision was made to maintain our comprehensive database in Microsoft Access. However, REDCap allows up to 1 TB of storage space and so is ideal for research projects utilizing large files. This capability was especially important for this research project, as multiple representative images from CT scans and histological images for each patient were uploaded into the database. Moreover, REDCap interacts easily with Access, communicating via Microsoft Excel or

an API call, and, like Access, REDCap encourages collaboration within and among institutions, as it is web-based and available freely.

In addition to facilitating more robust and novel analyses, this database structure also fosters intra- and inter-institutional collaboration. Microsoft Access is widely available for a minimal cost, and REDCap is available freely online to registered users. Moreover, researchers interested in adopting the Salgia Lab's TOPDP and TORP databases may access the lab's standard operating procedures (SOPs) for its Access[21] and REDCap[22] databases, which further detail the construction and utilization of the databases and are freely available on the iBridge network. Only by developing a common infrastructure will we be able to facilitate fast and easy collaboration in MPM research, which will be essential if the global biomedical research community is to overtake this increasingly global disease.

This informatics infrastructure is not without its limitations, however, one of which is that data must be captured via patient report or chart abstraction and then manually entered into the TOPDP database. This process is tedious, subject to error, and time-consuming. However, there are plans to automate this process by enabling data to be transferred immediately from the patient's electronic medical record (EMR), which will reduce workload and the potential for error considerably. In this investigation, data were transferred easily from the Access database to REDCap using Microsoft Excel as an intermediary and REDCap's data upload functionality. This method was sufficient for the purposes of the present study, but if necessary or desired, it is also possible to automate the data transfer process using the REDCap API. However, images must be uploaded manually using REDCap's online file upload field. The time required to upload images for this investigation was negligible. However, having to upload images manually would most likely be prohibitive of studies involving hundreds or thousands of patients.

~~Limitations~~

~~Study Limitations~~

~~While the TOPDP database has information on over 3000 patients, t~~

Our proof of principle investigation was also limited in various ways, for one ~~he study was limited~~ by sample size (n=22). ~~Only 22 patients met the inclusion criteria requiring that patients were diagnosed with MPM, treated with at least two cycles of carboplatin-pemetrexed or cisplatin-pemetrexed, and had CT scans acquired prior to and following two cycles of chemotherapy treatment.~~ As this study was retrospective, it was also limited by a lack of standardization: when possible, we selected a follow-up CT scan acquired immediately after the second cycle of chemotherapy, but for some patients, follow-up CT scans were only available after the third or fourth cycle. ~~Additionally, patients received different numbers of chemotherapy cycles.~~ Furthermore, ~~due to the study's retrospective nature,~~ some patient data remained unreported because it could not be found in physician notes during chart abstraction. Finally, tumor measurements were not acquired using Modified RECIST, so they cannot be said to be valid data from which we can draw clinical conclusions.

~~Informatics Limitations~~

~~Data were transferred easily from the Access to REDCap databases using Microsoft Excel as an intermediary and REDCap's data upload functionality. This method was sufficient for the purposes of the present study, but if necessary or desired, it is also possible to automate the data transfer process using the REDCap API. One limitation of the current informatics infrastructure is that data must be captured via either patient report or chart abstraction and then manually entered into the TOPDP database. This process is tedious, subject to error, and time-consuming. However, there are plans to automate this process by enabling data to be transferred immediately from the patient's EMR, which will reduce workload and the potential for error considerably.~~

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Conclusion

We sought to develop a relational database infrastructure that 1) efficiently incorporated images with proteomic, genomic, or other laboratory data; 2) could be implemented, used, and altered easily with little knowledge of coding; 3) and was available to collaborators at minimal cost;. ~~Informatics must continue to enable more robust cancer research by meeting evolving research needs. One of these needs has been the ability to utilize and store imaging as a part of translational cancer research. To fill this deficit area, we have implemented a novel tandem database using our TOPDP and TORP databases.~~ At first it seemed ideal to capture all our imaging and laboratory data exclusively in REDCap. However, moving entirely into REDCap would require giving up the relational component of our database infrastructure. Consequently, we developed the TORP REDCap database to be used in tandem with our TOPDP Microsoft Access database. In order to evaluate this informatics infrastructure, we performed an investigation into MPM tumor response to two standard chemotherapy regimens. In large part, our investigation was a success: as intended, we were able to implement a relational database that housed both laboratory and imaging data using database platforms that are available at negligible cost and are easily developed and utilized. However, in the course of the investigation, a limitation to our informatics model became apparent: while the time required to upload images in this investigation was negligible, the fact that images must be uploaded manually would most likely preclude large-scale studies. Consequently, we are now working to implement an SQL database, which will be slightly more complex to develop but will enable us to automate workflow and store imaging and laboratory data in a single relational database. In conclusion, it is to be appreciated that this tandem database infrastructure is a very useful tool for small datasets for both informaticians and non-informaticians. Moreover, one can ultimately envision utilizing the data model for this infrastructure as a basis for developing a larger, more-streamlined database.~~While our focus has been thoracic malignancies, it is our hope that this~~

~~example investigation has illustrated the potential of our informatics infrastructure for use in cancer research as a whole.~~

Supplementary Tables and Figures

Table 1 Patient Characteristics

	Number of Cases (%)
Total Cases	22 (100)
Sex	
Male	21 (95)
Female	1 (5)
Race	
Caucasian	17 (77)
African American	2 (9)
Other	0 (0)
Unspecified	3 (14)
Histology	
Mesothelioma – Sarcomatoid Type	2 (9)
Mesothelioma – Epithelioid Type	16 (73)
Mesothelioma – Mixed Type	4 (18)
Asbestos Exposure	
Occupational/Para-Occupational	18 (82)
Unknown	2 (9)
Not Reported	2 (9)
Age at Diagnosis (years)	
Median	65
Range	47-80

*Some patient underwent more than one procedure.

Table 12 Patient Characteristics and ~~Chemotherapy Details~~Tumor Measurements

	Number of Cases (%)* Entire Patient Pool	Carboplatin-pemetrexed	Cisplatin-pemetrexed
Total Cases	22 (100)	14 (100)	8 (100)
Sex			
Male	21 (95)	14 (100)	7 (88)
Female	1 (5)	0 (0)	1 (13)
Race			
Caucasian	17 (77)	11 (79)	6 (75)
African American	2 (9)	0 (0)	2 (25)
Unspecified	3 (14)	3 (21)	0 (0)
Histology			
Sarcomatoid Type	2 (9)	2 (14)	0 (0)
Epithelioid Type	16 (73)	11 (79)	5 (63)
Mixed Type	4 (18)	1 (7)	3 (38)
Age at Diagnosis (years)			
Median	65	68.5	58.5
Range	47-80	49-80	47-75
Performance Status			
0	11 (50)	9 (41)	2 (9)
1	8 (36)	3 (14)	5 (23)
2	3 (14)	2 (9)	1 (5)
Vital Status at Time of Study			
Alive	13 (59)	9 (64)	4 (50)
Deceased	9 (41)	5 (36)	4 (50)
Pleural Thickness Percentage Change			
Mean	-20%	-25%	-11%
Median	-19%	-18%	-19%

*Due to rounding, percentages may not sum to 100.

Table 3 Chemotherapy response details

Patient ID	Chemo-therapy Regimen*	Chemo-therapy Total Cycles	Follow-Up CT Scan Post-Cycle	Pleural Thickness Pre-Cycle 1 (mm)	Pleural Thickness Follow-Up CT Scan (mm)	Difference in Pleural Thickness (mm)
1	Cis/Pem	4	4	6.96	4.39	-2.57
2	Cis/Pem	4	2	19.67	17.06	-2.61
3	Cis/Pem	6	2	10.83	8.61	-2.22
4	Cis/Pem	4	2	34.53	28.29	-6.24
5	Cis/Pem	5	2	16.06	12.75	-3.31
6	Cis/Pem	6	2	25.28	17.01	-8.27
7	Cis/Pem	5	2	24.00	33.47	9.47
8	Cis/Pem	6	2	10.50	12.10	1.60
9	Carbo/Pem	4	2	16.75	14.21	-2.54
10	Carbo/Pem	4	2	18.94	12.52	-6.42
11	Carbo/Pem	3	2	13.30	9.19	-4.11
12	Carbo/Pem	3	3	41.82	44.29	2.47
13	Carbo/Pem	4	4	13.44	7.16	-6.28
14	Carbo/Pem	4	3	41.04	30.94	-10.10
15	Carbo/Pem	2	2	48.65	9.47	-39.18
16	Carbo/Pem	4	4	5.59	5.12	-0.47
17	Carbo/Pem	4	2	21.89	19.68	-2.21
18	Carbo/Pem	4	4	28.59	22.70	-5.89
19	Carbo/Pem	3	3	23.61	21.87	-1.74
20	Carbo/Pem	3	3	13.46	12.12	-1.34
21	Carbo/Pem	3	3	20.35	19.30	-1.05
22	Carbo/Pem	4	4	6.30	2.65	-3.65
Average	Cis/Pem	5	2.25	18.48	16.71	-1.77
Average	Carbo/Pem	3.5	2.93	22.41	16.52	-5.89

*Abbreviations: Carbo, carboplatin; Cis, cisplatin; Pem, pemetrexed

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Contributions

GBC, SK, and MS drafted the manuscript. GBC, SK, MS, AK, and CER were responsible for the design, implementation, and maintenance of the TOPDP and TORP databases. ASadiq, TH, EEV, WV, HLK, and RS provided clinical knowledge and support. NB, BR, RM, and PD provided REDCap support. SGA and AStarkey created the Abras imaging software. SGA acquired radiological measurements and selected representative CT images. AH reviewed pathology slides for each patient and provided the histological images. RS oversaw the development of the databases, as well as the drafting of the manuscript.

Competing interests

The authors have no competing interests.

Data sharing statement

No additional data available.

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