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Review Article

Developing a multidisciplinary prospective melanoma biospecimen repository to advance translational research

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Abstract: Several challenges face the development and operation of a biospecimen bank linked to clinical information, a critical component of any effective translational research program. Melanoma adds particular complexity and difficulty to such an endeavor considering the unique characteristics of this malignancy. We describe here a review of biospecimen bank and our experience in establishing a multi-disciplinary, prospective, integrated clinicopathological-biospecimen database in melanoma. The Interdisciplinary Melanoma Cooperative Group (IMCG), a prospective clinicopathological and biospecimen database, was established at the New York University (NYU) Langone Medical Center. With patients' informed consent, biospecimens from within and outside NYU, clinicopathological data, and follow-up information are collected using developed protocols. Information pertaining to biospecimens is recorded in 35 fields, and clinicopathological information is recorded in 371 fields within 5 modules in a virtual network system. Investigators conducting research utilizing the IMCG biospecimen resource are blind to clinicopathological information, and molecular data generated using biospecimens are linked independently with clinicopathological data by biostatistics investigators. This translational research enterprise acts as a valuable resource to efficiently translate laboratory discoveries to the clinic.

Key Words: Melanoma, clinical database, specimen bank, translational medicine, model

Introduction

Despite recent advancements in public awareness, melanoma remains a significant health problem in the United States. The incidence of melanoma has continued to rise sharply over the past few decades [1]. Although melanoma accounts for only 4% of the over 1 million people diagnosed with skin cancer each year, it is responsible for nearly three times the number of deaths as non-melanoma skin cancers [2]. Survival rates are high with early diagnoses but remain poor for patients diagnosed with late stage disease [1]. Importantly, melanoma is one of the more frequent cancers in young adults and is the second most common cancer among women ages 20-29 [3]. Because of the relatively young age of onset, the toll of melanoma in terms of "life-years lost" is second only to leukemia among all malignancies in the United States [2]. The annual estimated cost of treating melanoma in the United States is over $3.1 billion [4], with 90% of treatment costs associated with therapy for advanced disease [5]. The fact that this increasingly more common malignancy tends to strike young adults in the prime of life has a major impact on the productivity of society [6].

The results of this study represent the original work of the authors.

One of the major challenges facing translational research today is the lack of standardization in biospecimen collection linked to clinical data. In 2007, the National Cancer Institute (NCI) published "Best Practices for Biospecimen Resources" which presents guiding principles for: biospecimen collection, processing, storage, retrieval and dissemination; collection and managing clinical data; quality assurance/quality control; biosafety; biospecimen resource informatics; and ethical, legal and policy issues [7]. In addition, the International Society for Biological and Environmental Repositories (ISBER) published the second edition of their "Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research" in 2008. This document suggests guidelines for biospecimen repository organization, records management, facilities, storage equipment and environments, quality assurance and quality control, safety, training, biological material tracking, packaging and shipping, specimen collection, processing and retrieval, and legal and ethical issues for human specimens [8]. Adherence to either of these guidelines, however, is not mandatory [7, 8], leading to variability. Furthermore, melanoma translational research poses additional challenges. These include unique difficulties in the respective diagnoses of primary and metastatic melanomas and limitations in primary melanoma size (millimeters compared to centimeters in other cancers), which restricts the availability of tissue for research studies.

With these challenges in mind, we established the Interdisciplinary Melanoma Cooperative Group (IMCG), a prospective clinicopathological and biospecimen database, in 2002 at the New York University (NYU) Langone Medical Center. The objectives of the program are, among others, to identify new prognostic biomarkers for better prediction of treatment outcome, to identify new targets for melanoma treatment, and to evaluate the biologic heterogeneity of melanoma. The IMCG began with 6 investigators in 2002 and now includes 23 investigators from 11 departments. In this article, we address key difficulties that are unique to the development and management of such a program focused on melanoma.

Challenges of a clinicopathological biospecimen database

The development and expansion of a prospective multidisciplinary clinicopathological-biospecimen database of cancer patients is a challenging endeavor for several reasons. Success requires the cooperation of numerous physicians representing a variety of disciplines, in addition to well-trained supporting staff. Cohesive programmatic infrastructure that is integrated synergistically with the institution at large is a difficult but essential element of a productive research enterprise. Adequate resources are necessary for the procurement and banking of biospecimens, and access to extensive clinical, family, and follow-up information is critical. The collection and archiving of patient data and tissues in a secured database is of the utmost importance, and this information must be carefully annotated and validated. Lastly, research focuses are constantly evolving. Therefore, it is important for investigators to re-evaluate their needs and to adapt databases accordingly. We have ensured that the IMCG is a dynamic enterprise, as illustrated by our recent additions of a more in-depth ethnicity form in response to genetic research questions and the collection of fresh tissue specimens for sorting analyses (i.e. stem cell isolation). We have also recently begun to enroll patients with melanoma in-situ and no prior history of invasive melanoma in an effort to expand the breadth of disease that may be studied by IMCG investigators.

In addition to the predicaments in performing successful translational research in general, focusing on melanoma presents other unique challenges. Primary melanomas are relatively small tumors compared to other malignancies, almost always measuring a few millimeters or less in dimension. This severely limits the amount of tissue available for research. To address this issue, macro- and micro-dissection techniques have been adopted to ensure efficient utilization of tissue specimens.

Additionally, the overwhelming majority of melanomas are diagnosed in the offices of primary dermatology practices rather than on the campuses of academic institutions [9], complicating significantly the retrieval of primary tissue specimens. Not infrequently, discrepancies complicate the diagnoses of

melanoma [10, 11]. To address such challenges, all primary and metastatic lesions associated with the IMCG program are validated blindly by two pathologists, independently, to ensure accurate and consistent diagnoses.

The NYU interdisciplinary melanoma cooperative group as a model

Patient consent and eligibility criteria

The IMCG study is approved by the NYU Institutional Review Board (IRB). Patient accrual for the IMCG is conducted at the NYU Clinical Cancer Center, Tisch Hospital, and the Bellevue Hospital Center by IMCG clinical investigators (DP, RS, RB, and AP). The IMCG enrolls primary and recurrent/metastatic patients who present to NYU for treatment of melanoma.

Eligible primary patients are those who have been diagnosed with an invasive or in-situ melanoma within two months prior to accrual to the database. Patients with recurrent/metastatic disease, including those with regional or extra-regional metastases and those with unknown primaries, are eligible if they consent to the IMCG within six months of the initial or first recurrence diagnosis. For individuals referred from outside institutions, the diagnosis of primary or recurrent/metastatic melanoma is confirmed by the independent analysis of biopsy specimens by two IMCG pathology investigators (HK and FD).

If a patient is deemed eligible by the attending physician, he or she reviews the consent form with the patient and explains the basis of the IMCG. Patients are informed that with their consent, they are authorizing the release of previously excised melanoma tumor specimens, fresh tissue obtained during surgery, a small blood sample, and all previous and future medical records information. In addition, as some patients do not follow-up at the NYU Langone Medical Center or the Bellevue Hospital Center and follow-up information cannot always be retrieved from medical charts, patients are asked for permission to be contacted by the IMCG in the future to establish their melanoma status.

Clinicopathological database

Upon consent, IMCG participants are assigned a unique identification number. From review of patients' medical records, IMCG data managers capture clinical and pathological information in 371 fields in the Oracle platform database (Oracle Corp., Redwood Shores, CA). Physicians in the NYU Departments of Dermatology, Pathology, Surgery, and Oncology, as well as biostatisticians, were involved in the design of the database and the definitions of the data collection fields. Demographic background, personal and family history of disease, pathological diagnoses, radiological imaging reports, sentinel lymph node mapping, disease staging, treatment, and continuing clinical follow-up information, all compiled from thorough review of medical records and clinician interview, are incorporated into the database. Tissue and serum specimens are stored in the Freezerworks platform (description to follow) and physical biosamples are coded for linkage to corresponding clinicopathological data in Oracle. Information in the Oracle and Freezerworks databases can only be accessed by the principal investigator (IO) and data managers and are protected by several levels of security. Neither the name nor identifying information for an individual patient is used in publications related to the IMCG.

The newly updated Oracle network system is divided into 5 modules: on-study, treatment, pathology, follow-up, and off-study. The on-study module contains registration information (ethnicity, date of informed consent, personal/family history of cancer), biographical data (contact information, outside physicians, medical record number), and an eligibility criteria checklist. The treatment section records results of biopsies and surgical procedures, including lymphatic mapping and sentinel lymph node (SNL) biopsies, initial staging, and adjuvant therapy. For patients who present with recurrence and/or metastases, information is recorded for each event by site: regional, extra-regional cutaneous, lymph node, and organ metastases. The pathology module documents each biopsy performed, including hospital name, date, location of biopsy, and accession number. For primary and when possible for recurrent/metastatic patients, thorough information on the primary lesion is recorded (anatomic site, histological type, thickness, Clark's level, ulceration, mitotic

Table 1. Characteristics of all patients enrolled in the IMCG database

Characteristic	Number (%)
Total Patients	1,015
Stage at Sign On[1]	
Primary patients	812
Stage 0 (in-situ)	31 (3.1)
Stage I	558 (55.0)
Stage II	135 (13.3)
Stage III	88 (8.7)
Recurrent/Metastatic patients	203
Stage III	105 (10.3)
Stage IV	98 (9.7)
Primary Patients[2]	
Follow-up (months)[3]	
Range	0-69
Median	17
Number of patients that have recurred	86 (10.6)
Number of patients that have died	61 (7.5)
Recurrent/Metastatic Patients	
Follow-up (months)[2]	
Range	0-67
Median	12
Number of patients that have died	96 (47.3)
Site of First Recurrence in Primary Patients	
Local recurrence	3 (3.5)
Regional skin	26 (30.2)
Regional lymph node	18 (20.9)
Distant skin	4 (4.7)
Distant lymph node	1 (1.2)
Distant visceral	22 (25.6)
Multiple	12 (14.0)

[1]Percentages for Stage at Sign On are based on 1,015 patients total; [2]Primary patients are those who have been diagnosed with an invasive or in-situ melanoma within two months prior to accrual to the database; [3]Follow-up time includes 0 months as these data include recently enrolled patients who are not yet due for follow-up.

index, regression, etc.). When a SLN biopsy is positive, complete pathology results are documented. For metastatic lesions, Oracle contains fields documenting immunohistochemistry data and staging. Follow-up information is recorded every 3 months for metastatic patients, every 6 months for primary invasive patients, and every 12 months for primary melanoma in-situ patients (non invasive melanoma with <1% chance of recurrence). If a patient is removed from the study (by choice, lack of follow-up, or death), the reason is documented in this module.

The Oracle database is queried for research studies using the complementary software program Integrated Review (Integrated Clinical Systems, Inc.). Customized datasets for statistical analyses are created in SAS® and other analysis platforms. Integrated Review has 12 levels of security, with access limited to the IMCG data management personnel and the principal investigator (IO). Numerous safeguards have been implemented into the infrastructure of the IMCG to uphold patient confidentiality and regulatory obligations. All program activities and network systems are fully compliant with Health Insurance Portability and Accountability Act (HIPAA) guidelines.

Periodic evaluation of the IMCG database is critical to confirm the accuracy, standardization, and precision of all clinical and pathological information. Bimonthly database audits are performed for both the Oracle and Freezerworks platforms by the IMCG Clinical Research Supervisor and are subsequently reviewed with the clinical investigators of the program. The basis of any error is determined, the field is amended, and precautions are undertaken to avoid future discrepancies.

Table 1 describes the characteristics and follow-up data for the 1,015 patients enrolled in the IMCG database: 812 (80.0%) primary patients and 203 (20.0%) recurrent/metastatic patients. Patients with melanoma in-situ presenting with no history of invasive melanoma were recently added to the inclusion criteria for the IMCG database and account for 31 of the 812 primary patients. Follow-up times range from 0 months to 69 months, as these data include patients that have just been enrolled. One patient has withdrawn from the IMCG study.

Oracle has recently been expanded to include ethnicity information to accommodate current interests of investigators in melanoma translational research, and we have begun to collect this data.

Specimen inventory and distribution

Blood and tissues accrued for the IMCG are documented in Freezerworks, a secure network database linking biospecimens to corresponding clinical and pathological data. Freezerworks catalogues each blood and tissue sample's storage location, application in a study, quantity, and quality. There are 35 data fields that outline the pathology, clinical history, location, application, and quantity of each unique specimen. A portion of the fields in the respective tissue and blood virtual banks overlap, including the patient's study ID, gender, age, date of enrollment, and date of melanoma diagnosis. Queries with any combination of these fields can be generated directly by the software with adjustable selection criteria to customize the search. The barcode labeling of all specimens further enforces the connection between each sample and the parallel clinicopathological data. All tissue and blood samples are labeled with the patient's IMCG identification number, distinct from name and medical record number to protect confidentiality.

The Freezerworks platform additionally provides an automated audit trail to record every action in the database, including previously entered or edited data fields and specimen/aliquot transactions. The audit feature improves the accuracy of the virtual inventory by tracking the complete history of actions with user and date. The lifelong stages of samples from collection, procurement, update of clinicopathological data, study usage, and final depletion are recorded. This audit history ensures that no data is lost, regardless of any user modifications.

In order to utilize IMCG biospecimens and clinicopathological data for research, investigators present study proposals to the principal investigator (IO). The request is reviewed by the NYU Melanoma Steering Committee and the Institutional Tissue Banking Committee. Together, these committees decide the prioritization of biospecimen utilization.

Biospecimens processing for the IMCG database

Standard operating procedures have been implemented to minimize variations in biospecimen collection, processing, and storage as recommended by the ISBER "Best Practices for Repositories" [8]. The IMCG Biospecimen Bank site, adjacent to the IMCG Data Management Office, is utilized for the proper processing, cataloguing, and storage of patient samples. Formalin fixed paraffin embedded (FFPE) specimens sectioned on glass slides are stored in durable slide boxes. Retrieved FFPE tissue blocks pending sectioning are stored in a contained biohazard compartment within a 4˚C cold storage room. Blood samples are collected in BD Vacutainer® plastic EDTA (anticoagulant salt) tubes and BD Vacutainer® glass serum tubes. The blood is initially processed in a tissue culture room under a hood and separated into whole blood, plasma, and sera components. Blood in the BD Vacutainer® plastic EDTA tube is aliquoted into 4 vials (250 µl each) to comprise the whole blood samples. The remaining blood is then centrifuged for 10 minutes at 1300 X g at 25˚C. The supernatant (plasma) is then aliquoted into two vials (approximately 1 ml each) to constitute the plasma samples. The BD Vacutainer® glass serum tube is centrifuged for 10 minutes at 900 X g at 10˚C, and the supernatant (serum) is then aliquoted into two cryovials to store the sera samples. All blood components are barcode labeled, registered into the Freezerworks platform, and stored in the -80˚C deep freezer for future research studies. A portion of the aliquoted whole blood is used to isolate DNA samples, which are stored in -20˚C and -80˚C freezers. To ensure high quality specimens for numerous studies, remaining blood samples are separated into several aliquots to prevent multiple freeze-thaw cycles. These methods used for blood processing were chosen to optimize DNA quantity and quality and to optimize collection of serum and plasma.

For fresh tissue samples (metastatic melanoma tumors sufficient in size to provide a piece for research), the surgically excised tissue mass is placed in a sterile container and covered in the RPMI/saline media (containing antimicrobial and antifungal) to preserve the viability of tumor cells and to avoid contamination. The specimens are

Table 2. Baseline clinicopathological Characteristics of patients with primarymelanomas

Characteristics	Number (%)
Total Primary Melanoma Patients[1]	781
Age at Diagnosis (years)	
Range	18-97
Mean	57.7
Median	59
Sex	
Male	424 (54.3)
Female	357 (45.7)
Thickness (mm)	
Range	.12-30
Mean	1.66
Median	0.85
Ulceration	
Absent	652 (83.5)
Present	121 (15.5)
Unknown	8 (1.0)
Clark's Level	
II	212 (27.1)
III	172 (22.0)
IV	339 (43.4)
V	33 (4.2)
Unknown	25 (3.2)
Histological Type	
Acral lentiginous	20 (2.6)
Desmoplastic	18 (2.3)
Lentigo Maligna	26 (3.3)
Nodular Melanoma	186 (23.8)
Superficial Spreading	445 (57.0)
Other Known but Rare	36 (4.6)
Unknown	50 (6.4)
Anatomic Site	
Axial	431 (55.1)
Extremity	350 (44.8)

[1]Of note, 6 patients were signed on with two primaries diagnosed the same day. In these cases, the thicker melanoma was used for this table.

processed for the establishment of melanoma cell lines and the potential isolation of melanoma stem cells. A representative histological slide of the fresh tissue sample is reviewed by the NYU Department of Pathology. If a melanoma neoplasm is diagnosed and is large enough to partition for research, a piece of the tumor is frozen, sectioned, and captured in several magnified microscopic images. The photographic image files and absolute tumor content (%) are linked to the patient's IMCG identification number, and the corresponding biospecimen samples are documented in the Freezerworks database. We do not retain a fresh tissue specimen if the majority of it is necrotic tissue or if the tumor piece is so small piece that the attending pathologist reviewing the fresh specimen decides that he/she needs to retain the whole piece of tissue for diagnostic purposes. Nevertheless, the success rate of collecting fresh tissues has been 112 / 117 (95.7 %).

Remaining fresh tissue sections are distributed into preserving reagent tubes for melanoma stem cell isolation, the establishment of melanoma cell lines, dendritic cell research, as well as an OCT frozen media cassette and an RNAlater tube for RNA extraction. The respective preserving tubes for stem cell isolation, melanoma cell lines, and dendritic cell research are immediately processed by the corresponding investigators, while the OCT block and the RNAlater tube are barcode-labeled and stored in a -80˚C deep freezer.

To date, the IMCG has collected 2,228 biospecimens (974 blood specimens stored as 10,625 aliquots, 1,142 formalin fixed paraffin embedded (FFPE) specimens, and 112 fresh tissue specimens). **Table 2** describes the characteristics of the primary melanomas for which the primary patients were enrolled to the IMCG. Superficial spreading melanoma was the most common histological type (57.0%) with nodular melanoma accounting for the next largest proportion (23.8%). The median thickness was 0.85 mm (range 0.12-30.0 mm).

Differences between the single institution database and a national database

We recognize that a drawback of the IMCG is that it is a single center database. Therefore, caution is advised when generalizing results of an IMCG-based study to the rest of the melanoma patient population. The baseline characteristics of our study population in comparison with the NCI Surveillance,

Epidemiology, and End Results (SEER) data [12], however, demonstrate that our patient cohort is fairly representative of the national population. For the IMCG and SEER Registry melanoma patient cohorts, respectively, mean age at diagnosis (57.43 years vs. 55.50 years), sex (55% male, 45% female vs. 56% male, 44% female), and anatomic site (42% extremity, 58% axial vs. 43% extremity, 52% axial) were found to be similar in a comparison of baseline characteristics of a group of primary invasive melanomas. This set included the first invasive primary melanoma in white, non-Hispanic adults (ages 20 or greater) collected by the SEER-13 Registries during the years 1992 to 2003 and a cohort with the same selection criteria from the IMCG.

Key differences, however, were also found: melanomas in the IMCG cohort were thicker (mean=1.79 mm, median=0.98 mm) compared to those in the SEER cohort (mean=1.15 mm, median=0.64 mm) and more likely to be of the nodular histological type (26% vs. 8%). Notably, in a separate SEER analysis described by Demierre et al, nodular melanomas were found to be diagnosed at thicknesses greater than or equal to 2 mm over 50% of the time, accounting for more than one third of melanomas greater than or equal to 2 mm [13]. The greater thickness found in the IMCG cohort is likely a function of the higher percentage of nodular histological subtype (mean thickness for nodular histological type=3.50 mm compared to 1.17 mm for all other histological types, which is similar to the SEER mean of 1.15 mm). Nodular melanomas tend to be clinically aggressive, and recent evidence suggests that this histological type is also biologically and genetically distinct [14-16]. The finding that the IMCG database has a higher percentage of nodular melanomas compared to national statistics in the SEER Registry highlights the need for collaboration among groups to create multi-center melanoma clinicopathological-biospecimen databases. This level of cooperation is necessary to accommodate the research interests of melanoma investigators as they continue to seek a more comprehensive understanding of this malignancy and strive to improve melanoma patient care.

Effective utilization of database resources is a key element of success

Studies utilizing the resources of the IMCG involve serum-based assays [17], immunohistochemistry [18, 19], tissue microarrays, and gene expression profiling. In one study using a novel serum-based assay, serum of patients with melanoma were assessed for the shedding of HU177, a cryptic epitope exposed by cleavage of type IV collagen during remodeling of the extracellular matrix. Serum levels of HU177 were found to be associated with nodular melanoma subtype [17], lending support to the growing body of evidence that nodular melanoma is a biologically distinct type of melanoma [14-16]. Subsequently, elevated serum levels of HU177 in patients with primary melanomas were found to be associated with worse disease free and overall survival (unpublished data). Using immunohistochemistry, the clinical relevance of Neutral Endopeptidase (NEP/CD10) and cancer/testis antigen NY-ESO-1 have been studied. NEP/CD10 and NY-ESO-1 were found to be overexpressed in metastatic melanoma tumors compared to primary melanoma specimens [18, 19], and the results of the NY-ESO-1 study[19] have been incorporated into clinical trials [20].

Meanwhile, we continue to explore purely clinical questions using the IMCG database [21-23]. Imaging at the time of initial diagnosis of T1b-T3b, clinically N0, M0 melanoma was found to be of limited utility and to have a high false-positive rate, suggesting that imaging of asymptomatic patients at the time of diagnosis may not be warranted [21]. Subsequently, a comparison of the IMCG database with the earlier NYU Melanoma Clinical Cooperative Group database (active 1972-1982; follow-up through 1992) identified a statistically significant shift over 35 years to earlier stages of disease at diagnosis for superficial spreading melanomas but not for nodular melanomas. These findings suggested that improvements in the early detection of melanoma were limited to superficial spreading melanoma and that public education and screening practices may need to be modified to improve nodular melanoma detection rates [22]. Lastly, in an assessment of sentinel lymph node biopsies of patients with thin (<1 mm) melanomas, a practice that lacks standardized guidelines, no clinical or histopathologic criteria was identified that could reliably identify thin melanoma patients who might benefit from this intervention.

Considering the increasing incidence of thin melanoma diagnoses and the cost and potential morbidity of the sentinel lymph node biopsy procedure, these findings highlighted the need for alternative strategies to identify patients at risk for nodal disease [23].

Conclusion

The importance of tissue banks linked to de-identified patient data has even been recognized on a national level with databases funded by the NCI [24, 25]. However, to the best of our knowledge, this is the first published description of an integrated, longitudinal clinicopathological-biospecimen database dedicated exclusively to melanoma. Other institutions are reported to have clinical data-tissue collection systems in melanoma, but the details are not public.

With advances in technology and a trend toward increasing translational research in melanoma, a greater need for specimens linked with reliable clinical information is apparent. We have chosen to publish the overall infrastructure and specifics of the IMCG program at NYU to offer our design as a model for other groups that may follow suit, and additionally to introduce the idea for a multi-center clinicopathological-biospecimen database targeting melanoma in the future.

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