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REVIEW ARTICLE – BREAST ONCOLOGY

Clinical Trials for the Surgical Oncologist: Opportunities and Hurdles

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ABSTRACT Advancements in clinical practice usually require level one evidence from clinical trials that directly compare new approaches to standard of care. While clinical trials have provided data to guide advances in practices across surgical oncology, all too often accrual to clinical trials is slower than anticipated, and once results are presented and published, adoption in clinical practice is slow. Why and how can surgeons be successfully involved with clinical trials? An expert panel discusses the basic infrastructure of clinical trials, investigator-initiated trials, the National Clinical Trials Network, and opportunities for surgeon involvement. Two national clinical trials, NSABP B-51/RTOG 1304 and PROSPECT N1048, are discussed to highlight the role of the surgical oncologist.

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OVERVIEW OF INVESTIGATOR INITIATED TRIALS

There are many opportunities for surgical oncologists to become clinical trialists. There is a wide range of clinical trial types, including trials about the safety and/or efficacy of a particular operation or therapeutic trials to determine the safety/efficacy of a therapy or device in a surgical patient population. Other trials may be aimed at ameliorating a particular health disparity or addressing a quality of life issue. The one common thread to all of these studies is the investigator-initiated trial (IIT). IITs are proposed upon the initiative of a clinical investigator designed to answer a scientific question without a company or nonprofit organization taking the role as a sponsor (unsolicited).[1] These clinical trials often are designed by clinical scientists, called the Principal Investigator or PI.

As the product of independent research, IITs are a cornerstone of clinical research. While they may involve the use of unapproved devices or drugs that are being developed by industry, IITs can determine new uses of drugs/devices or expand product safety beyond what is intended by the companies, which can greatly improve the health of patients. Data accrued through clinical trials can lead to creation of a repository of potential new clinical biomarkers, which can have diagnostic or prognostic applications in patient management. This is another area where expertise and involvement of surgical oncologists can create new opportunities for improving patient care

through clinical trials. Because IITs are unsolicited, there often is a greater weight attached to the data generated by them.[1]

Single-Center IITs

Single-center IITs often are preferred, because they simplify the study conduct; only two parties are involved in the contract (the institution of the PI and the sponsor who is providing the drug or device utilized in the trial) and data collected is from one institution. However, many clinical endpoints, such as overall, recurrence-free, or progression-free survival, require large numbers of patients and most centers outside of a few very large centers cannot accrue this volume alone. Therefore, single-center IITs often are limited in scope and include: pilot studies; phase 0 studies in which the endpoint may be a laboratory study to confirm mechanism of action of a new drug; phase I studies to determine safety in patients receiving a new drug or undergoing surgery with a new device; or small, nonrandomized, phase II studies.

Multicenter IITs

Multicenter IITs are conducted across a consortium of centers to meet the accrual needs of these studies, often with a clinical endpoint and larger sample size, in a timely fashion. In informal consortiums, the participating centers are assembled, because they see high volumes of a particular patient population that the study requires. In these cases, usually the consortium is assembled by the PI. There also are a number of formal consortiums, both non-for-profit (e.g., Hoosier Cancer Research Network, Big Ten Cancer Research Consortium, Translational Breast Cancer Research Consortium) and for-profit (e.g., Sarah Cannon, U.S. Oncology).

One of the major challenges in running a multi-institutional study involves negotiating and finalizing contracts between all participating institutions. Legal issues, such as contracts, can cause major delays in study rollout. Contract research organizations (CROs), such as the Hoosier Cancer Research Network, have minimized this delay by developing a master contract between the main study site and its 128 member institutions. This can significantly shorten the time that it takes to open a study at a particular institution. CROs assist with regulatory issues, such as filing Investigational New Drug (IND) applications, as well as data management across all centers participating in the study. For correlative science studies, these CROs can serve as a central storage repository for patient samples and can ship samples to laboratories for analysis.

NATIONAL CLINICAL TRIALS NETWORK (NCTN)

On the national level, there are well-established cooperative groups with which surgeons can become involved to develop and conduct surgical oncologic clinical trials. The National Cooperative Group program of the National Cancer Institute (NCI), first established in the 1950s, was responsible for many clinical trials that helped to define and refine the standards of cancer care in the United States. However, over the ensuing years, the program became more inefficient and ill-suited to address challenges of conducting high-quality clinical cancer research in the twenty-first century.[2] It was therefore transformed into the current NCTN structure in 2014.[3] Nine previously established cooperative groups were consolidated into four adult groups: Southwest Oncology Group (SWOG) Cancer Research Network, the Alliance for Clinical Trials in Oncology, Eastern Cooperative Oncology Group—American College of Radiology Imaging Network (ECOG-ACRIN) Cancer Research Group, and NRG Oncology; and one pediatric group: Children's Oncology Group (COG). The structure also includes the National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG). Each of these groups has its own operations, statistics, and data management and tissue bank scores. The Alliance was created from the merger of the American College of Surgeons Oncology Group (ACOSOG), North Central Cancer Treatment Group (NCCTG), and Cancer and Leukemia Group B (CALGB). NRG Oncology was the merger of the National Surgical Adjuvant Breast and Bowel Project (NSABP), Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG). The NCTN system has a centralized institutional review board (IRB) and cancer trials support unit (CTSU) as part of the Cancer Therapy Evaluation Program (CTEP), Imaging and Radiation Oncology Core (IROC) group, and a common data management system.

Each of the NCTN cooperative groups has a membership comprised of individual institutions located across the United States and Canada, and each of these member institutions can belong to one or more groups within the NCTN. Moreover, membership in any single cooperative group allows an institution to participate in any trial led by any other NCTN group.

NCI oversight is conducted by scientific steering committees charged with facilitating the exchange of information across the cooperative groups and improving the efficiency of trial design and conduct.[4] These committees establish strategic priorities for the network, develop, and maintain a national clinical trials portfolio and prioritize and approve individual trials. The activities of the steering committees are accelerated through the work of disease site task forces, which discuss protocol

concepts in real time and coordinate trials among the cooperative groups. This new organizational structure was meant to be more responsive, efficient, and collaborative—and less competitive—than its predecessor. More than 3100 institutions and 14,000 investigators now enroll approximately 25,000 patients on treatment trials conducted within the NCTN annually.[5]

OPPORTUNITIES FOR SURGEONS WITHIN THE NCTN

Outstanding opportunities are available to surgeons within the NCTN. Surgeons may accrue their patients to clinical trials designed to answer relevant therapeutic and diagnostic questions; such trials have recently informed the practice of surgery for patients with breast cancer, gastrointestinal stromal tumors, pancreatic cancer, and others.[6–8]

Other opportunities, such as attending the biannual cooperative group meetings, provide a forum for surgeons to network with other leaders both inside and outside of their field of interest. Exposure to physicians and scientists who practice at other institutions, both informally and formally through committees, allows new mentoring relationships to blossom. Work within disease site or treatment modality committees offers valuable experience and leadership training. Furthermore, active investigators may be eligible to respond to group requests for application to funding mechanisms. Surgeons may find countless other opportunities within fields as diverse as education, quality, and health policy.

The learning curve in opening a new program can be daunting but is attainable, especially with the support available within the National Clinical Trials Network. In a community program the economic costs are manageable and reimbursement is adequate. A very important aspect is to recognize the facility's strengths and weaknesses based on available resources. Success in enrollment to clinical trials in the community setting depends on the selection of trials that match the local patient population, with which patients and investigators are comfortable, and on the availability of appropriate resources for the conduct of trials by the local facility.

DEVELOPMENT AND ACTIVATION OF NATIONAL CLINICAL TRIALS

Surgical oncologists also may lead national clinical trials. The NCTN trials typically allow the study of large, diverse populations; facilitate more generalizable discoveries more rapidly; provide an opportunity to address relatively rare cancers; and require less reliance upon industry. Multiple clinical trials currently active within the NCTN are led by surgeons, including Alliance A011202 (Judy Boughey, PI), RTOG-0848 (Andy Lowy, Co-PI) and SWOG S1505 (Syed Ahmad, Co-PI). Nonetheless, the road between a good research idea and activation of a clinical protocol is a notoriously long and difficult one. The process can be political, and it requires commitment, mentorship, and time to navigate successfully.

Although the specific process required to take a trial from idea through activation varies by cooperative group, the general approach follows a basic plan:

1. *Idea generation and refinement* An investigator, likely one who has shown commitment to and collaboration on previous trials, generates a trial idea within a disease-site or treatment committee. The idea is subsequently refined as a concept by a group of colleagues with support of a statistician and committee leadership. The concept is progressively refined during biannual meetings and conference calls, typically with the support of the applicable NCI task force. Approval of the concept is ultimately achieved at the committee level.
2. *Group review and approval of concept* The concept is written up in standard format and submitted to the group's central concept review committee.
3. *NCI review and approval of concept* The concept is submitted to the NCI as a letter of intent (LOI) for approval through the appropriate steering committee.
4. *Protocol development* The approved LOI is developed into a complete protocol in addition to other supporting documents.
5. *NCI review and approval of protocol* The completed protocol is submitted to the NCI for approval. Once the trial is approved case report forms are developed.
6. *Protocol activation* The protocol is activated. Member sites become eligible to open the study.

The process between idea generation and study activation can take a long time (in some cases years), but strict deadlines now exist that limit the duration of time of each step between LOI receipt by the NCI and study activation.[9]

RESPONSIBILITIES AND FUNCTIONS OF AN ENROLLING SITE PRINCIPAL INVESTIGATOR

When a surgical investigator assumes the responsibility of an enrolling site principal investigator (PI) for a clinical trial, they make a commitment to three main tasks: caring for the clinical condition of the patient as a highly competent oncologic physician, upholding the integrity of scientific investigations, and protecting the safety of the

human subjects. The enrolling site PI oversees and coordinates several key tasks to ensure the successful implementation of clinical trials. These tasks can be broadly grouped into three areas: protocol regulatory requirements, protocol execution, and quality assurance (Table 1).

Protocol Regulation

Protocol scientific review: NCTN studies are reviewed by a central IRB and then studies go through the local IRB for expedited review before activation at the specific institution.

Protocol administration: Local IRBs assist the enrolling PI with protocol approval and updates. The enrolling site must keep track of amendments to both the protocol and the informed consent and of any status change of the protocol on a national level. Institutions often will have a separate financial team to handle grants, contracts, and capitation-related accounting issues.

Protocol Execution

Protocol adherence: The site PI is responsible for ensuring that processes are in place to conduct review of eligibility criteria for enrolled subjects, to execute randomization and blinding or unblinding procedures as specified by the protocol, to provide assessments, treatments, or interventions whose nature and timing are compliant with protocol requirements, to ensure adverse events are reported expeditiously, and to collect and submit study data in a complete and timely manner.

Accountability for investigational agents: The site PI is held accountable for the use of protocol-related investigational agents. Compliance with policies from the CTEP and FDA concerning investigational agents is required. The PI and the enrolling site must maintain an approved Federal Wide Assurance (FWA) status.

Quality Assurance

Prevention, detection, and correction of errors: The site PI is responsible for and should promote best practices regarding protocol conduct, record-keeping, and data reporting to minimize errors in protocol execution.

Routine monitoring procedures and data audits: The sponsoring organization of the clinical trial typically has structures in place for Quality Assurance Audits at enrolling sites and for interim analyses of data through Data Safety Monitoring Boards (DSMBs) to monitor for safety thresholds and stopping rules as specified in the protocol. The site PI would be responsible for organizing and maintaining source documentation for audits. Periodic internal monitoring and data audits represent proactive methods for continuous improvement toward the goal of high-quality clinical trials research.

KEY ELEMENTS OF AN OPERATIONAL ENROLLING SITE

Successful clinical trials research requires both a commitment from the PI and supportive and operational infrastructure at the enrolling site. Studies have demonstrated that recruiting physician attitude regarding the clinical trial directly impacts enrollment—physicians with a positive attitude towards clinical trials tended to have higher accrual than those who did not.[10,11] In a prospective evaluation of breast cancer clinical trial accrual, when patients were introduced to a nonsurgical clinical trial by their surgeon the accrual to the study was higher.[12]

It is critical for the local PI to assemble two teams when planning to participate in a clinical trial. First, a multidisciplinary treatment team should be assembled with key personnel identified from each discipline. This is particularly important for oncology clinical trials that involve multimodality therapy and require coordination of treatment among disciplines. Second, a clinical research team is critical for success. Through study coordinators, the team is responsible for scheduling and coordinating protocol visits with clinical visits, communicating with the clinical team, performing minor assessments and protocol laboratory tests, organizing data for Case Report Forms (CRFs), and communicating with local IRB and grants/contracts offices.

The enrolling site also should be equipped with dedicated space including examination/interview rooms for the study coordinator to assess patients and secure office space to safeguard health information of the study subjects, regulatory binders, source documents, and CRFs. The facility should have capabilities for phlebotomy/laboratory, pharmacy, shipping, and storage.

Achieving the anticipated accrual to a study is often the most challenging aspect of a clinical trial. There are multiple strategies that can be used to increase accrual to a study at a site. The clinical team should consider studies most appropriate for patients seen in the clinical practice. Some teams have a huddle and review the patients scheduled for that day before the start of the clinic schedule. This can help the team by reminding them about open clinical trials and start them considering which patients are eligible for open studies. Research study coordinators can screen patients coming in for clinic visits and identify patients that meet study eligibility ahead of the visit and notify the medical team, so they remember to discuss the study with the patient. While direct advertising is not commonly employed, media articles and social media regarding the

TABLE 1 Key responsibilities of an enrolling site PI for clinical trials

Protocol regulation	
1.	Protocol scientific review
2.	Protocol administration (Institutional review board, Grants/contracts)
Protocol execution	
1.	Protocol adherence
	(a) Eligibility review
	(b) Procedures for randomization, registration, blinding/unblinding
	(c) Protocol compliance
	(d) Adverse event reporting
	(e) Study data management and submission
2.	Accountability for investigational agents
Quality assurance	
1.	Prevention, detection, and correction of errors
2.	Monitoring and data audits

clinical trial availability can raise awareness and encourage patients to consider the trial and seek care at a site where the trial is open. IBM Watson™ for Clinical Trial Matching enables clinicians to more easily and quickly find a list of clinical trials for an eligible patient, and in the clinical trial office, find patients that are potentially eligible for any of the site's trials.

CASE STUDY: NSABP B-51/RTOG 1304 TRIAL

One of the NRG's current clinical trials is evaluating the benefit from comprehensive radiation after sterilization of involved axillary nodes with neoadjuvant chemotherapy in patients with operable breast cancer (NSABP B-51/RTOG 1304 trial).

Rationale for the NSABP B-51/RTOG 1304 Trial

In patients with large operable breast cancer, neoadjuvant chemotherapy (NAC) downstages involved axillary nodes in up to 40–50% of patients, particularly in those with triple-negative and HER2-positive disease.[13–16] With increasing use of NAC, a commonly encountered clinical scenario involves patients who present with documented axillary involvement, receive NAC, and have pathologically negative nodes at surgery. For such patients, there is an active debate on the appropriate use (and extent) of regional radiation (XRT). On one hand, these patients presented with positive axillary nodes, are at high risk for locoregional recurrence (LRR), and should receive comprehensive XRT. On the other hand, sterilization of involved axillary nodes by NAC lowers risk for LRR, questioning the need for postmastectomy and/or comprehensive regional nodal XRT.

Although there is ample information on rates and predictors of LRR in patients with early-stage breast cancer who undergo surgery first, information on rates and predictors of LRR after NAC is limited.[17,18] Existing evidence suggests that node-positive patients who convert to node-negative with NAC have low rates of LRR and can potentially be spared postmastectomy and/or regional nodal XRT.[19] However, before such a strategy becomes standard of care, a prospective, randomized clinical trial is needed to demonstrate that elimination of XRT in selected patients would not significantly increase breast cancer recurrence.

Trial Design/Aims/Eligibility

The primary objective of the trial is to evaluate whether the addition of comprehensive XRT will significantly reduce breast cancer recurrence. Secondary objectives include the evaluation of whether comprehensive XRT will significantly prolong overall survival, reduce LRR, or distant recurrence. The study also will evaluate patterns of post-mastectomy reconstruction and the effect of XRT on cosmetic outcomes and quality of life following postmastectomy reconstruction.

Eligible patients should have clinical $T_{1\text{-}3}N_1M_0$ breast cancer at presentation with histologic confirmation of axillary nodal involvement by fine-needle aspiration or core needle biopsy. They should have completed at least 8 weeks of NAC with an anthracycline and/or taxane-based regimen (plus anti-HER2 therapy for HER2-positive disease). At surgery, all removed axillary nodes must be histologically negative.

Role of the Surgical Oncologist

Involvement of the surgical oncologist is key to the success of the trial. The surgical oncologist plays an important role in referring appropriate candidates for

consideration of NAC, discusses the potential for NAC to reduce the extent of locoregional therapies, stresses the importance of axillary nodal downstaging for de-escalation of surgical management of the axilla and articulates the rationale for de-escalating use of XRT. Furthermore, the surgeon monitors clinical response, coaches patients through NAC and surgery, and refers appropriate candidates for trial participation after discussion with the multidisciplinary team. As NAC and targeted therapy use is increasingly being used in many disease sites, this provides an excellent opportunity for oncologic surgeons to not only lead trials focused on local–regional therapy questions, but also on systemic therapy, novel drugs, drug targets and biomarker development.

Trial Progress

After several years of planning, the trial was activated in August 2013 with an intended sample size of 1636 patients. As of April 17, 2020, a total of 1489 patients have been randomized. Accrual to the trial started slowly but after considerable efforts in promoting the trial within the NCTN the monthly accrual has now reached the projected monthly accrual. It is anticipated that the trial will complete its accrual in the summer of 2020.

CASE STUDY: PROSPECT N1048

The PROSPECT N1048 trial is an Alliance phase II/III prospective randomized trial, which has recently completed accrual of patients with locally advanced rectal cancer in the United States. The rationale for the trial was that although the current standard of care commits all patients with clinical stage II and III rectal cancer (clinical T3/4, N+) to receive tri-modality therapy (chemotherapy, radiation, and surgery), pelvic radiation directed to the local tumor carries both short and long-term morbidities while at least a subset of patients face higher risks of distant relapse than local failure. Therefore, pelvic radiation likely represents overtreatment for some patients. Thus, the trial is designed to determine whether selective rather than routine use of radiation is a reasonable alternative strategy for stage II/III rectal cancers.

In anticipation of becoming an enrolling site to PROSPECT N1048, a detailed evaluation of the protocol is required. A multidisciplinary study team should be assembled to ensure compliance with protocol requirements. In addition to surgical, medical, and radiation oncologists, experts from pathology and radiology should be consulted for key trial components of eligibility determination, randomization criteria, and endpoint assessment. For example, eligibility criteria rely on clinical staging as defined by the pelvic MRI. Additionally, only those patients demonstrating response of greater than 20% to upfront systemic chemotherapy as assessed by imaging are randomized to the option of omitting radiation. Finally, determination of local recurrence and distant relapse endpoints relies on pathologic and radiographic assessments.

Surgical quality assurance is uniquely critical to the PROSPECT trial, because a backbone of high-quality surgical treatment must be assured for all patients who are randomized to routine versus selective use of a second local treatment modality (i.e., radiation). The surgical PI must understand and complete a quality assurance process for a site to be eligible for patient enrollment. The quality assurance program is specifically designed during protocol development, including specific requirements for submission of operative records, pathology reports, and specimen photos (e.g., view, camera pixels, imaging processing, and file format). In addition, there is a process for continuous improvement if initial review does not confirm high-quality specimens.

The PROSPECT N1048 trial was designed as a randomized phase II leading into phase III trial with prespecified early stopping rules. Therefore, after the first 366 patients were enrolled nationwide, an interim analysis was conducted. It was noted that the early data did not meet either of the early stopping rules based on R0 resection rate or time to local recurrence. Therefore, an additional 644 patients were enrolled and randomized during the phase III portion of the trial, resulting in a total of 1194 patients (of 1180 total expected) enrolled to this trial.

CLINICAL TRIALS IN A COMMUNITY PRACTICE—HOW AND WHY

Clinical trials also can be an integral part of practice for surgeons in community or solo practice. It can be difficult to keep pace with rapid advances in the treatment of cancer in a community setting. Involvement in clinical trials is one way to stay on the cutting edge academically and also give community members access to services that otherwise they would have to travel great distances to receive. In the process, the individual surgeon or practice can gain recognition as a regional expert in their field. These benefits are well worth the effort to invest the time and infrastructure in a community setting.

Most cancer patients are treated in the community and not at academic centers. Availability of clinical trials provides access to new therapies. In addition, the data obtained from these patients provide a real-world patient population for analyzing new therapies. Barriers certainly exist but can be overcome. Economic barriers include establishing sufficient infrastructure and securing hospital “buy-in.” The

hospital benefits significantly from community awareness of the success of the research program. Additionally, enrollment to clinical trials is one of the standards with which sites must comply to achieve accreditation by the Commission on Cancer. Success also is driven by continuous physician engagement, addressing patient concerns, and selecting an appropriate trial menu tailored to the physician's practice.

CONCLUSIONS

Clinical trials are vital in advancing the care of patients in surgical oncology. Surgical oncologists can and should be involved with clinical trials and can be study PIs for single or multi-center IITs or NCTN trials. National groups through the NCTN program conduct a wide range of randomized, clinical treatment trials and imaging trials in adults and children across cancer types. Given there are many opportunities for surgeons to get involved in this collaborative process, surgical oncologists at both academic and community centers should seize the opportunity to get involved. Clinical trials provide opportunities for patients to receive novel treatments and for surgeons to continually advance their knowledge and skills.

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