The Future Of Global Interventional Radiology

Austin-Marley Windham-Herman

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The Future of Global Interventional Radiology

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Austin-Marley Windham-Herman

2021
Abstract

Interventional Radiology (IR) has become an integral component of modern, developed healthcare systems. The minimally invasive, image-guided procedures that the field offers are highly effective and often lead to significantly less morbidity than alternative surgical options. The growth of IR globally is in an early phase; however, patients and healthcare systems stand to benefit from its rapid expansion and integration around the world.

Globally, billions of people are without access to safe surgery and diagnostic imaging. However, the democratization of radiology resources such as portable ultrasound and low-cost medical devices is making IR more accessible than ever before. Global healthcare trends have seen governments investing more in hospital infrastructure, and in the development of local residency programs to train future practitioners in the specialty.

This thesis examines multiple aspects of the future of IR in a global setting, which represent an amalgamation of different, simultaneous approaches to advancing IR practice in these settings. A review of locoregional catheter directed therapies demonstrates the value of developing an interventional oncology (IO) program, a branch of IR that has become standard of care in multiple indications in the US. Further explored are the results of a retrospective single-institution study of response to a specific IO therapy, TACE. This is one of the most common and effective interventional approaches to treating primary liver cancer as well as liver metastases. The value of specific imaging metrics to assess treatment response and viability for retreatment are discussed. These IO techniques are extremely exciting for their potential in low- and medium-income
countries that are implementing IR programs. Additionally, this thesis reviews the creation of a simulation device to be used by IR trainees in resource limited areas.

Also demonstrated is a method for designing new medical devices through ideation and prototyping phases, and lastly discussed, is a venture working to create frugally designed medical devices that can be rapidly deployed into developing IR and IO programs. IR is a specialty that is driven by innovation, which necessitates the use of often expensive medical devices. Low-cost innovation and redesign of these devices can make them more accessible and more useful in lower resource settings. Innovation using these frugal methods can be helpful in accelerating the growth of IR globally, and treating more patients effectively and safely.
Acknowledgements

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Introduction

While Interventional Radiology (IR) has existed for more than 40 years, it remains a relatively new specialty with growing demand due to its significant advantages compared to traditional surgery across a broad range of indications [1,2]. The field is positioned to bring substantial benefits to patients around the world. Currently, reports estimate that 5 billion people are without access to safe surgery, and 4 billion are without access to diagnostic imaging [3,4]. This definition of access includes capacity, safety, timeliness, and affordability. The individual and societal cost of lack of access is estimated in the trillions of dollars, and there has been a call for significant investment into expanding access for safe surgery globally.

In this context, IR offers several advantages in improving surgical care globally. Minimally invasive procedures have the potential to be faster, safer, lower-cost, and at least as efficacious as traditional surgical methods. Technological innovations such as portable ultrasound and reusable medical devices are laying a foundation for IR to scale rapidly in low- and middle-income countries [5]. These innovations also address another important barrier, underdeveloped and costly medical device supply chains. In this regard, optimizing device reusability and promoting local manufacturing may contribute significantly to cost reduction in low-resource areas, as well as ensure consistency and quality. For example, Africa consistently demonstrates some of the highest global prescription drug prices, despite manufacturers charging less in these regions, because distribution is such a large component of the total price. Low-cost, reusable devices that can be manufactured regionally will drastically reduce costs and increase access to
specialized IR equipment. IR additionally offers some of the most cost-effective interventions in high prevalence indications, such as cancer diagnosis and treatment, vascular disease, and women’s health.

As a broad overview of the field and specific global health related topics, this thesis synthesizes selections of the candidate’s previous written work from published research as well as manuscripts in preparation and other writings. The material highlights sectors of interventional radiology that are particularly suitable for global application, from interventional oncology therapies and associated imaging modalities, to innovations in medical device development with a highlight on biopsy.

Interventional oncology (IO) has been integrated alongside surgical, medical and radiation oncology and is now recognized as a fundamental 4th pillar of cancer care [6]. For example, Transarterial Chemoembolization (TACE) is now considered standard of care for multinodular intermediate BCLC stage Hepatocellular Carcinoma [7]. However, globally, this integration process is still nascent, with many regions unfamiliar with the benefits of IO. Recently, the first-in-country TACE was performed in Tanzania by residents in the relatively new IR program at Muhimbili Hospital in Dar es Salaam. Education, training, and allocation of resources towards the development of similar programs will continue drive the proliferation of IO globally. The selected chapters within detail the advantages and differences between various locoregional embolization therapies for hepatic tumors, as well as imaging characteristics that can guide treatment and retreatment decision making.

In the context of IR, the concept of “Frugal Innovation” is defined as the process of reducing complexity and cost of a medical device in order to make it accessible to a wider
number of physicians and patients [8]. The need for this is driven by market forces, with a large unmet need and rapidly rising demand for safe and minimally invasive procedures on one hand, and a medical device industry that has historically been focused on developed markets, making more complex and more expensive devices, on the other. These two factors create a care gap that can be bridged by focusing on frugal innovations that target this large emerging space. Frugal innovation is an important factor in the global development of IR programs. One included manuscript details the extreme low-cost construction of a procedural training phantom for ultrasound and computed tomography (CT) guided procedures. These have been successfully deployed in global training sites. The final chapter describes a biopsy device under development that utilizes frugal innovations to deliver increased quality, improved logistics, and lower cost to developing IR programs. This can serve as a roadmap for a new approach to medical device design that is tailored for the needs of developing healthcare systems.
Statement of Purpose

This thesis presents a summation of work from the candidate, including one published review article, selections from one original research project manuscript in progress, one educational exhibit submitted for presentation, one book chapter accepted for publication, and selected grant applications of an operating venture.

The purpose of these selected works is to describe multiple facets of the future of interventional radiology in a global setting. The summation of these works should demonstrate that interventional radiology has a bright future in global healthcare settings, with potential for improved patient access and outcomes.

The works presented are listed below.

1. Minimally Invasive, Image-Guided Therapy for Liver Cancer
2. Outcome of Repeat Transarterial Chemoembolization in Patients with Metastatic Hepatic Lesions
3. Low-cost Construction of a CT Biopsy Phantom
4. Device prototyping: Iterative refinement, Optimization Process
5. A Low-Cost, Reusable Core Needle Biopsy Device for Low-Resource Settings
Minimally Invasive, Image-Guided Therapy for Liver Cancer: What Every Oncologist Needs to Know

The work presented in this chapter was published in the American Journal of Hematology/Oncology. 2017;13(11):30-36. The candidate was the primary author of the manuscript.

Abstract
Liver cancer continues to be a growing healthcare challenge worldwide. Both primary and secondary liver cancers are among the most commonly reported causes of cancer-related death, and the incidence rates of primary liver cancer, or hepatocellular carcinoma (HCC), are expected to grow in the United States and Europe. The majority of patients’ cancers are diagnosed at stages that are not amenable to surgical or curative therapy. However, alternative options for the treatment of HCC have expanded greatly in recent years, mostly due to technical innovations in interventional oncology. Advancements in imaging capabilities have allowed the integration of innovative, image-guided, catheter-based, intra-arterial therapies into clinical practice. New modalities of these minimally invasive therapies have become widely adopted, which has allowed larger-scale studies to clarify their appropriate role in the multidisciplinary clinical management of patients. In parallel, basic and translational research continue to break new ground in therapy paradigms, including the introduction of new generations of drug-eluting beads and radioembolic microspheres. This review highlights the history of these therapies, and discusses the
value of novel, emerging, image-guidance technologies as well as the most recently presented data from prospective trials on the combination of local tumor therapies with systemically administered anticancer agents.

**Introduction**

Hepatocellular carcinoma (HCC) ranks globally as the second most common cause of cancer-related death, and its incidence continues to rise [1]. The medical and surgical management of patients with HCC is often complicated by multiple factors, including progression to advanced disease by the time of diagnosis, lack of highly effective systemic therapies, and limited surgical options due to the high comorbidity of HCC and chronic liver disease [2].

Interventional oncology (IO), a newly organized subspecialty of interventional radiology, offers several image-guided minimally invasive techniques to treat cancer, with the ultimate goal of improving patient outcomes with both curative and palliative intent (Figure). Among several therapeutic modalities that are at the disposal of an interventional oncologist, the catheter-based intra-arterial approach has become the most commonly used delivery route for anticancer agents, such as drugs and therapeutic radiation that can be delivered at high doses directly to the liver tumors while dramatically reducing systemic side effects. These techniques have been used and validated for the past 30 years and have been incorporated into all major guidelines and endorsed by several societies and study groups worldwide [3,4]. However, progress in the field continues, and the armamentarium of IO practices has continued to grow and improve in
response to the need for improved management of patients with nonresectable liver cancer. The development of innovative technologies in image-guided procedures has allowed for widespread clinical adoption of previously niche, locoregional tumor therapies over the past decade.

Many of these therapies, specifically variations of transarterial chemoembolization (TACE) procedures, take advantage of the unique anatomy of HCC tumors, which are vascularized almost completely by the hepatic artery, with normal liver parenchyma supplied by the portal vein, which improves targeting and allows for the preservation of nontumoral tissues. There are various intraarterial therapy (IAT) modalities currently in clinical use; the most widely used is conventional TACE (cTACE), which employs a cocktail of chemotherapeutic agents, most commonly doxorubicin or cisplatin, suspended in an ethiodized oil, Lipiodol, followed by administration of additional embolic particles [5]. Other IAT options include bland transarterial embolization (TAE), drug-eluting bead TACE (DEB-TACE), and radioembolization with microspheres containing yttrium 90 (90Y). This review highlights general principles, indications for use, and comparisons of efficacy between the various IATs, discusses imaging biomarkers of treatment response, and examines evidence from recent clinical trials of systemic therapies used in conjunction with IATs.

Rationale for Intra-Arterial Therapy and Patient Selection

Most patients with primary liver cancer are not considered to be candidates for curative surgical therapy at the time of diagnosis, and until today, there was no systemic
chemotherapy, with the exception of sorafenib, that has been shown to improve patient survival. Locoregional tumor therapies offer an additional line of treatment and have demonstrated excellent local tumor control rates and an improved overall survival (OS) compared with best supportive care (BSC) [6]. As such, and given the lack of therapeutic alternatives, embolotherapy continues to be the primary or secondary therapeutic choice in over 70% of all patients with liver cancer and is applied both in a palliative setting as well as in a bridge-to-transplant scenario [7,8]. Selection of patients for locoregional therapies requires a collaborative approach of a multidisciplinary team of experts, often composed of hepatologists, oncologists, transplant surgeons, radiation oncologists, and interventional radiologists.

From a technical perspective, IATs exploit the fact that HCC tumors are almost exclusively fed by the hepatic artery, while normal liver tissue is mostly supplied by the portal vein. This difference in blood supply allows for a highly selective embolization of, and cytotoxic drug delivery to, tumors with relative sparing of surrounding normal tissue. Embolization of the vascular supply leads to ischemic necrosis of the tumor tissue while also slowing washout of chemotherapeutic agents, allowing higher levels of drug delivery to target tissues than would be possible with systemic therapy. Conversely, bland embolization is performed without any chemotherapeutic agent, while in 90Y radioembolization, tumoricidal radiation is delivered locally into the tumor using radioactive microspheres. Regardless of payload, IATs carry substantial benefits in terms of quality of life and—across the board and regardless of the modality—are able to provide excellent local tumor control [9].
Choice of Intra-Arterial Therapy

Multiple IAT modalities are available for tumor management, and the most commonly performed worldwide is cTACE, a Lipiodol-based embolotherapy. The procedure consists of an initial targeted infusion of a chemotherapeutic agent suspended in Lipiodol, an iodinated, poppy seed oil-based medium, followed by infusion of embolic particles or sterile compressed sponge. The suspension of Lipiodol increases the viscosity and x-ray visibility of the agent, and the embolic particles further delay washout of chemotherapy from the tumor. This promotes a slow, sustained delivery of the agent within the tumor while also promoting embolic blockade. Lipiodol therefore serves as an effective drug carrier, embolic agent, and imaging response biomarker while also minimizing systemic concentrations of chemotherapeutic agents [10].

While both Lipiodol-based cTACE and bland TAE have been used clinically for many years, there has yet to be a completed, well-controlled trial directly comparing the 2 therapies, and the determination of superiority of cTACE over TAE remains unclear [11]. While more recent randomized controlled trials (RCTs) have investigated the efficacy of DEB-TACE versus TAE, the latest available RCT that directly compared TAE, TACE, and BSC in patients with HCC was published in 2002, but was aborted after demonstrating clear superiority of cTACE over BSC. Follow-up in this trial was thus not sufficient to compare the TAE and cTACE arms [6]. However, today, Lipiodol-based cTACE remains the more widely utilized therapy, and is supported by a greater body of data demonstrating its efficacy. Although Lipiodol is currently only approved for imaging purposes in the
United States, it has been used extensively for therapeutic purposes of primary and secondary liver cancer in both Europe and Asia for nearly 3 decades.

A 2016 systematic efficacy and safety review of Lipiodol-based cTACE, which drew data from over 10,000 patients with HCC, reported an objective response rate of 52.5% and an OS of 70.3% at 1 year, 51.8% at 2 years, and 32.4% at 5 years (median, 19.4 months) [12]. Of more than 20,000 reported adverse effects, liver enzyme abnormalities were most common, followed by postembolization syndrome. Overall treatment-related mortality was 0.6%, most often attributed to acute liver insufficiency. These data re-established cTACE as the standard of care with respect to IAT for liver cancer, and demonstrated that this IAT modality continues to be the safest and more effective choice around the world.

In addition, data gathered recently from the GIDEON study [13], a large observational registry that included more than 3000 patients with HCC, indicated that nearly half of these patients received cTACE at some point during their treatment course. It also re-established the findings of previous RCTs that demonstrated clinically significant survival benefits of cTACE over BSC.6 The GIDEON registry additionally found that 47% of patients received TACE prior to systemic sorafenib, with Lipiodol-based cTACE accounting for up to 74% of these procedures. One notable discrepancy was in the United States, where DEB-TACE was administered more commonly. Additional and more recent evidence of efficacy was demonstrated with the data from the prospective BRISK-TA study (NCT00908752), a randomized phase III protocol that is investigating the impact of treatment with brivanib plus chemoembolization versus chemoembolization alone on OS.
in patients with advanced-stage HCC. This report, in one of the largest ever reported prospective cohorts of patients with HCC, demonstrated that patients undergoing chemoembolization alone within the control arm achieved a median OS of almost 26 months, which can now be seen as the new standard and benchmark, at least for patients with intermediate-stage disease [14].

As for DEB-TACE, this technique has been introduced in hopes of addressing some of the challenges of cTACE, such as accurate drug dosing and systemic toxicities. Ever since the advent of DEB-TACE a decade ago, the technique has been thoroughly investigated in several prospective clinical trials and identified as safe and effective in terms of local tumor control [15,16]. In recent years, DEB-TACE has become universally accepted and integrated into clinical practice, effectively dominating the choice of therapy in many US care centers [17]. The most common drug-eluting beads (DEBs) currently used are DC Beads loaded with doxorubicin (DEBDOX), which range in size from 100 to 300 µm. Smaller beads such as the LC Bead M1 (diameter range, 70-150 µm range) are being investigated for their potential to penetrate more distally into the tumor vasculature, and have shown greater drug delivery to tumors in preclinical studies [18]. Despite high overall efficacy, DEB-TACE has not yet demonstrated the ability to fulfill the promise of improved survival outcomes over cTACE and, from a global perspective, has not yet reached the status of a standard-of-care therapy.

A similar statement can be made about 90Y radioembolization, which utilizes far smaller particles (with a range of 30 to 60 µm, depending on the product) to deliver a tumoricidal
dose of beta-radiation directly to the tumor [19]. Several retrospective studies and small RCTs have compared radioembolization to cTACE and have shown some improvements in time to progression (TTP), but no difference in OS [20,21]. On the horizon are some potentially impactful improvements to microsphere-based therapies, including the use of radiopaque beads (LC Bead LUMI), which allow more accurate intraprocedural visualization of microsphere delivery and embolic endpoints. However, as of today, cTACE continues to be the clinical standard of care, both from a standpoint of worldwide utilization as well as available data.

**Intraprocedural Image Guidance With Cone-Beam Computed Tomography**

Combinations of ultrasound, computed tomography (CT), magnetic resonance imaging, fluoroscopy, and digital subtraction angiography (DSA) have conventionally been used in the process of planning, performing, and postoperatively assessing IATs. While 2-dimensional DSA imaging has often been the mainstay of intraprocedural guidance, its diagnostic potential is hampered by suboptimal anatomic differentiation due to superimposed vessels and poor soft-tissue contrast. The intraprocedural utilization of 3D imaging modalities may therefore allow for more accurate treatment delivery and improved outcomes.

Cone-beam CT (CBCT) is an imaging modality that has been increasingly integrated into clinical practice over the past decade, and has been used with high success in the guidance of complex intra-arterial procedures. Intraprocedural visualization of 3D images of vessels and soft tissue enables the operator to better reach and map the tumor tissue,
while also allowing immediate and improved postprocedural validation of therapeutic endpoints. Operatively, CBCT imaging is based on rotational image acquisition around the patient by a C-arm machine with an x-ray source and flat panel detector with subsequent 3D reconstruction. Immediate generation of high-accuracy 3D CT-like images allows for super-selective catheterization and much more accurate vessel targeting. This has greatly improved intraoperative catheter guidance, detection of feeding vessels, and assessment of embolization endpoints [22]. CBCT has also shown benefit in early detection of treatment response after cTACE [23]. More importantly, CBCT has become an independent determinant of OS, with patients receiving Lipiodol TACE under CBCT guidance, demonstrating significantly higher OS and local progression-free survival (PFS) compared with patients under angiography guidance alone (OS, 74% vs 44% at 3 years) [24-26]. With this in mind, CBCT has been widely incorporated into clinical practice, and is now becoming a platform for advanced image-guided approaches to treating liver cancer and beyond.

**Imaging Biomarkers of Response**

Evaluation of embolotherapy response is an integral part of the treatment course and informs further therapeutic decision making. While survival continues to be the ultimate endpoint in clinical trials, therapeutic efficacy and decisions on whether or not to re-treat a patient with a particular therapy must rely on surrogate markers for therapeutic efficacy. Both for IO and beyond, imaging biomarkers for tumor response have been widely accepted as an integral part of the therapy assessment algorithm. In addition, outcome surrogates such as PFS and TTP, which are often used as endpoints, rely completely on
accurate radiographic response evaluation. Thus, a rigorous and standardized imaging schedule is typically required for all IO procedures, with baseline imaging being performed 2 to 3 weeks prior to treatment and follow-up imaging being obtained 4 to 6 weeks afterward [27].

Changes in anatomic lesion size or diameter have historically been used to evaluate tumor response; however, no universal consensus on evaluation criteria existed in the past [28]. The World Health Organization (WHO) first published 2D tumor response criteria in 1981, based on the sum of 2 long-axis measurements of the tumor diameter to calculate percentage of shrinkage in tumor size [29]. Since that time, multiple new criteria have been proposed and validated; one of the most widely accepted has been the Response Evaluation Criteria In Solid Tumors (RECIST) system for evaluation of systemic chemotherapy, which relies upon single longest plane measurements [30]. However, most IATs induce tumor ischemia and necrosis, with little to no immediate tumor shrinkage. As such, purely anatomic markers of tumor change were ineffective in near-term response evaluation to embolotherapy [31].

In an effort to find improved markers of response to embolotherapy, the European Association for the Study of the Liver (EASL) guidelines were published with the inclusion of bi-dimensional tumor contrast enhancement as a relative biologic marker of change due to tumor necrosis [4]. Modified RECIST criteria (mRECIST) were introduced soon after to improve EASL guidelines by incorporating enhancing tumor single-axis measurements into the previous RECIST criteria. Unfortunately, frequent variation of
tumor anatomy and the inhomogeneity of necrotic tumor volumes often limit the reliable application of these criteria, and they are subject to large inter- and intra-observer variability. Nevertheless, both EASL and mRECIST criteria have demonstrated superior efficacy in evaluating treatment response and predicting survival outcomes [32].

Even with the inclusion of enhancing diameters, both single-axis and bi-dimensional criteria are still hampered by similar challenges and can only provide surrogate volumetric assessment of tumors. Currently under investigation are 3D volumetric assessment criteria, which attempt to address the problems associated with lower dimensional analysis. Initial studies have demonstrated the feasibility and efficacy of 3D quantitative analysis in the locoregional therapy response assessment of liver tumors. Further investigation found that quantitative 3D volumetric analysis correlated well with histopathologic findings [33]. Most recently, a 2016 study compared the predictive correlations of non-3D methods (RECIST, EASL, mRECIST) with quantitative 3D criteria, and found that the non-3D criteria were unable to distinguish treatment responders from nonresponders, while the quantitative 3D method demonstrated significant between-group differences [27]. The quantitative 3D criteria, primarily quantitative EASL, are currently the most predictive response criteria of patient survival, and their adoption into clinical practice may prove beneficial in therapeutic decision making.

**Combination Therapies**

The basic mechanism of action for all embolotherapies is the induction of an ischemic insult to the tumor tissue. While instantaneously effective, this mechanism may also
induce severe tissue hypoxia followed by a massive surge of pro-angiogenic mediators, such as the vascular endothelial growth factor, a molecule known to promote vascular proliferation, and thus revascularization of the tumor tissue. Therefore, combining locoregional therapies with molecular targeted inhibitors of this pathway is theoretically appealing. As of today, sorafenib, an orally active multi-tyrosine kinase inhibitor, continues to be the only systemically applicable therapy for HCC, and has demonstrated both survival benefit and activity along the aforementioned molecular pathway. Established in 2 large prospective trials, the SHARP and the Asia-Pacific trials, sorafenib is able to modestly improve median OS in patients with advanced-stage HCC by no more than 3 months compared with placebo [34].

As a result, several trials that combined sorafenib with TACE followed around the world. The previously mentioned GIDEON registry demonstrated that nearly half of patients received TACE before starting sorafenib (37% in the United States, 71% in Japan), and 10% received TACE while taking sorafenib [35]. A recent phase II trial found that the combination of TACE and sorafenib was well tolerated and effective, reporting an 83% survival at 3 years, while a separate retrospective study found that combination therapy increased TTP compared with sorafenib alone, but did not significantly affect OS [36-38]. Most importantly, the recently published multicenter RCT, the SPACE study [39], which investigated safety and efficacy of DEB-TACE combined with sorafenib, failed to demonstrate a survival benefit of the combination when compared with DEB-TACE alone. While the combination of sorafenib with TACE continues to be of questionable benefit, several ongoing clinical trials are investigating the combination of 90Y radioembolization
with sorafenib [40], including the SORAMIC (NCT01126645), SARAH (NCT01482442), and STOP-HCC (NCT01556490) trials.

**Conclusion and Future Perspectives**

Over the past 2 decades, IO has become an innovative and clinically indispensable pillar of cancer care around the globe, with liver cancer being the central scope of expansion. While young as a profession, IO is driven by technical progress and interdisciplinary collaboration, which transcends professional boundaries and limitations. In this regard, basic and translational research into the therapeutic mechanisms of local tumor therapies and their interactions with systemic therapies are vital for continued development in the field. Further understanding of the systemic effects of locoregional therapies is also necessary, and will lead the way toward broader acceptance within the oncology community. Emphasis should be placed on the discovery of novel, molecularly targeted, pharmacologic therapies that will enhance and improve the efficacy of IO therapies in an adjuvant setting. As for the future of clinical practice, further work is needed to accurately direct treatment recommendations, improve and standardize radiographic evaluation criteria, and further advance drug carrier systems and their delivery using novel image-guidance instruments. While developments in technology can be expected to shape the future of the IO landscape, all advancements must be measured by the benefit they ultimately bring to patient survival and quality of life.
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Outcome of Repeat Transarterial Chemoembolization in Patients with Metastatic Hepatic Lesions

The work presented in this chapter is a selection from a manuscript in progress. The candidate was the primary author of the manuscript.

Abstract

Purpose: To evaluate image-based tumor response in patients with metastatic liver lesions treated with multiple sessions of conventional transarterial chemoembolization (cTACE).

Methods: 150 patients with a variety of metastatic hepatic tumors who underwent conventional transarterial chemoembolization between 2001-2015 were retrospectively enrolled in this single-institution study. Radiographic response to treatment was determined by RECIST, mRECIST, and qEASL criteria. Overall survival and image based response were compared between patients who received single or multiple embolization sessions.

Results: A total of 286 TACE sessions were performed with an average of 1.9 per patient. There was a total of 200 distinct metastatic targets, with an average of 1.33 per patient (range, 1-3). The mean time ± SD between baseline imaging and first TACE session was 14 days ± 13.9. The mean time (± SD) between first TACE session and follow-up imaging was 30.8 days ± 13.6 (range, 14-84 days). The 30-day survival was 98% after the initial TACE session. At the last follow-up, 109 of the 150 patients had died, with a median
overall survival of 15.1 months. The mean number of TACE sessions required to achieve response was similar for CRCs compared to NETs (1.3 vs. 1.4 respectively, p=0.556).

**Conclusion:** Repeat cTACE improves the rate of response in the non-responders, however, it is efficient beyond the 2nd cTACE.

**Introduction**

Metastatic liver cancer continues to be a growing healthcare challenge worldwide, and secondary liver cancers are among the most commonly reported causes of cancer-related death. In recent years, advances in imaging technologies have facilitated the widespread adoption of catheter-based, embolic, intra-arterial therapies (IATs) such as conventional trans-arterial chemoembolization (cTACE) into clinical practice. These loco-regional tumor therapies offer an additional avenue for treatment, and they have demonstrated both excellent local tumor control rates and improved overall survival when compared with best supportive care [1]. Many patients undergo multiple and consecutive IAT sessions over the course of their treatment, especially in lesions that do not respond after the first treatment. A 2007 study demonstrated that the survival times of initial responders and of initial non-responders who later responded to follow-up treatments were similar [2], and initial data for primary liver cancer suggests that at least two consecutive IAT sessions should be performed in a lesion before switching therapy due to non-response [3]. A paucity of data exists with respect to the efficacy of multiple retreatment in a variety of secondary liver malignancies. This study evaluated imaging based response and
survival outcomes in a selected patients with metastatic liver lesions treated by cTACE using 1D and 3D quantitative image assessment techniques.

Methods and materials

Study design

This retrospective, single-institution study was conducted in compliance with the Health Insurance Portability and Accountability Act and approved by the institutional review board. The requirement to obtain informed consent was waived. The study was performed with financial support from the National Institutes of Health (5 T35 DK 104689-3) and Philips Healthcare.

Patient Population

A prospectively collected database of 560 consecutive patients with metastatic hepatic tumors, who underwent a total of 1,320 IAT sessions from 2001 to 2015, was retrospectively evaluated for inclusion into this study. Patients were included if they received initial Lipiodol based TACE and received baseline and follow-up contrast enhanced magnetic resonance (MR) imaging within 90 days before and after TACE. Patients were most frequently excluded because of inadequate imaging (n=277), with many image sequences unable to be retrospectively recovered, and some unable to be analyzed due to substantial imaging artifacts. Additionally, patients who received either Ytrrium-90 radioembolization (Y90), or drug-eluting bead TACE (DEB-TACE) as initial therapy were excluded (n=183). The inclusion and exclusion criteria are summarized in Figure 1.
The final study cohort contained 150 patients with 200 unique metastatic targets. Baseline characteristics (age, sex, ethnicity, number of TACE treatments, dates of imaging and treatment, tumor cell type, serum bilirubin, albumin, INR, presence of ascites, encephalopathy, and survival time) were recorded. Baseline characteristics are summarized in Table 1.

**Figure 1.** Study flow chart.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Image Analysis Cohort (n = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>66 (44)</td>
</tr>
<tr>
<td>Age, median (range), years*</td>
<td>60 (18-88)</td>
</tr>
<tr>
<td>Male</td>
<td>61 (18-83)</td>
</tr>
<tr>
<td>Female</td>
<td>59 (32-88)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>115 (76.7)</td>
</tr>
<tr>
<td>African American</td>
<td>23 (15.3)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (8)</td>
</tr>
</tbody>
</table>
TACE treatments, median (range) 2 (1-6)

Tumor type, n (%)  
- Neuroendocrine 75 (50)  
- Colorectal Carcinoma 32 (21)  
- Lung Carcinoma 11 (7)  
- Melanoma 9 (6)  
- Sarcoma 8 (5)  
- Other 15 (10)

Serum total bilirubin, median (range) 0.5 (0.2-4.6)

Serum albumin, median (range) 4 (2.4-5)

Serum INR, median (range) 1 (0.9-1.6)

Ascites, n (%)  
- Absent 127 (85)  
- Slight 16 (11)  
- Moderate 3 (2)  
- Unknown 4 (3)

Encephalopathy, n (%)  
- Absent 147 (98)  
- Present 0 (0)  
- Unknown 3 (2)

Child-Pugh Class (%)  
- A 122 (81)  
- B 28 (19)

Table 1. Patient demographics. *p-value = 0.1773

**Conventional Transarterial Chemoembolization (cTACE)**

All patients initially received conventional transarterial chemoembolization (cTACE). All patients received baseline contrast MR imaging and follow-up contrast MR imaging.
between two weeks and three months post procedure. If more than three months had elapsed from a previous TACE session, patients received further follow-up/re-staging imaging before an additional TACE session. All patients had recorded intraprocedural angiography or cone beam computed tomography (CBCT), or postprocedural noncontrast computed tomography (CT) imaging within 1 month, to determine embolization targets.

**Image Analysis**

Image-based tumor response was evaluated by a single reader for each TACE session for up to two dominant lesions in the targeted region. The target regions were identified by intra-procedural angiography, CBCT, or post-procedural CT. Tumor characteristics were measured by Response Evaluation Criteria in Solid Tumors (RECIST), modified RECIST (mRECIST), and quantitative European Association for the Study of the Liver (qEASL) metrics (Figure 2), both on the pre and post TACE imaging sequences for each procedure. response was categorized into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR and PR were defined as “Response,” while SD or PD were defined as “Non-response.” RECIST and mRECIST values were generated by measuring the long axis of the tumor, or longest enhancing axis of the tumor, respectively (RadiAnt DICOM viewer, Medixan, Poland; Figure 3). To produce qEASL values, a 3D segmentation of the tumor boundaries was created. Segmentations were acquired by using a semi-automated segmentation software to generate volumetric maps of the tumors (IntelliSpace Portal ver 8.0, Philips Healthcare, Haifa, Israel). The accuracy and inter-reader reproducibility of the segmentation software has been previously demonstrated [4, 5]. Finally, a manual selection of a 3D region of
interest (ROI) from the non-tumoral liver parenchyma allowed quantification of enhancing tumor volume (Figure 4).

**Figure 2.** Response Evaluation Criteria in Solid Tumors (RECIST), modified RECIST (mRECIST), Volumetric RECIST (vRECIST), and quantitative European Association for the Study of the Liver (qEASL) provide 1-dimensional to 3-dimensional measurement criteria, with and without consideration of enhancement. Light gray regions represent enhancing tumor while dark gray represent overall tumor border.
Figure 3. 2-dimensional RECIST and mRECIST long-axis measurements on pre and post TACE contrast enhanced arterial phase T1-weighted MR images.
Figure 4. 3-dimensional segmentation and qEASL volumetric enhancement analysis on pre and post TACE contrast enhanced arterial phase T1-weighted MR images.
**Statistical Analysis**

Many patients had multiple target lesions, treated in variable sequences and over varying timelines, so individual target response could not be directly correlated to overall survival. Thus, analysis was done separately on both the level of individual target lesions as well on a patient level. A distinct metastatic target was defined as including up to two dominant lesions in the embolized lobar or segmental region of the liver during a TACE session. Up to 3 distinct metastatic targets were tracked for individual response assessment per patient. Descriptive response rates of targeted lesions after sequential TACE are reported. Lesions were tracked until response (or until last included TACE session) and reported as either responsive or non-responsive based on qEASL criteria.

For patient-based analysis, in order to correlate patient baseline characteristics and survival outcomes, patient-level response assessment was evaluated by comparing the sum of enhancing tumor volumes (of all target lesions) by qEASL criteria at each baseline timepoint and then at each final post-TACE timepoint. Patients were excluded if they had incomplete imaging data and received additional TACE sessions after the last available follow-up imaging. Included patients were subclassified by the timeline of their response to TACE. Groups were further subdivided by tumor cell type. The independent t-test and χ² test were used to evaluate significant differences in continuous and categorical characteristics between groups. Kaplan-Meier curves were plotted and log-rank tests were used to compare overall survival (JMP®, Version 13.0.0., SAS Institute Inc.). Patients alive or not known to be deceased at the time of last follow-up (July 15th, 2017) were censored.
Results

Demographics Characteristics

A total of 286 TACE sessions were performed with an average of 1.9 per patient. The maximum number of sessions for any individual patient was six and the maximum number of TACE sessions for any specific metastatic target was five. There was a total of 200 distinct metastatic targets, with an average of 1.33 per patient (range, 1-3). The mean time (± SD) between baseline imaging and first TACE session was 14 days ± 13.9. The mean time± SD (range) between first TACE session and follow-up imaging was 30.8 days ± 13.6 (range, 14-84 days). The 30-day survival was 98% after the initial TACE session. No patient died before receiving at least one follow-up imaging assessment. At the last follow-up, 109 of the 150 patients had died, with a median overall survival of 15.1 months.

Target lesion-based analysis

Most patients had one (n=107) or two (n=36) target lesions, corresponding to metastatic lesions which were embolized in a unilobar or bilobar fashion, respectively. Three distinct targets were occasionally able to be identified in patients who received super-selective embolization within a single lobe (n=7). The response chronology of the 200 distinct metastatic targets is summarized in Figure 5. In Figure 6, response chronology is detailed for the two most common tumor cell types, colorectal carcinoma (CRC) and neuroendocrine tumors (NET). The mean number of TACE sessions required to achieve response was similar for CRCs compared to NETs (1.3 vs. 1.4 respectively, p=0.556).
Figure 5. Metastatic tumor targets tracked until response criteria were met ("1st response"), or treatment was not continued or further treatments were excluded from analysis ("Exiting"). The response rate after the 1st TACE session was 28.5%. Of those targets which failed initial TACE and underwent retreatment, the response rate was 30.8%. 

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Figure 6. Tumor target response chronology subclassified by neuroendocrine metastases and colorectal carcinoma metastases.

**Patient-based analysis**

A total of 109 patients were included in the patient-based analysis, with 41 excluded due to incomplete imaging data. Of patients who received a single TACE, 20 of 52 responded (38.5%). Of patients who received two TACE sessions, 6 of 29 responded (20.7%). Additionally, 5 of 17 patients who underwent a 3rd TACE responded (29.4%), and 4 of 8 patients who underwent a 4th TACE session responded (50%). 2 of 3 patients who underwent a 5th TACE session responded radiographically to treatment (66.7%). There were no significant differences in survival between responders and non-responders.
Overall response and median survival for each metastatic cell type is detailed in Table 2. There was no difference in median survival between responders at 1\textsuperscript{st} TACE (8.4 months, n=39) and responders at 2\textsuperscript{nd} TACE (9 months, n=18, $p=0.43$) for the overall cohort, or within tumor cell type.

<table>
<thead>
<tr>
<th>Tumor Cell Type</th>
<th>Responders/Total (%)</th>
<th>Median Survival (months)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responers</td>
<td>Non-responders</td>
<td>Responders</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>14/48 (29)</td>
<td>16.5</td>
<td>31.3</td>
</tr>
<tr>
<td>Colorectal Carcinoma</td>
<td>9/23 (39)</td>
<td>9</td>
<td>7.9</td>
</tr>
<tr>
<td>Lung Carcinoma</td>
<td>5/11 (46)</td>
<td>6</td>
<td>5.2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4/7 (86)</td>
<td>4.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1/7 (14)</td>
<td>30.5</td>
<td>12</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0/3 (0)</td>
<td>-</td>
<td>4.8</td>
</tr>
<tr>
<td>Endometrial</td>
<td>1/2 (50)</td>
<td>32.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Prostate</td>
<td>1/2 (50)</td>
<td>29.2</td>
<td>-</td>
</tr>
<tr>
<td>Ovarian</td>
<td>0/2 (0)</td>
<td>-</td>
<td>7.1</td>
</tr>
<tr>
<td>Germ Cell</td>
<td>1/1 (100)</td>
<td>8.4</td>
<td>-</td>
</tr>
<tr>
<td>Granulosa Cell</td>
<td>1/1 (100)</td>
<td>6.1</td>
<td>-</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>0/1 (0)</td>
<td>-</td>
<td>6.8</td>
</tr>
<tr>
<td>Adrenal</td>
<td>0/1 (0)</td>
<td>-</td>
<td>25.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>37/109 (34)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Overall survival of patients classified as either Responders or Non-responders, subclassified by tumor cell type. There were no significant differences in survival noted between response groups.
Discussion

While overall survival of responders after retreatment with TACE compared to responders after a single TACE session were similar, there was also no significant difference detected between responders and non-responders overall. However, there are a number of studies which have previously demonstrated the survival benefit of TACE in liver metastases.

Locoregional therapies such as TACE play a well-documented role in the management of metastatic hepatic tumors, particularly in NET, CRC, and uveal melanoma [6-8]. However, the utility of repeated therapy in unresponsive lesions has not been well described. The retreatment of lesions with repeated TACE may be informed by accurate classification of treatment responders and non-responders.

The primary finding of this study is that a substantial proportion of patients with liver metastases will respond radiographically to TACE after multiple sessions. Additionally, this study demonstrated that a large proportion of patients who failed initial TACE demonstrated radiographic response after retreatment, with similar survival times for both groups. Non-response after an initial TACE session should not be an indication to abandon therapy. Re-treatment with at least one additional session should be attempted in order to achieve higher response rates. After more than two embolizations of the same target region, target lesion response rates may reach a plateau and continued non-response after this point may be an indication to switch therapies.

Comparisons of response criteria demonstrated an appreciable difference between RECIST and mRECIST/qEASL in determining response in treated lesions. The qEASL metric has been demonstrated as a superior metric for predicting tumor response to IAT.
in NETs, CRCs, Sarcoma, and Uveal Melanoma [9-12]. This is likely due in part to the differing effects of embolotherapy on the local tumor environment compared to systemic chemotherapy. While systemic agents produce tumor shrinkage, IATs induce tumor necrosis often with little to no initial change in tumor diameter. This impairs the usefulness of purely anatomic response criteria such as RECIST, and favors the use of biological criteria in assessing response to IATs [13]. The increased adoption of biological response metrics such as qEASL and mRECIST in clinical practice may improve the efficacy of response assessment and management decisions.

**Advantages and Limitation:**

This study includes a large cohort of relatively rare tumor types. Patients were treated and imaged utilizing consistent protocols.

This study had several important limitations, including multiple factors that would be expected to influence survival or radiographic response which were not controlled for in the analysis. It was unknown if patients had received systemic chemotherapy or what type of therapy they received. Systemic chemotherapy could be expected to affect the ischemic response of tumors as well as overall survival. Many patients had preserved baseline liver function with the majority being Child-Pugh class A, limiting the generalizability to patients with more severe liver dysfunction. Additionally, the presence of comorbidities and the extent of extrahepatic metastatic spread were not accounted for. The effects of different IAT modalities (such as Y90 or DEB-TACE) were not explored, and certain IATs may be more effective at treating specific tumor types or stages. Finally, clinical indications for retreatment or switching therapy, which are often non-standard and vary between institution and operator, were not accounted for in this study.
Conclusion:

Second cTACE improves the response in the non-responders and repeat cTACE should not be abandoned based on the first cTACE result.

References


2. Varker KA, Martin EW, Klemanski D, Palmer B, Shah MH, Bloomston M. Repeat transarterial chemoembolization (TACE) for progressive hepatic carcinoid metastases provides results similar to first TACE. J Gastrointest Surg. 2007;11(12):1680-5.


Low-cost Construction of a CT Biopsy Phantom

The work presented in this chapter is from an educational exhibit submitted for presentation at the Society of Interventional Radiology annual conference, 2021. The candidate was the primary author of the report.

Abstract

There is a need for low-cost CT-biopsy and cone-beam CT phantoms for use by radiology trainees. We describe the creation of multiple durable phantoms, with dense biopsy targets and rigid obstacles. These phantoms can be used to augment procedural training in image acquisition workflow, needle placement, and use of specific devices.

Introduction

Computed tomography (CT) guided biopsy has long been an effective means for obtaining a cytologic diagnosis in various organs [1]. Additionally, CT guidance is used for numerous other procedures including the placement of drains, soft tissue ablations, and vascular access. Performing CT-guided procedures is an essential skill that requires practice in freehand needle placement, image acquisition, and coordination. A phantom is an ideal platform to practice competency in these skills.

The use of homemade ultrasound biopsy and vascular access phantoms is well documented [2, 3]. Ultrasound phantoms can serve the purpose of simulating both tissue echogenicity as well as physical characteristics. However, we were unable to find similar literature on CT biopsy phantoms. We report the construction of a CT phantom that
primarily simulates the physical characteristics of tissue, target lesions, vascular structures, and bony obstructions for less than $50.

**Methods**

The agar gel phantom is prepared from a commercially available agar powder (Carolina Biological Supply Company), as well as a mixture of chlorhexidine liquid to prevent putrefaction in a sealable plastic container of the desired size (between 2-10Ls). Obstacles were created from plastic or wood, and biopsy targets were created in various ways. Materials and costs are catalogued in Table 1.

*Creating the Agar Gel:* The agar gel can be prepared either in a microwave or on a standard stovetop pot. Add in the desired amount of cold water, and then while heating, slowly stir in the agar powder to an agar/water ratio of 30g/L. Our agar powder had an approximate density of 0.59 g/mL, so to avoid the use of a scale, it is also possible to do a volumetric ratio of 51cc agar/1 L water. Increasing the agar to water ratio results in a denser gel. Next, add in chlorhexidine liquid, we used a ratio of 40 drops per Liter. Bring the mixture to a boil for 1-2 minutes. Avoid adding agar powder to hot water, as this resulted in clumping and spoiled the batch. Pour the gel into your container and allow it to set overnight. The gel block can be flipped upside down and removed from the container during scanning and biopsies to allow access from all angles. The end product had a mean Hounsfield units (HU) of 9.5. We found the resistance to needles and feedback to be closer to in vivo human tissue than ballistic gel or fixed human cadavers from our cadaver lab.
Creating the Targets and Obstacles: We experimented with multiple methods for creating the phantom architecture. For targets of appropriate CT density, we found the simplest option was to use Plumber’s Putty (Oatey Plumber’s Putty) rolled into balls around a knot of string (Everbilt Diamond Braid Nylon Rope) and hung from above the agar gel at various depths (Figure 1). Plumber’s Putty is heat stable and sinks in the agar gel solution, which allowed easy positioning. Mean HU for the putty was 1469. A more complex option is to use an agar and iodinated contrast mixture inside of a rubber container, such as the tied-off finger of a surgical glove. For these surgical glove type targets, we anchored each target in place to prevent them from floating (Figure 2). We used paint sticks and craft sticks for obstacles, which we affixed to the walls of the container with silicone paste (GE 100% Silicone Paste) to prevent floating when the agar is poured in. Additionally, we used suction tubing filled with silicone to create vessel-like obstacles (Figure 3).

Discussion

Simulation devices are widely used in the training of medical residents and allow for more efficient oversight and workflow optimization without sacrificing patient safety. Ultrasound models are commonly used by interventional radiology trainees, either commercial tissue-replicating phantoms or homemade models, both for practice of visualization and for biopsy or vascular access. The efficacy of simulation training in endovascular models has also been shown, demonstrating a significant decrease in contrast volume, fluoroscopy and overall procedure time in trainees [4]. Our low-cost, durable, CT-biopsy phantom offers an easily accessible option for programs to incorporate into a training program for IR residents.
Weaknesses of this model include the lack of anatomic accuracy, and the lack of tissue specific simulation. The agar gel provides lower and more consistently uniform resistance to needle passage than true human tissue. One option to improve anatomic accuracy is demonstrated by Pasciak et al. who created a homemade fluoroscopic phantom with a realistic vertebral anatomic model [5]. However, this does lead to increased cost. Additionally, this model was made with ballistic gel, which we believe is less similar to true human tissue than agar gel.

The strengths of this phantom are its extremely low-cost, reusability, customizability, and long shelf life. At the time of writing, we can state that the phantom will last at least 6 months in an unrefrigerated, sealed container without putrefaction, which is a significant improvement over gelatin-based models (Figure 4). The process of making the phantom is an engaging team activity and could be undertaken by incoming radiology trainees and used in a standardized training process for CT-guided biopsy as well as cone-beam CT guided procedures. Further research is necessary to determine the specific efficacies of CT-biopsy simulation on IR trainees.

**Conclusion**

We present a low-cost, durable, customizable, CT-biopsy phantom for use in IR training. The time required in preparation of the phantom is variable and determined by desired complexity, but does not require specialized knowledge and can be completed with readily available materials.
## Tables and Figures

<table>
<thead>
<tr>
<th>Item</th>
<th>Price</th>
<th>Location Purchased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agar Powder, Reagent Grade, 100g</td>
<td>$23.25*</td>
<td>Carolina Biological Supply</td>
</tr>
<tr>
<td>Sterilite container</td>
<td>$15</td>
<td>Home Depot</td>
</tr>
<tr>
<td>GE 100% Silicone Paste</td>
<td>$4</td>
<td>Home Depot</td>
</tr>
<tr>
<td>Oatey Plummer’s Putty</td>
<td>$3</td>
<td>Home Depot</td>
</tr>
<tr>
<td>Everbilt Diamond Braid Nylon Cord</td>
<td>$3</td>
<td>Home Depot</td>
</tr>
<tr>
<td>Paint Sticks</td>
<td>Free</td>
<td>Home Depot</td>
</tr>
<tr>
<td>Hibiclens, surgical gloves, silk ties</td>
<td>Free (case surplus)</td>
<td>Hospital supply cabinet</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$48.25</strong></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Item Unit Cost.

*quantity allows creation of three 10cm X 10cm X 10cm models.
Fig. 1. Simplified Target Phantom (model A). Targets are hung from wood pieces until the agar is solidified and then the string is cut at the agar surface. Other wood pieces are arranged to provide rigid obstacles to needle access from the bottom side (agar block can be removed from the container and flipped upside down during use). A piece of nasal oxygen tubing is also seen, it can be filled with silicone paste to simulate a blood vessel.

Fig. 2. Complex Target Phantom (model B). A more complex model with surgical glove type targets anchored at various levels.
**Fig. 3.** CT cross sectional view of model A. T, target; O, obstacle; V, vessel.

**Fig 4.** CT Cross section of phantom model C. This image was acquired after multiple biopsies and subsequent 3 months room temperature storage. Note some air around targets and needle tracks.
References


Device prototyping: Iterative refinement, optimization process

The work presented in this chapter is from a book chapter accepted for publication in Adam E.M. Eltorai & Sanjeeva P. Kalva (Eds.); Designing and Conducting Research in Translational Medicine: Interventional Radiology. The candidate was the primary author of the chapter.

Why it Matters?

Design is an iterative process, represented by a repeating sequence of ideation, prototyping, and evaluation. You can imagine the process like a cone (Figure 1), progressing from very broad to very narrow. It is helpful to follow discrete stages when designing a clinical solution, an example framework is detailed in Table 1 [2]. The ideation phase begins with understanding not just the clinical problem you seek to solve, but the entire environment, including the competitive space, customer needs, and overall market structure. The prototyping and evaluation phases are the empirical methods then used to Reduce to Practice and narrow the scope of solutions, informing through successive improvements or failures. Having a complete understanding of the fundamentals is vital to informing the direction of the design process and can prevent costly mistakes and engineering misadventures down the road.
Fig 1. The “funnel” framework for developing a clinical solution. Each star represents a different idea, approach, or prototype.
<table>
<thead>
<tr>
<th>Phases</th>
<th>Purpose/Goal</th>
<th>Resources Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem Scoping</td>
<td>Need Identification: Identify opportunity areas that align with your personal interests and strengths</td>
<td>Experience and observation</td>
</tr>
<tr>
<td></td>
<td>Problem Definition: Set boundaries around the problem and its scope</td>
<td>Formalized requirements and constraints</td>
</tr>
<tr>
<td></td>
<td>Gathering Information: Develop a full understanding of the problem space and environment</td>
<td>Customer interviews, competitor technical benchmarking, market research</td>
</tr>
<tr>
<td>Developing Alternative Solutions</td>
<td>Generating Ideas: Brainstorm a large number of potential approaches to solving the problem, including all methods, materials, and processes.</td>
<td>Sourcing diverse opinions from advisors and industry experts</td>
</tr>
<tr>
<td></td>
<td>Modeling: Create physical version of design to be evaluated for function, ergonomics, durability, etc</td>
<td>CAD programs, basic materials (wood, screws, springs, tubing), 3D printing</td>
</tr>
<tr>
<td></td>
<td>Feasibility Analysis: Determine if major functional elements of design are viable</td>
<td>CNC machining, preclinical testing, cost and value modeling</td>
</tr>
<tr>
<td></td>
<td>Evaluation: Prove function, ergonomic quality, durability, etc of physical model</td>
<td>Customer beta testers, usability and efficacy studies</td>
</tr>
<tr>
<td>Project Realization</td>
<td>Decision: Decide on final designs and major manufacturing processes</td>
<td>Expert manufacturer opinion, expert mold / tool makers, industrial designers</td>
</tr>
</tbody>
</table>
Table 1. Design Process Framework [2]

| Communication | Coordinate between stakeholders: investors, manufacturers, distributors, customers, regulators | Expert legal counsel, skilled team to implement across each domain |
| Implementation | Adjust design (DFA/DFM) to suit major processes, and initiation of at-scale manufacturing | Manufacturing facilities, distribution, and sales infrastructure |

Prototyping

Customer Requirements and Technical Benchmarking

Sourcing Customer Requirements is a key part of the ideation phase, and should be formalized through well performed customer interviews and technical translation of customer needs into design parameters and constraints [1]. For example, if a customer desires a “lightweight” device, the resultant technical constraint might be “less than 100 grams.”

It is also important to establish key capabilities of competitor products early in the design process. Known as Technical Benchmarking, this process sets concrete design goals, and creates useful constraints for engineers. Without such constraints, the design process can be unnecessarily prolonged, as it may appear that there are too many viable paths to a solution, and it can be unclear how to proceed. Understanding the nature of the problem prior to delving into detailed design is critical. Indeed, expert designers spend nearly twice as much time identifying requirements and constraints as novice designers [2].
Types of Prototypes

Prototypes serve many purposes and come in many forms. A prototype does not have to “look good” or be fully functioning to bring value to the design process. As an example, a prototype can be completely non-functioning, but its shape and texture can quickly provide deep insights into ergonomics that move the design process forward. Conversely, a prototype can bear little to no resemblance to the final device, but illustrate the function of a key mechanism, proving its viability. These bits of information can be collected in pieces, and later assembled into a final prototype that contains all design elements and functions as intended. It is important to keep an open mind during the prototyping process, remembering that each prototype brings information to the table—even if it doesn’t work as expected. As detailed in Biodesign: the Process of Innovating Medical Technologies, prototypes can be thought of as works-like, looks-like, feels-like, is-like, or looks-like/is-like models [3]. The last category, looks-like/is-like is the best type of prototype to test user experience, as it is a robust, functional prototype that is close to the final look and design.

Iterative Design

Each prototype is evaluated according to technical benchmarking specifications, changes to the design are ideated, and the cycle repeats itself as work begins on the next prototype. This process continues until all design goals are satisfied and the design is optimized. Each action taken in the design process serves to inform the next, even if the action fails to behave as predicted. A failed prototype can lead a designer to consider a different design strategy, which may lead to the discovery of new intellectual property. In
this way, the design process can be viewed as a cascading series of small experiments, as the designer works to uncover the optimal solution. The cascading nature of the design process illustrates why it is important to properly define and constrain project requirements early on as an incomplete problem definition can lead to a series of design iterations in a direction that is not viable.

**Prototype Fidelity**

Prototype fidelity should increase over time, with initial prototypes being detailed enough to demonstrate shape, feel, or functionality, but not exceeding this level of detail. It may be tempting to spend time in the beginning creating highly detailed prototypes, but inevitably it will slow the design process. This is likely to happen because large changes to the design typically occur early in the design process, causing premature design detail to be abandoned. Initial low-fidelity prototypes can be made from materials on-hand, such as wood, cardboard, or plastics, or they can be 3D printed on hobby grade machines. As the design process progresses, specific materials will be selected as candidates for the final design. At this point, parts can be machined from these materials to more closely approximate the feel and function of the final design. Finally, Design for Manufacture/Design for Assembly (DMF/DFA) considerations can be considered and the design transitioned from prototype to high volume production.

**Real World Examples**

Virtual Incision – Highly complex medical devices may take many years of prototyping and design iteration to come to fruition, some more than a decade. One example is the miniature surgical robot for abdominal procedures, pioneered by Virtual Incision
corporation. While the final product is a highly articulated robot capable of precisely resecting and cauterizing tissue, initial prototypes of this robot had no arms at all, and simply demonstrated that motors could operate in vivo [4]. A subsequent prototype added two simple hinged arms to the robot, demonstrating tissue resection and cautery within the limited reach of the arms [5]. Finally, highly articulated prototypes were built and tested, performing colectomies in porcine models, shortly followed by an autoclavable, highly miniaturized prototype capable of performing a human colon resection [6,7,8]. This process took over 10 years from first prototype to human trial, and tens of prototypes were iterated along the way, illustrating how prototypes increase in fidelity and complexity over time. Technical benchmarking was performed by comparing the robot to the da Vinci Surgical System, the most comparable commercially available device.

TVA Medical – Moderately complex devices may have a quicker path to market, but still rely on a process of iterative design. TVA Medical developed a system for creating percutaneous AV fistulae in the arm, starting in 2008 and completing initial clinical trials within five years [9]. An important piece of the solution was an armboard for the cath lab table that would immobilize the arm but not interfere with IV access or catheter access sites. Engineer Michael Hemati started by examining average sizes and shapes of human hands and arms, and cutting plywood models and velcro straps to size [10]. A few weeks were spent iterating sizes, strap positions, and left/right handed dual compatibility with wood models, and testing on office staff. Another 2-3 weeks were spent designing CAD models, and another 2 weeks to order and receive a machined Delrin armboard. The armboard worked very well, it was rigid enough to withstand repeated use, and could be easily cleaned. However, when this model was eventually used in clinical trials it revealed
a previously unknown use requirement which necessitated a major design change. The arm board was too large and heavy to be easily shipped to hospitals around the world. A lightweight, folding carbon-fiber version with the same fundamental design was then created and used for subsequent clinical efforts. The company received FDA approval for their percutaneous technology in 2018, and the armboard is now distributed to hospitals globally [11]. This example highlights the value of early stage, rapid prototyping (Figure 2) and of conducting a broad Failure Mode and Effects Analysis (FMEA).

Theranova – Engineers at Theranova were challenged to prepare an at-home neuromodulatory stimulator device for initial demos on a short timeline and strict budget [10]. They were tasked to create a handheld enclosure for the electrical components and interface but needed to decide what route they would take for manufacturing. Low volume 3D printed parts could be made cheaply and be modified rapidly, compared with injection molded parts which required extremely high upfront costs and were difficult to modify, but which had lower per unit costs at high volume. To make the decision, they needed to reach a Value Inflection point at which the decision had been optimally risk reduced. With relatively little expense, they were able to quickly iterate on the design using in-house 3D printers. With post-processing, sanding and application of primer and paints to the printed housing, they had created a professional looking device. However, the use case of the device necessitated it be sturdy enough to withstand drops, and only molded parts could deliver the necessary strength. With the confidence of having a functional looks-like/is-like prototype, they could proceed with the more costly investment of creating injection molds.
**Fig. 2.** The inverse relationship between design influence and cost of making changes.
Get Started

- Develop a complete understanding of the problem space.
- Conduct customer interviews and technical benchmarking.
- Iteratively downselect solutions and prototypes.
- Develop and evaluate the most viable options until the appropriate value inflection point.

Definitions

Reduction to Practice – The process of developing an invention past the conception stage. Can be actual, creating a working device, or constructive, creating a patent application with appropriately detailed descriptions.

Customer Requirements – Customer Requirements are specifications that originate with customers as opposed to internal stakeholders and are used to inform the design process.

Technical Benchmarking – Technical Benchmarking is the process of quantitatively assessing or testing the capabilities of competitor devices, to generate functional baselines for the design of a new device.

Design for Assembly – Design for assembly (DFA) is the process of designing products for ease of assembly, often with the goal of reducing total part count.
Design for Manufacturing – Design for Manufacturing (DFM) is the process of designing parts with the goal of simplifying manufacturing techniques, such as reducing mold complexity, using commonly available materials, and relaxing dimensional tolerances.

Value Inflection – An event that results in a significant change in the value of a company or process; in an engineering process it centers around the concept of minimizing risk.

Failure Mode and Effects Analysis (FMEA) – The process of early analysis of all possible routes of device failure, with the goal to proactively design protections against failure early on in the design process.

References


A Low-Cost, Reusable Core Needle Biopsy Device for Low-Resource Settings

Project Abstract

Global trends in healthcare have led to a shifting focus in developed countries towards minimally invasive procedures and cost reduction. Concurrently in developing countries, there has been a shift away from infectious diseases and towards the treatment of noncommunicable illnesses, notably cancer. Globally, hospitals are eager to build their oncology services, which has resulted in a surge in demand for minimally invasive biopsy devices. Image-guided core needle biopsies (CNB), critical to cancer diagnosis, are one of the most common and effective biopsy procedures. In developed markets, biopsies are a high-volume procedure with high per-procedure costs that allow substantial room for cost saving innovations. In developing countries, however, many people are unable to attain these necessary procedures due to lack of affordable equipment. In Africa and India alone, the lack of early biopsy-proven diagnosis of lymphoma, liver, pancreatic, lung, and kidney cancers can be estimated to contribute to an additional 100,000 deaths annually (Figure 4) [1].

Biopsy programs in developing countries are hindered by equipment limitations, with two main categories of biopsy devices available. Disposable devices have high iterative costs and require large stocking volumes. Metal reusable devices have prohibitive upfront costs and regular servicing requirements, leading to device downtime and accompanying supply management difficulties. There is a clear opportunity for a hybrid, low-cost
solution. The ReCore team is creating a reusable core needle biopsy device from medical grade thermoplastic which can be sterilized like traditional metal devices, but which is lightweight and nimble, and does not require time intensive repair services. The team has designed innovations that will reduce part count and cost to deliver a device that creates value, meets the highest global quality standards, and increases access in the developing world.

ReCore was founded by students from the Yale School of Medicine, School of Management, and School of Engineering. The current team consists of two Yale MD/MBA dual-degree candidates, one Mechanical Engineering PhD candidate, one MBA candidate. This is an entirely student led team. ReCore is a C-Corp incorporated in Delaware and registered in the state of Connecticut. ReCore is in the pre-seed stage, with funds from winning two Yale-associated student grant awards, and a CTNext EIA grant.

**Unmet Clinical Need and Market**

The global biopsy devices market was valued at $2.73 billion in 2018 and is expected to reach $4.31 billion by 2026 [2]. Rising prevalence of cancer, increased patient awareness, and desire for minimally invasive procedures have led to a surge in demand for CNBs. Core needle devices are used in a large percentage of breast biopsies (Figure 1) and are used for the majority of soft tissue biopsies (Figure 2). Additionally, the market for biopsy needles alone is expected to reach US $500 million by 2025 [3].
Reusable devices demonstrate clear long-run cost superiority over disposables. However, current reusable devices have very high upfront prices, are heavy, less versatile, and require regular maintenance leading to potentially costly servicing by the manufacturer and supply management challenges caused by equipment downtime. For these reasons, disposable devices are used more commonly in the US despite their higher overall costs. Customer interviews in the US and Canada have demonstrated a demand for a lightweight device with no maintenance requirements like a disposable, yet with the cost saving economics of a reusable.

In developing countries, the costs of biopsy equipment are often prohibitive. Additionally, many physicians are unable to access high quality equipment. Together, these factors generate a large unmet demand for reusable products, with each additional reuse cycle directly translating to one additional patient who is able to be treated. Physician outreach demonstrated an interest in adopting reusable biopsy technology as it would lower cost for patients, be life changing for the patient journey, change treatment outcomes, and would be preferable to a metal reusable or plastic disposable device.

**Product Solution and Preliminary Data**

**A. Proposed Product Solution and Background**

The attributes innate to current CNB devices on the market effectively restrict access for low-resource hospitals. Plastic disposable devices have the highest long-run costs and large stock space requirements. Metal reusable devices are more cost efficient in the long
run but have a very high upfront price and require an ongoing maintenance (and financial) relationship with the manufacturer. ReCore’s “Reposable” design integrates the best features of reusable and disposable devices, with a low upfront price, lowest long-run costs, and no maintenance requirements.

When performing a biopsy with ReCore, a single-use biopsy needle can be attached to the reusable handle, the biopsy taken, and the needle detached and discarded while the handle is sterilized and restocked. Once the handle reaches its useful lifespan (targeted at 50 reuse cycles), it does not need to be sent out for repairs but can simply be discarded and replaced. It is important to note that while each individual handle is designed to have a low upfront price, the cost saving innovations of ReCore actually come from the logistics of reusability. The individual unit price can exceed that of a disposable device and long run costs will still be substantially lower.

In addition to lowering costs, ReCore offers significant design improvements over disposable devices. For example, despite their higher costs, disposable devices are often preferred in the US due to their low weight and smaller size. ReCore is nearly as lightweight and small as a typical disposable, yet still delivers the superior economics of a reusable. Some masses are difficult to reach by virtue of their anatomical position and require precise, real time imaging to help guide the procedure. The plastic ReCore handle is radiotransparent and won’t block x-rays during image guided procedures, unlike all other reusable devices.
ReCore can also improve workflow efficiency compared to traditional reusables. Specifically, metal reusable devices tend to misfire due to precisely dimensioned part geometry within their firing mechanisms. After repeated use, these surfaces can accumulate residue from sterilization, such as buildup from ethylene oxide gas or mineral buildup from the steam within an autoclave. The close part tolerances also require lubrication before each use, much like the oil for the moving parts of a car. ReCore utilizes a novel, patent pending device firing mechanism and a streamlined design that is not sensitive to minor changes in part geometry or accumulation of sterilization byproducts, thus substantially reducing the risk of misfiring after device reuse. Current prototypes demonstrate two promising features for device improvement: a simpler, more reliable firing mechanism and a reduction in overall device part count.

**Photo 1.** Render of ReCore biopsy device handle with attached coaxial biopsy needle.

**Detailed Design:** A rendering of the device is demonstrated above in Photo 1. Regarding the means of device improvement, the engineering team has shown that a firing mechanism can be made that is less sensitive to slight changes in part geometry by
reducing kinematic constraints. Typically, commercially available devices utilize sliding single degree-of-freedom (DOF) prismatic joints. In metal reusable devices, this prismatic joint is realized by a linear bearing on precisely ground steel rails, which are expensive and require constant lubrication. In single-use disposable devices, this prismatic joint is in the form of a low-friction plastic carriage (typically Delrin) sliding within a tightly tolerated channel, that constrains all of the carriage’s rotational DOF, and two translational DOF, leaving a single axis free for motion. While straightforward, this design is susceptible to slight changes in geometry at the interface between the channel and the carriage. Imperfections or changes to this interface can lead to jamming of the carriage, causing the carriage to become lodged in the channel when the device is fired. The ReCore engineering team has already prototyped mechanisms that reduce the number of constraints while achieving the required amount of linear motion of at least 20mm. ReCore believes this will result in a device that is less likely to misfire and can confirm this once the team has performed testing with a fully functional device prototype made of the final production materials, rather than polylactic acid 3D printer filament (PLA).

As the second avenue for device improvement, the team has shown that reducing the number of constraints within the firing mechanism allows us to use fewer parts than commercially available firing mechanisms. As a rule of thumb, the cost of a product scales with its number of constituent parts, due to both the cost of additional raw material, and to the increase in cost from more complex assembly.

B. Preliminary Technical Data
Tests were performed to measure the capabilities of competitor biopsy devices (Figure 3), to determine quantitative benchmarks for the development of ReCore’s device. Specifically, cutting speed and force were measured, as cutting power (the product of force and velocity) is strongly correlated with the quality of core samples.

Needle firing speed was determined using high speed video. Image frames of the needle tip were collected at 660Hz over 500ms while competitor biopsy devices were fired. Firing time and firing distance, either 10mm or 20mm, depending on the device, were determined. Using these two measurements, the needle firing speed was estimated.

Needle cutting force in competitor biopsy devices was approximated by determination of the spring constant for the standard compression springs. The spring force was measured at known lengths, and approximate firing forces were calculated using Hooke’s law.

**Proposed Project Pathway**

**Resulting Product:** ReCore’s work will culminate in a reusable plastic biopsy gun handle with corresponding biopsy needles. While commercially available devices are typically made from metal if they are reusable, ReCore plans to manufacture its device from a sterilizable plastic base because it can offer the lowest per procedure cost along with a low upfront cost. Biopsy needles of various sizes can be fitted to the reusable handle, a biopsy taken from a patient, and then the needle disposed of while the handle is sterilized and reused a number of times. Akin to a “Razor and Blades” model, ReCore will also supply the biopsy needles with a proprietary attachment mechanism.
**Regulatory Pathway:** ReCore’s regulatory consultants believe the combination handle and needle system will be classified as a Class II device with a required 510k approval by the FDA. The existence of predicate devices with substantial equivalence will greatly simplify the 510k process, with ReCore having the same regulation number, intended use, indications for use, and target population/conditions. Differences in design and sterility assurance will necessitate the collection of benchtop data including: number of samples, penetration depths, stylet to handle tensile strength, working needle lengths, integrity of the sterile barrier, performance after ship testing, and needle protection after shipping and storage, as well as biocompatibility testing as per ISO 10993-1. Clinical trials are not necessary, and will not be performed.

**Product Reimbursement:** In the US, biopsies enjoy robust coverage as a necessary procedure within existing reimbursement schemes. Core needle biopsies are both routine and critical procedures for the diagnosis and treatment of cancer with numerous associated CPT/ICD-10 codes. For many payers, qualifying for reimbursement with a new device requires improved clinical value to be demonstrated. ReCore specifically targets the cost reduction component of clinical value. ReCore would already be covered by existing reimbursement codes. ReCore can be sold directly to physicians and hospitals who can bill for the procedure under existing codes, generating increased value for their practice.

The approach to reimbursement outside the US is domain specific. European and Canadian payer groups are strongly motivated by cost innovation, and will recommend
lower cost alternatives of equal quality. In many countries in Africa, and elsewhere, biopsy
devices are acquired directly out of pocket by patients with a prescription through
equipment wholesalers or pharmacies.

**Value Analysis:** ReCore’s main value proposition to physicians is improved workflow
efficiency, and a superiorly nimble and lightweight device. Physicians place the greatest
emphasis on the quality of tissue samples and the technical usability of the product.
ReCore will be both as user-friendly and as capable of collecting high-quality tissue
samples as the best options on the market.

ReCore’s value to hospitals is cost reduction, smaller stocking volumes, and tighter
supply control. ReCore’s pricing models have demonstrated cost savings of 40% or more
over conservatively priced disposable devices. Absolute cost savings depend directly on
biopsy volumes, for example, 10 biopsies per week in Lagos Hospital, Nigeria or 75 per
week at Yale New Haven Hospital translate to $13,480 (₦ 5,257,200) and $101,400 in
annual savings, respectively. ReCore’s “razor and blades” model will actually increase
biopsy volume, as patients would only need to buy a needle as opposed to an entire
disposable device - a far more reasonable cost. In the US, Medicare reimbursement for
a lymph node biopsy (HCPCS Code: 38505) ranges from $67 to $160 (non-facility vs
facility), which is often exceeded by the cost of supplies (~$90) and labor+overhead
(~$85). For many biopsy indications, ReCore can turn an otherwise losing procedure into
a profitable one.
**Critical Assumptions:** Before offering ReCore’s biopsy device for sale, there are a number of critical clinical assumptions that must be validated. First, the team must demonstrate that ReCore’s product is capable of delivering high-quality cores consistently. It will be important to conduct quality control studies (described in later sections) to establish non-inferiority or superiority to the disposable plastic and reusable metal products currently available on the market. Along those lines, it will also be critical to develop a reasonable, data-driven expectation for product lifetime, as this will have substantial implications for per procedure costs and unit pricing. Lastly, it will be necessary to demonstrate that various standard autoclaving procedures are sufficient to sterilize the ReCore handle.

**High Risk Gaps in Technical Data:** The selection of the most appropriate final thermoplastic material to use for the body of ReCore’s device is ongoing. Two candidate materials, PEEK and Ultem, are commonly used in sterilizable medical components, and are being evaluated for cost and manufacturing features. These plastics are capable of withstanding autoclave procedures, and can tolerate ethylene oxide sterilization protocols. It is also critical that ReCore develops a strong understanding of how many autoclave cycles the product can tolerate. Closely related is how dimensionally stable a plastic device will be over repeated autoclave cycles. Finally, it must be demonstrated that the force generated by its biopsy gun is sufficient to take diagnostic-quality tissue samples across each unit's lifetime, both by matching or exceeding competitor engineering specifications as well as through empirical testing.
Conclusion

ReCore is affordable due to the ability to sterilize and reuse the thermoplastic handle, with the lower cost needle being the only consumable. The handle itself is much lower cost than other reusable devices on the market (with a minimal unit cost of production likely 100x less). ReCore is appropriate, while existing devices are not, for multiple reasons. Primarily, ReCore does not require ongoing servicing/warranty contracts with the device manufacturer for repairs, as it is designed to be reused a set number of times and then disposed of. By making biopsy devices more affordable and accessible, patients around the world can avoid delays in care. These patients can start cancer treatment earlier and improve their chance of survival.

Figures

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Figure 1. Breast biopsies represent a large market, but are not performed uniformly with CNB devices (ie. 47% are done with vacuum assisted biopsies in the US while the majority are CNB in Asia-Pacific) [4].
### Soft Tissue Biopsies ($ millions) [4]

<table>
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**Figure 2.** Soft tissue biopsies represent a more moderately sized market, but the majority are performed using CNB devices [4]. Examples of “soft tissue” include lymph node, pancreas, liver, lung, and kidney tissue. CAGR: Compounds annual growth rate.

<table>
<thead>
<tr>
<th>Specifications</th>
<th>Bard Magnum</th>
<th>Bard Disposable</th>
<th>SuperCore Disposable</th>
<th>BioPince Disposable</th>
<th>ReCore Target Specifications</th>
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**Figure 3.** Technical specifications of competitor devices. *Addition of introducer needle and biopsy needle costs (for reusables).
Selected References


2. The global biopsy devices market was valued at $2,728 million in 2018 and is expected to reach $4,310 million by 2026: Biopsy devices market by product (needle-based biopsy instruments, biopsy forceps, localization wires, and other products), application (breast biopsy, gastroenterology biopsy, prostate biopsy, liver biopsy, lung biopsy, kidney biopsy, gynecological biopsy, and others), imaging technology (MRI-guided biopsy, stereotactic-guided biopsy, ultrasound-guided biopsy, CT scan, and others), and end user (diagnostic and imaging centers, hospitals, and others): Global opportunity analysis and industry forecast, 2019-2026. NASDAQ OMX's News Release Distribution Channel. Oct 29 2019.


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