HHS Public Access

Author manuscript

Kidney Cancer J. Author manuscript; available in PMC 2016 March 04.

Published in final edited form as:

Kidney Cancer J. 2015 ; 13(1): 10–17.

Ethical Issues in the Management of Renal Cell Carcinoma

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Introduction

Kidney cancer is a common and lethal cancer; in 2014 it will account for an estimated 63,920 new diagnoses and 13,860 deaths in the United States alone[1]. The clinical care of affected patients, as well as participation in clinical research involving kidney cancer, poses many potential ethical challenges for the clinician and investigator. The issues discussed in this review, while commonly encountered in this setting, are not exclusive to kidney cancer and will be relevant to many facets of medical care and clinical research.

Informed Consent, Disclosure of Surgeon Experience, and Outcomes

Surgical therapy is the mainstay of treatment for renal cell carcinoma[2] and, therefore, issues of informed consent prior to surgical intervention are paramount. The concept of informed consent developed in the early 20th century as advances in surgical and anesthetic techniques made elective surgery possible[3]. Today, informed consent is well-accepted as a central aspect of the surgeon-patient relationship. Traditional informed consent has required the surgeon to disclose certain procedure-specific factors: potential surgical complications and risks, benefits of the proposed surgery, available alternatives and likely outcomes of the treatment. The American Urological Association goes even further in its Code of Ethics, requiring the surgeon to provide the patient with “all of the information necessary to consent and to make his own choice of treatment, regardless of my own advice or judgment. The information provided must include known risks and benefits, costs, reasonable expectations and possible complications, available alternative treatments and their cost, as well as the identification of other medical personnel who will be participating directly in the care delivery”[4].

The need to disclose physician-specific factors (experience, previous outcomes, training), however, is more controversial. Studies have correlated surgeon volume[5] and objective ratings of surgeon skill[6] with patient outcomes; these findings suggest that disclosure of these surgeon-specific factors may be relevant to patients' informed decision making. A survey of patients supported this, as a majority of respondents found information on surgeon volume and outcomes essential[7]. Legal opinion on this matter, however, is conflicted. Many states have adopted a “reasonable person” standard for determining the content of an informed consent discussion[3,8] and two State Supreme Courts have addressed the specific

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issue of surgeon experience[9]. In 1996, the Wisconsin State Supreme Court held that physician experience and outcomes as compared to other physicians' is a meaningful part of the "alternative treatment options" that need to be discussed during the process of informed consent[9]. In 2001, however, the Pennsylvania State Supreme Court defined informed consent as including procedure-specific factors only and categorized information about the physician as outside of the scope of informed consent[9].

The ethical principle of autonomy is central to this debate. If knowledge of surgeon experience is necessary for patient decision making, its disclosure enhances patient autonomy and therefore is appropriate. While the Wisconsin Supreme Court categorized this information as an important aspect of "surgical alternatives", Clarke and Oakley[10] argue that surgeon ability is an important risk factor, and therefore an essential component of any informed consent discussion. While accepting the importance of patient autonomy, Burger reasons that disclosure of surgeon-specific performance information is only imperative if it is accurate enough to affect patient decision-making[9]. She contends that physician-specific outcomes data is often tied to arbitrary end-points, can be manipulated by patient selection, and is unfairly biased against younger surgeons[9].

The issue of disclosure of surgeon experience is very relevant to the surgical management of renal cancer. Laparoscopic and robotic-assisted partial nephrectomy have become popular and widely utilized interventions for small renal masses[11]. Several studies have demonstrated a learning curve with the use of these surgical modalities and surgeon experience has been shown to independently predict patient outcomes[12]. Whether currently available individual surgeon-level data is of high enough quality to impact patient decision-making is unclear. Nevertheless, most authors agree that providing this information when asked by the patient is imperative to maintain an open and honest physician-patient relationship[8]. With patients' increasing use of internet data sources, the proliferation of physician rating systems, and a widespread interest in healthcare quality improvement, the question of individual physician-level outcomes data is likely to be an area of discussion for the foreseeable future.

Referral to Other Surgeons or Medical Centers

The optimal management of kidney cancer adds another facet to this discussion - that of referral to other surgeons. Surgeons are sometimes reluctant to refer a patient to another surgeon for multiple reasons: to keep patients close to home and their local health system, to avoid the loss of income from performing surgery, and to avoid the loss of referrals from primary care providers[13]. In this era of rapidly advancing technology, there are multiple surgical options for renal cancer utilizing new instruments and surgical techniques[14]. It is reasonable to expect that not all urologic surgeons will be able to provide every available option to a patient seeking minimally-invasive surgery, nephron-sparing approaches, cytoreductive nephrectomy, or care in other complex situations (i.e. solitary kidney, local recurrence after therapy, familial renal cancer syndrome, etc.). The referral of a patient who would be best served by a procedure that one cannot offer, or not offer well, is relatively easy to accept. More difficult, however, is the question: is a surgeon ethically obliged to refer a patient to another surgeon or institution who reports better results?

The American Urological Association advises each surgeon to “respect my colleagues, seek their counsel when in doubt about my own abilities, and assist my colleagues whenever requested. I will accept that “competence” includes having adequate and proper knowledge to make professionally appropriate and acceptable decisions regarding management of the patient's problems, as well as the ability and skill to perform what is necessary to be done and to ensure that the aftercare is the best available to the patient”[4]. While this guidance emphasizes the need for honest evaluation of a surgeon's own competence and the humility to seek assistance when needed, it does not address the question of referral to another provider or medical center based on outcomes data or for procedures that he or she does not offer.

An analogous question has been discussed in the thoracic surgery literature[13]. In support of the obligation to refer, Kouchoukos argues that not referring the patient to a more experienced surgeon is unethical as it places self-interest above the patient's best interest. He concedes that there are no clearly established guidelines for this situation, but the ethical principle of avoiding harm (nonmaleficence) and general professionalism should compel a referral to a more-experienced and better performing surgeon[13]. Cohn, on the other hand, argues that such a referral is not an ethical imperative. While having the best surgeon in the world operate on every patient may seem ideal, he argues, it is not possible nor is it truly desirable[13]. Cohn contends that it would not be physically possible for a small group of experienced surgeons to perform all of one type of surgery and it would undesirable to limit the dissemination of knowledge of a new technique[13]. Ultimately, both authors agree that there are certain situations (i.e. a procedure with which a surgeon has no experience or one which requires a vast expenditure of resources or coordinated team) in which referral to a more experienced surgeon is ethically necessary. As universally applicable guidance on this issue is not likely to be produced, each surgeon must, in the context of honest discussion with patients, make such decisions on a case-by-case basis.

While individual physician-level data collection has not been widely adopted, the UK National Health Service (NHS) has published nephrectomy data that includes mortality, complications, and length of stay. This data, collected by the British Association of Urological Surgeons (BAUS), has recently been the source of significant controversy due to errors[15,16]. These errors have led to a recommendation from the BAUS to revise or close the NHS website hosting this data[17]. This experience underscores concerns that the problems inherent in widespread public reporting of individual surgeon-level data can compromise the quality of any analysis drawing on such data. Furthermore, the effects of these data on patient selection strategies and access to surgical treatment for high-risk patients are not yet fully understood.

When considering the question of referral to a higher-volume or better performing institution, many of the same issues exist: questions of patient-selection, fear of lost revenue and the quality of publicly-reported data can diminish enthusiasm for referral to high volume centers. Nevertheless, Becker et al. examined the hospital volume-outcome relationship for nephrectomy and found that patients treated at lower-volume hospitals were at higher risk of adverse outcomes[18]. Smaldone et al demonstrated that the use of partial nephrectomy for small renal masses increased as hospital volume increased[19]. Monn and colleagues

demonstrated that high hospital volume is associated with fewer blood transfusions and complications after robotic assisted partial nephrectomy[20]. The movement towards regionalization for cancer care has occurred in multiple fields of oncology, including prostate and bladder cancer[21].

One resource for the transfer of cancer patients in the United States is the National Cancer Institute's (NCI) cancer center program. Forty-one institutions have been designated “Comprehensive Cancer Centers” by the NCI and are centers of excellence in the research and clinical care of oncology patients. Patients treated at NCI-designated cancer centers have been shown to have lower surgical mortality rates[22], improved post-operative and long-term survival[23], and a higher number of harvested lymph nodes[24] for various malignancies. While the outcomes of kidney cancer patients treated at NCI-designated centers have not been specifically studied, these data make a compelling case for regionalization.

Clinical Research

Clinical research aims to advance our understanding of the pathophysiology and treatment of disease and ultimately to improve the care and health of the patient[25]. Unfortunately, such research often carries a risk of harm to participating subjects. Possible harms include side effects and complications of treatment, loss of confidentiality, and exposure to additional procedures or tests. Balancing these risks with benefits is essential for the ethical conduct of clinical research. Several policy statements exist to guide researchers; these include the Nuremberg Code[26], the Declaration of Helsinki[27], and the Belmont Report[28]. All of these documents emphasize the importance of protecting the research subject and ensuring respect for subjects’ rights. While these documents have laid the historical and ethical framework for modern research ethics, they are not without limitations. Some have argued that the Nuremberg Code, drafted in response to the atrocities perpetrated by Nazi doctors in World War II, is inadequate in its protection of research subjects and provides loopholes for the conduct of unethical research[29]. The Declaration of Helsinki, a document that has undergone several revisions since its initial adoption in 1964, has been criticized as being too restrictive and vague in its recommendations regarding placebo-controlled and phase 1 clinical trials [30]. The Belmont Report, which emphasizes the ethical principles of autonomy, beneficence and justice, does not provide guidance on how to navigate situations in which these principles come into conflict with each other[28].

In 2000, Emanuel and colleagues proposed a universal list of requirements for ethical research [25] (Table 1). The seven elements described below are, the authors propose, like a constitution – a good framework for the ethical conduct of research, but in need of occasional interpretation and revision [25]. As a framework, it is a flexible set of rules that is broadly applicable to human research across many domains: all phases of clinical trials, oncology and non-oncology studies, and research done in both developed and economically developing communities.

Mandatory Research Biopsies

Having presented some guidelines for the ethical conduct of clinical research in general, we turn now to a discussion of some specific issues in kidney cancer research. One issue is that of mandatory research biopsies. Traditionally, renal mass biopsies were used sparingly and in limited clinical scenarios. The expansion of efficacious targeted agents in metastatic renal cell cancer has increased the desire for pre- and post-treatment renal mass research biopsies[31]. Additionally, improvements in image-guided biopsy technique and increased incidental diagnosis of small renal masses have led to renewed interest in the utility of biopsy for small, localized renal masses[31]. One study has demonstrated that patients can be assigned to surgery or surveillance with 97% agreement between biopsy and final pathology [32]. Unlike renal biopsies performed in the course of the clinical care of a patient, however, research biopsies will often not provide any direct benefit to the patient. This has led commentators to question the ethics of making such biopsies mandatory in clinical trials [33-35].

Peppercorn et al [33] argue that research biopsies that are a condition of enrollment in a clinical trial may be coercive to prospective subjects. This argument alludes to the concept of therapeutic misconception – that patients who are considering clinical trials often believe the trial will benefit them in some way that standard therapy will not. Operating under that assumption, patients may feel coerced to agree to a biopsy in order to obtain the benefits of trial participation they implicitly expect. How can we remedy this issue? The solution is not to make research biopsies optional, argue Peppercorn et al, but to ensure that potential subjects understand the nature of the study, how it differs from standard care, and the risks and lack of direct benefit of the biopsy [33]. Furthermore, research biopsies should not be part of a research protocol without “strong scientific rationale, meaningful informed consent and a low to minimal risk of expected complications” [36].

Overman et al evaluated all clinical trials with research biopsies at MD Anderson Cancer Center from 2005-2010 to determine how the scientific rationale for biopsy was presented to subjects, if the biopsy was mandatory, and if the risks and benefits were clearly communicated in the informed consent document [34]. Of 57 clinical trials examined, 67% included at least one mandatory biopsy. Of these, 71% of studies had biopsy as an eligibility criterion. The complication rate of research biopsies was 5.2% (overall) and 0.8% (major). The study found that discussion of biopsy-related risks was inadequate in the informed consent documentation: the discussion of biopsy risks spanned fewer words on average than that of venipuncture, and risks were rarely presented in a site-specific manner [34]. Furthermore, the statistical rationale for number of research biopsies needed was rarely present or adequate [34].

To better understand the varying roles biopsies can play, Peppercorn et al categorize them into three categories: clinical biopsy, research biopsy for correlative science, and research biopsy for integral biomarker research[33]. Clinical biopsies are used in the care of the patient and have a direct benefit to the patient. These biopsies may be useful for research if excess tissue is used or stored for future study. Research biopsies for correlative science are used to correlate a novel or known biomarker with a patient's clinical outcome or response to treatment, and will not impact the care of the subject in any way. Finally, research biopsies

for integral biomarker studies are used to establish the presence of a biomarker that is necessary for patient enrollment in a study that is assessing or validating that biomarker. Clinical biopsies should be considered ethical based on their risk and benefit to the patient, as the primary utility of this biopsy is in the direct clinical care of the patient. Research biopsies for integral biomarker research, while not providing a definite benefit to the patient, will direct the patient's care by allowing their inclusion in a trial or in a particular arm of a trial. The most ethically challenging research biopsy is that for correlative research. Opponents argue that tissue for this purpose can be often obtained from clinically indicated biopsies or tissue banks, and therefore could be made optional rather than mandatory for many research protocols[33].

While there is certainly utility to research biopsies, they should not be mandatory without appropriate scientific justification and detailed statistical planning. As with all aspects research, thorough informed consent is essential. The purpose of the biopsy and the risks specific to it, stratified by the site of biopsy, must be discussed with prospective subjects.

Placebo-controlled trials

Randomized, controlled clinical trials are one of the most important tools of clinical research. The issue of what to use as the control, however, can be controversial. Placebo-controlled studies often raise the greatest concern, and have been used frequently in the targeted therapy era. (Table 2)

Emanuel and Miller have compared the merits of placebo-control and active-control trials[46]. Placebo-control advocates argue that methodological purity requires the use of placebo as a control group. Often, they argue, new treatments may not demonstrate benefits over an existing therapy due to variances in response, small effect sizes, or spontaneous improvement in some patients[46,47]. Furthermore, proponents claim, even if a treatment isn't better than an existing therapy, it may have fewer side effects or less cost[46]. This argument centers on the idea that placebo controlled trials are the most scientifically sound and therefore should be allowed. Conversely, supporters of an active-control argue that withholding the standard therapy from the control group is not morally acceptable. Additionally, they argue that the superiority of a new intervention over placebo is not as clinically relevant as its ability to show improvement over an active control[46]. Allowing the use of placebo, they argue, would be to prioritize scientific rigor over the well-being of patients.

Emanuel and Miller argue that there are ethical problems with each of these views and that a middle ground is called for[46]. They argue that withholding efficacious medication from a placebo group, even if it does not result in lasting harm, can lead to increased suffering and is therefore unethical[46]. The active-control argument also has flaws, they argue, as it creates a false dichotomy between rigorous science and ethical research[46]. (Table 1)

Emanuel and Miller remind us that in order for research to be ethical, it must be methodologically sound, as exposing subjects to any risk without the possibility of scientifically useful results (as in a methodologically unsound study design) is unethical[25]. Further, they contend, the harm of placebo can occasionally be non-existent or so small as to

be negligible. Indeed, in many studies the placebo effect can lead to significant clinical improvement. Finally, Emanuel and Miller argue that the use of placebo allows for increased statistical power, and in some cases may allow for meaningful results from a study with fewer participants – therefore exposing overall fewer patients to potential harm from an investigational therapy[46]. In general, they argue, that most scientists will agree that when live-saving or life-prolonging interventions are available and assignment to placebo would significantly increase the chance for harm, it is unethical to randomize patients to placebo[46]. Similarly, in research involving non-serious ailments, where the chance for harm or discomfort is negligible, placebo-control is ethical[46].

In controversial cases, between these two extremes, placebo controlled trials should only be used when methodologically necessary: there is a high placebo response rate; the condition has a waxing-waning course or spontaneous improvements; existing therapies have serious side-effects or only partial efficacy; the disease is so rare that a trial with active-control would require so many participants as to make the trial not feasible[46]. If these criteria are met, they argue, the use of placebo control should be evaluated for potential risks of death, disability, harm or discomfort[46,48]. Only in the absence of a substantial difference in these risks can a placebo control ethically be used[46].

While previous revisions of the Declaration of Helsinki prohibited the use of placebo when any active treatment existed for a condition[48], the most recent revision (2013) allows for the use of placebo controls when "for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.[27]"

Daugherty et al emphasize that placebo-control trials can be ethical in oncology as placebo should always be accompanied by the best available palliative and supportive care[48,49]. In many scenarios in advanced cancer, available third- and subsequent-line therapies do not offer a high probability of benefit and do carry the risk of significant toxicities[50]. In this setting, there may be equipoise, or uncertainty, when comparing placebo with best supportive care to these active control options[48]. Daugherty et al also propose several methodological strategies to minimize the potential harms of placebo. First, the use of clinically relevant surrogate endpoints instead of survival can shorten the duration of a study and therefore decrease exposure and risk of harm to subjects[48]. Additionally, creative study methodology such as cross-over and randomized withdrawal designs can minimize ethical dilemmas and potential harms related to the use of placebo controls[48].

A recent example of the use of placebo in clinical kidney cancer trials is the 2010 Phase III trial of pazopanib in metastatic and locally advanced kidney cancer[41]. This study compared pazopanib with placebo in patients enrolled from 2006-2007. Around this time, evidence was emerging for the benefits of targeted therapy with tyrosine-kinase inhibitors (TKIs). Furthermore, prior to the widespread adoption of TKI therapy, cytokine-based therapy was the standard of care for advanced renal cancer. The investigators justified the use of placebo

in this study by allowing for the enrollment of patients without prior systemic therapy only if "they were living in countries where there were barriers to the access of established therapies"[41]. Furthermore, the authors cited limited access to targeted therapies and emerging doubts about the value of cytokine based therapy as their rationale for the use of placebo in this study. The pazopanib trial also raises the issue of performing clinical research in resource-limited settings.

Joffe and Miller, in considering the use of placebo in clinical trials in developing countries, argue that the ideal research design would utilize two comparison groups – the best available (therapeutic, diagnostic, or prophylactic) intervention as well as the local standard of care[51]. This design is the most scientifically sound and allows for the most useful analysis. The most controversial design, as in the case of the pazopanib study, is the use of a local standard of care control only. Critics argue that the use of placebo in this case is a disadvantage to participants as it is inferior to the best available therapy. Joffe and Miller argue, however, that this is a flawed argument that ignores the reality of the alternatives available to potential participants in low-resource settings [51]. If placebo and supportive care is equivalent to the best care available to potential participants, no harm is being done by enrollment in the study. On the contrary, entry into the trial is beneficial as it gives the patient a chance of being assigned to a potentially beneficial therapy. In cases such as this, Joffe and Miller support the use of the "independent clinician" heuristic – "ask how a knowledgeable independent clinician responsible for an eligible patient would advise her, bearing in mind the available treatment options" [51].

The high burden of cancer in the developing world highlights the need for clinical research in low-resource settings[51]. Such research is essential but can be ethically challenging and requires thoughtful experimental design, adherence to established principles of ethical research, as well as consideration of the needs and societal values of host communities.

Conclusion

The field of kidney cancer is robust with clinical scenarios and research questions that may pose ethical dilemmas. In this review, we have attempted to discuss a few of these dilemmas and provide some framework for arriving at a practical and ethically sound solution. We strongly recommend the use of clinical and research ethics consultations when considering complex ethical questions. These resources are invaluable in assisting ethical decision-making as well as involving key stakeholders during routine patient care or the design and conduct of clinical research.

Due to the growth of clinical research in this field as well as the increasing incidence of kidney cancer, continued and nuanced examination of these ethical issues, and others, will be needed. Moreover, an understanding of these issues is an important aspect of the training of clinicians and researchers at all levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding:

This work is supported by a grant from the National Cancer Institute (P30CA072720).

Glossary

NHS	National Health Service
BAUS	British Association of Urological Surgeons
NCI	National Cancer Institute
TKI	Tyrosine kinase inhibitor

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Table 1

Seven requirements for determining whether a research trial is ethical.

Table 2. Seven Requirements for Determining Whether a Research Trial Is Ethical*

Requirement	Explanation	Justifying Ethical Values	Expertise for Evaluation
Social or scientific value	Evaluation of a treatment, Intervention, or theory that will improve health and well-being or Increase knowledge	Scarce resources and nonexploitation	Scientific knowledge; citizen's understanding of social priorities
Scientific validity	Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data	Scarce resources and nonexploitation	Scientific and statistical knowledge; knowledge of condition and population to assess feasibility
Fair subject selection	Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research	Justice	Scientific knowledge; ethical and legal knowledge
Favorable risk-benefit ratio	Minimization of risks; enhancement of potential benefits; risks to the subject are proportionate to the benefits to the subject and society	Nonmaleficence, beneficence, and nonexploitation	Scientific knowledge; citizen's understanding of social values
Independent review	Review of the design of the research trial, Its proposed subject population, and risk-benefit ralo by individuals unaffiliated with the research	Public accountability; minimizing Influence of potential conflicts of interest	Intellectual, financial, and otherwise independent researchers; scientific and ethical knowledge
Informed consent	Provision of information to subjects about purpose of the research, Its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Respect for potential and enrolled subjects	Respect for subjects by **(1)** permitting withdrawal from the research; **(2)** protecting privacy through confidentiality; **(3)** informing subjects of newly discovered risks or benefits; **(4)** informing subjects of results of clinical research; **(5)** maintaining welfare of subjects	Respect for subject autonomy and welfare	Scientific knowledge; ethical and legal knowledge; knowledge of particular subject population

*Ethical requirements are listed in chronological order from conception of research to its formulation and implementation

Table 2

Key Phase 3 Trials of FDA-Approved Targeted Therapies for Advanced Renal Cell Carcinoma

Therapy	Target	Treatment Line	Comparison Arm	Primary Endpoint
Axitinib [37]	VEGFR	Second-Line	Sorafenib	PFS
Bevacizumab + IFN- α (AVOREN) [38]	VEGF	First-line	**Placebo** + IFN- α	OS
Bevacizumab + IFN- α (CALGB) [39]	VEGF	First-line	IFN- α	OS
Everolimus	mTOR	VEGFR Failure	**Placebo**	PFS
Pazopanib	VEGFR	First-line or Cytokine Failure	**Placebo**	PFS
Sorafenib [42]	VEGFR	Cytokine Failure	**Placebo**	OS
Sunitinib[43]	VEGFR	First-line	IFN- α	PFS
Temsirolimus [44]	mTOR	First-line	IFN- α	OS

IFN, interferon; mTOR, mammalian target of rapamycin; OS, overall survival; PFS, progression-free survival; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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