Ethical Issues in Non-intervention Trials for Thyroid Cancer

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Abstract

In recent years, the increasing numbers of small, apparently indolent thyroid cancers diagnosed in the world have encouraged investigators to consider non-intervention as an alternative to surgical management. In the following pages, the prospect of a non-intervention trial for thyroid cancer is considered with attention to the ethical issues that such a trial might raise. Such a non-intervention trial is analyzed relative to 7 ethical considerations: the social or scientific value of the research, the scientific validity of the trial, the necessity of fair selection of participants, a favorable risk-benefit ratio for trial participants, independent review of the trial, informed consent, and allowing the study participants to withdraw from the trial. A non-intervention trial for thyroid cancer is also considered relative to the central concept of equipoise.

Key Words

Ethics, thyroid cancer, equipoise, non-intervention, research ethics, clinical trials

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Introduction:

In recent years, there has been an increasing number of thyroid cancers diagnosed worldwide. The reasons for this rise are certainly multi-factorial, but central to the increasing incidence are the large numbers of subclinical and very small papillary thyroid cancers found in many patients. As the implementation of screening programs in countries such as South Korea have increased, the numbers of small papillary thyroid cancers have also increased.[1] Many investigators believe that the primary reason for the world-wide rise in small papillary thyroid cancers has been driven by "overdetection" or "overdiagnosis."[2] Prior autopsy studies have shown that many patients have occult papillary microcarcinomas that have seemingly had no impact on the person's death.[3]

In 1993, Dr. Akira Miyauchi of the Kuma Hospital in Japan first proposed an "observation without immediate surgery" clinical trial for small (<1 cm) papillary thyroid cancers.[4,5] This non-operative approach to small papillary thyroid cancers has come to be known commonly as "active surveillance." The group of 1235 patients from the Kuma hospital cohort has been followed for a mean of approximately 5.0 years. As has been widely reported in several manuscripts from the Kuma authors, when followed for tumor progression or the development of metastatic disease, only 15.5% of patients needed thyroidectomy while under surveillance.

A second single center study of active surveillance of papillary microcarcinomas in Japan has also been completed. Sugitani et al.followed 322 patients with papillary microcarcinomas for a mean of 6.5 years and found that only 8.7% ultimately needed thyroidectomy.[6] These studies have been widely referenced in the literature and seem to reinforce the clinical impression of many thyroid surgeons and endocrinologists that most small papillary thyroid carcinomas rarely become clinically apparent and have a very indolent course. There has been little attention to studies to replicate the Japanese data in other settings. However, based on these data and the widespread impression that papillary thyroid microcarcinomas may not all require treatment, there has been increasing popularity for considering active surveillance as a legitimate treatment option by many physicians.

There is no doubt that active surveillance is commonly used for many low risk (Gleason 6) prostate cancers where it is considered standard of care.[7] Furthermore, some patients with low risk ductal carcinoma in situ (DCIS) of the breast have been followed without undergoing immediate surgery.[8] Nevertheless, the common practice for the treatment of papillary thyroid microcarcinoma in most parts of the world remains immediate thyroidectomy—either partial or total.[9] In view of this contrast between an increasing interest in non-intervention for thyroid cancers and the common practice of thyroidectomy upon diagnosis of such cancers, we sought to explore the ethical issues associated with non-intervention trials for thyroid cancer. In this context, as in all aspects of clinical research, the roles of patient/subject and physician/researcher can be challenging. The clinician should

not make recommendations that are not beneficial to patients. Yet, in a research study, the *subject* may be asked to take on risks that a *patient* might not be willing to assume. This issue remains potentially problematic in all clinical research and should clearly be noted.

Certainly it would be possible to study the outcomes of patients who have opted for active surveillance rather than immediate surgery for low risk papillary thyroid cancer without the use of a randomized controlled trial RCT). However, in the hierarchy of evidence, an RCT would certainly be the strongest evidence to support active surveillance. For this reason, we sought explore the options for such a trial.

Materials and Methods (The Ethics of Clinical Trials)

Deciding what is ethical and what is unethical is challenging since many people believe that determinations of right and wrong are purely subjective. Nevertheless, there has been considerable scholarship in the medical ethics literature exploring what distinguishes ethical from unethical human subjects research. Although a full exploration of this research ethics literature is beyond the scope of this manuscript, it is nevertheless critical to take lessons from that literature and apply them to the current debate about active surveillance for thyroid cancer.

Perhaps the most comprehensive and helpful analysis of the ethical issues in clinical research was provided by Emanuel et al. in 2000.[10] These authors suggested that there are 7 requirements for determining whether a clinical trial is ethical or

not: 1) There must be social or scientific value to the research. In other words, the research question must be relevant to improving the health or well-being of the population. 2) The research must have scientific validity meaning that the appropriate scientific methods should be applied so that the data obtained is valid. 3) There must be fair patient selection to ensure that vulnerable individuals are not targeted as subjects of risky studies nor the socially powerful favored for potentially beneficial research. This ensures that justice is maintained. 4) There must be a favorable risk-benefit ratio such that the risks are minimized and only proportionate to the benefits to the subject and society. 5) Independent review of the study is necessary to ensure that there is public accountability and minimization of conflicts of interest. 6) Informed consent is necessary to ensure that subjects can make informed and voluntary choices about whether to participate or not in the clinical trial. 7) Study participants must be respected by allowing them to withdraw from the study, maintaining their privacy, and informing them of newly discovered risks and benefits from the research.[7]

In order for a clinical trial to be considered ethical, according to Emanuel et al., it must meet all 7 of the criteria listed above. Certainly, underlying all of these issues is the critical importance of equipoise. "Equipoise" means that researchers must not know which therapy in a clinical trial is better or else it would be unethical to allow patients to receive an inferior treatment. Another way of putting it is that it is unethical to run a clinical trial that compares treating an infection with antibiotics or a placebo. Even if someone was willing to enter such a study, it would be unethical for a researcher to allow a person to enter such a study since we know

that antibiotics are effective against infections but a placebo is not. As we now consider non-intervention trials for thyroid cancer, it is helpful to assess how each of the criteria listed above would be addressed.

Results

In order for a non-intervention trial for thyroid cancer to be ethical, we must first agree that there is a state of equipoise. In other words, researchers must be convinced that there is uncertainty about whether intervention or non-intervention is better. For many clinicians who treat papillary thyroid cancer, at the current state of knowledge, there can be no equipoise for non-intervention of large papillary thyroid cancers or those that have evidence of local invasion or macroscopic nodal involvement. Most physicians would consider it outside of the realm of clinical equipoise to allow a patient with a large primary papillary thyroid cancer or with clinical evidence of local invasion or macroscopic nodal disease to enroll in a non-intervention trial even if the patient wanted to because the preponderance of the evidence indicates that such cancers should be treated when diagnosed. However, when it comes to "small" papillary thyroid cancers, the Japanese data suggests that non-intervention may be safe for some patients. As noted previously, the Japanese studies followed selected patients with less than 1.0 cm papillary thyroid cancers. In this context, although not all clinicians would be in a state of equipoise, at least many would consider it ethical to enroll their patients in a clinical trial where non-intervention was one possible arm of the trial. As is evident, equipoise is initially an individual decision for the researcher, but it is not enough for the researcher alone

to believe that there is a question of what is a better approach to the disease. The fourth and fifth criteria discussed below address the examination of the data available for a risk-benefit analysis, and the need for a larger body to help establish equipoise.

In order for a clinical trial to be acceptable, according to Emanuel, there must be social or scientific value to the research.[7] This consideration immediately brings us outside the beliefs of an individual researcher to the broader question of whether there is real value to society or science in the study. When considering small papillary thyroid cancers, there is little doubt that understanding the optimal treatment method—whether it be surgery or active surveillance—has great value. The numbers of patients affected and the health care costs to society of this burden of small papillary thyroid cancer warrants further study.

Moving on to consider the second criteria of ethical clinical research, we must consider whether the study in question has scientific validity. As is readily evident, one cannot assess a class of studies (non-intervention for thyroid cancer) as scientifically valid or not. Only an individual trial can be tested for scientific validity. The study must be designed in such a fashion (e.g. with adequate power) that the results will be valid and potentially generalizable. Thus, this second criteria for ethical clinical trials must be reassessed for every study.

The third consideration is whether the trial allows for fair subject selection so that the benefits and burdens of the trial are equally distributed. Again, when it comes to justice, we must consider each proposed clinical trial for non-intervention individually against this criterion. For example, if only patients without medical

insurance were to be offered entry into a non-intervention trial of thyroid cancer, most observers would consider such a trial to be unethical. Investigators must, therefore, ensure that any proposed non-intervention trial does not push those patients without resources toward the non-intervention arm.

The fourth criterion to consider is whether there is a favorable risk-benefit ratio for the study. When examining this criterion, we must carefully assess the data that we have from prior studies that allow estimates of risks to subjects. Since the primary data available to support non-intervention trials in thyroid cancer is from the 2 Japanese studies noted above, we must be careful not to significantly extend their results beyond what their data support. For example, in both studies, patients with papillary thyroid cancers less than 1.0 cm were reportedly given the option of having surgery or close follow up. Based on this data, one could not conclude, for example, that cancers greater than 2.0 cm would respond the same way. Certainly it is not necessary to restrict clinical trials to only those therapies that have been used previously, but investigators and Institutional Review Boards must carefully assess whether the prior data supports the acceptance of added risk. Because of the necessity to avoid putting subjects at undue risk, changes in treatment for malignant conditions evolve slowly.

Since we know that surgery for papillary thyroid cancer is very effective, a trial that puts patients in an active surveillance arm should be designed so that the boundaries of what tumors can be followed are only expanded slowly. At the present time, with only a fine needle aspiration biopsy, we have little more than the age of the patient and the size of the papillary thyroid cancer to allow clinicians to

assess the safety of non-intervention. In the future, we should all hope for the benefit of molecular markers or genetic signatures obtained through fine needle aspiration biopsy specimen to allow more accurate assessments of the likely clinical behavior and the risk for thyroid cancer patients involved in non-intervention trials. However, the risk of non-intervention should be balanced against the known risks of surgery as the standard of care (recurrent laryngeal nerve injury, hypocalcaemia, hypothyroidism and scar). Such risks are variable and dependent on features of the patient, the patient's co-morbidities, and the experience of the operating surgeon

The fifth criterion for an ethical clinical trial is the necessity of independent review of the protocol and the protections of research subjects. In the US and many countries, such oversight of human subjects occurs through Institutional Review Board oversight. It is critical that the investigators are able to prove to the appropriate external oversight group that the research project meets all of the criteria noted above. Local laws and regulations apply in each country and it is incumbent upon all researchers to ensure that there is a high quality of review and oversight of the studies whose data we eventually look to as support for changing treatment paradigms or for further investigation.

The sixth criterion for an ethical clinical trial is that the subjects must give informed and voluntary consent to participate in the research. When it comes to a non-intervention trial for a disease that is very treatable such as thyroid cancer, there must be a high bar set for the level of information that subjects are given about their disease and their treatment options. It is critical that thyroid cancer patients entering a non-intervention trial understand that the current standard of

care is surgery, which has its own risks of complications and sequelae. Certainly, there may be benefits of avoiding surgery for select patients with small and presumably low risk cancers. These patients must also be informed that they can opt out of the trial at any time and have surgery, or surgery can and would be undertaken if there is a demonstrable growth in the size of the tumor. Yet the patients must understand that active surveillance is being studied and, as such, it is uncertain exactly the level of risk that is being taken by entering into such a clinical trial.

The seventh and final criterion is that participants in ethical clinical research must have their privacy continually protected and they must be allowed to withdraw from participation in the trial at any time. Furthermore, they must be informed of newly gathered data that might alter their choice to continue in the trial. When the clinical trial involves a non-intervention arm for thyroid cancer, the option of being able to withdraw from the study and obtain surgery at any time is of particular importance. Thyroid cancer patients must never be pressured to continue on the non-intervention arm of the trial if they wish to withdraw for any reason.

Discussion

There is no doubt that it is theoretically possible to construct and run an ethical study that compares non-intervention and active surveillance with surgery for low risk intrathyroidal papillary microcarcinomas. However, such a study must be carefully designed and managed in order for it to meet the seven criteria noted above to ensure that it is ethical. Central to all of the considerations noted above is

the responsibility that investigators have of ensuring that patients (subjects) are put at the lowest possible risk and that they clearly understand the risks that they are assuming by choosing active surveillance. Based on the current data, we can only state that among selected Japanese papillary thyroid cancer patients with very small tumors and no evidence of nodal spread, many can safely avoid surgery. At this point, we lack data on the quality of life of such thyroid cancer patients who are in the active surveillance mode. However, the quality of life of such patients must be compared with patients who undergo surgery for such small thyroid cancers since the quality of life after thyroidectomy is diminished for many patients compared to before thyroidectomy. Undoubtedly, such information is necessary for patients to make truly informed decisions about whether active surveillance is a reasonable option to consider. In the years to come, only carefully designed non-intervention trials that slowly broaden the criteria for entry into the trial on the basis of choosing the lowest risk patients should be undertaken. If we are to put patients at risk by entering such studies, we must ensure that the scientific validity of the trial is sound and that the risks are minimized and clearly communicated to patients.

The current evidence for active surveillance is based on limited data, and its immediate widespread use, with extrapolation of published results to other patient populations is debatable from an ethical standpoint.Many other questions remain concerning active surveillance that can only be adequately addressed by controlled clinical trials with sufficient statistical power to ensure a high level of evidence. Some of the questions that remain are:

-What is the outcome of active surveillance in populations other than from Japan?

- What is the optimum timing for follow-up surveillance?

-What is the safe size limit for active surveillance of thyroid cancers?

-What is the optimal age group for active surveillance?

-What other factors influence outcome of active surveillance (TSH levels, dietary idodine, BMI, environmental factors, etc.)?

-How does active surveillance affect quality of life, as compared to traditional surgical management?

-What is the cost of active surveillance as compared to traditional surgical management in terms of patient quality adjusted life years and overall burden to the patient and/or health care system?

As has often been the case with well-differentiated thyroid cancer patients, the excellent prognosis makes studying treatment options very difficult. Not only is it necessary to have very large numbers of patients followed for many years in order for differences in outcomes to be identifiable, but also non-intervention trials must be very carefully designed in order to provide answers to the above questions as well as to minimize risks to patients since the outcomes for treatment are so good.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.