Decision Making with Prostate Cancer: A Multiple-Objective Model with Uncertainty

Jay Simon, Paul Merage School of Business, University of California, Irvine

Abstract

When diagnosed with prostate cancer, a patient has a difficult decision to make. There are several different treatment alternatives available, with varying cure rates and probabilities of side effects over a period of many years. This paper describes a well-informed, objective, and personalized model for comparing treatments and helping a patient make the best possible decision.

Keywords: Health care: Treatment, Utility-preference: Multiattribute, Utility-preference: Applications, Decision Analysis, Decision Analysis: Applications

Introduction

Over 200,000 men will be diagnosed with prostate cancer this year in the United States alone (Carroll 2005). It is an issue that most men will have to confront at some point in their lives. Thus, any enhancement in decision making after diagnosis would provide enormous benefits to society. Management science techniques can be applied to this decision, using a decision analysis approach. The methods and the model described in this paper have the potential to eventually improve the lives of many people.

Prostate cancer is a challenging disease from an analytical perspective. Treatment decisions for many diseases are trivial; if a disease has a high probability of death within

a short period of time, or if there is only one commonly used type of treatment, then a decision analyst has very little work to do. Prostate cancer, however, is a much different story. It is often a very slow-growing cancer, which means that symptoms may not occur for a decade or more following diagnosis. The probability of death from prostate cancer is often fairly low, even if it is not treated. In addition, there are several different treatments available. Surgery is a very common alternative, as are a few different radiation methods. In general, surgery tends to have a high cure rate (low probability of death from cancer), but also a high probability of a few different side effects occurring. Radiation techniques tend to have lower cure rates, but also lower risks of side effects. Choosing a treatment when faced with prostate cancer requires a detailed analysis of many alternatives.

Two main problems must be tackled before making the treatment decision. First, the uncertainties involving death and side effects over time must be quantified as probabilities. This is accomplished mainly by collecting and analyzing historical data reported in medical journals. Second, the patient's individual preferences must be elicited and incorporated into the analysis. Since the outcomes involve multiple attributes (length of life and side effects), it is necessary to know the relative importance that the patient places on each attribute. This is closely related to the concept of quality-adjusted life years, which I will discuss in detail later. The theoretical foundation of the model and analysis is multi-attribute utility theory. Once the preferences and uncertainties have been quantified, it is possible to evaluate each treatment alternative and compare the results.

The methods described in this paper are being implemented by Prostate Cancer Decision Analyst (PCaDA). PCaDA is a web-based interface which can be found at http://www.PCaDA.com. Among other features, the site provides very helpful analysis and comparisons between treatment options. This paper is based on my past experience as a consultant for PCaDA and on follow up academic research. I helped develop the model discussed in this paper, which is currently being used on the website.

Literature Review

This paper draws from two main streams of literature. The first is the decision analysis literature, particularly those works which focus on medical decisions. The second is the medical literature related to prostate cancer. The former provides a theoretical basis for the model described in this paper, and the latter supports the analysis with observed historical data.

The fundamental decision process in the model is guided by the principles of multi-attribute decision making; that is, how to appropriately make tradeoffs between different objectives. This concept is addressed in detail by Keeney and Raiffa (1976) and by Dyer and Sarin (1979). They discuss the use of an additive model, and the independence conditions required for these models to be valid. Keeney (1974) discusses the use of a multiplicative model. I will apply a model which has both additive and multiplicative components.

There is also a fairly large stream of literature analyzing the application of these principles to medical decisions. One of the most widely applied concepts is "quality-adjusted life years," or simply "QALYs." QALYs can be used to measure the length of a

person's life, adjusted for the quality experienced during that time. For example, a 10-year experience in a health state deemed to be half as desirable as an ideal state is equivalent, in QALY terms, to a 5-year experience in the ideal state. QALYs are discussed in greater detail by Pliskin et al. (1980), Hazen (2004), Miyamoto (1999), and Torrance and Feeny (1989). Some aspects of the model used in this paper are conceptually very similar to the QALY model.

The papers from the prostate cancer literature are vital to the accuracy of the PCaDA model. I refer to papers which provide information on the efficacy of each treatment, and the likelihood of the occurrence of each side effect following each treatment. Information on cancer death following the various treatments are obtained from Han et al. (2003), Kuban et al. (2003), Catalona et al. (1999), Zelefsky et al. (2001), and Kupelian et al. (2004). In the case of no treatment, this information is obtained from Han et al. (2001) and Holmberg et al. (2002).

The side effects used explicitly in the model are impotence, incontinence, and toxicity. The details of these will be discussed later. Information on impotence following treatments are obtained from Potters et al. (2001), Stock et al. (2001), Zelefsky et al. (1999), Roehl et al. (2004), and Schover et al. (2002). Information on incontinence can be found in Catalona et al. (1999), Eastham et al. (1996), and Malmsten et al. (1997), and information on toxicity can be found in Zelefsky et al. (2002), Zelefsky et al. (2000), Gelblum and Potters (2000), and Zelefsky et al. (1999).

It is important to note that the specific conclusions drawn in these individual papers from the prostate cancer literature are usually not germane to the purpose of the prostate cancer decision model. They are valuable here because they provide large quantities of

data which can be aggregated and incorporated into a decision model that includes many factors specific to the individual patient.

Decision Model and Results

This decision model considers five alternatives for the treatment decision: surgery, external radiation, seed radiation, dual radiation, and no treatment. Surgery (radical prostatectomy) consists of the surgical removal of the prostate. External radiation is the oldest radiation method; a radioactive beam is sent through the prostate in an attempt to kill the cancer cells. There are many different methods of external radiation, but they all follow this general principle. Seed radiation is the implantation of tiny radioactive pellets into the prostate. It is less invasive and has a lower risk of side effects, but is only effective at treating very localized cancers. Dual radiation is a combination of seed and external radiation at lower doses. No treatment, obviously, consists of making no attempt to fight the cancer.

Development of the decision model consists of two primary tasks. First, the uncertainties must be specified and evaluated. Second, the preferences of the decision maker must be taken into account. I will discuss both of these processes in this section.

There are several uncertainties relevant to this model. For each potential concern of the patient, the goal is to determine an individualized probability distribution over time. Different patients will generally face different probabilities of side effects occurring, as well as different survival curves. Thus, it is important to analyze not only the effects of each treatment alternative, but also the effects of many characteristics of the particular patient. Figure 1 shows a screenshot of a section of a patient's PCaDA.com profile.

Further information can be obtained for each profile item. Figure 2 shows the window that pops up when the "Help" link for PSA Level is clicked.

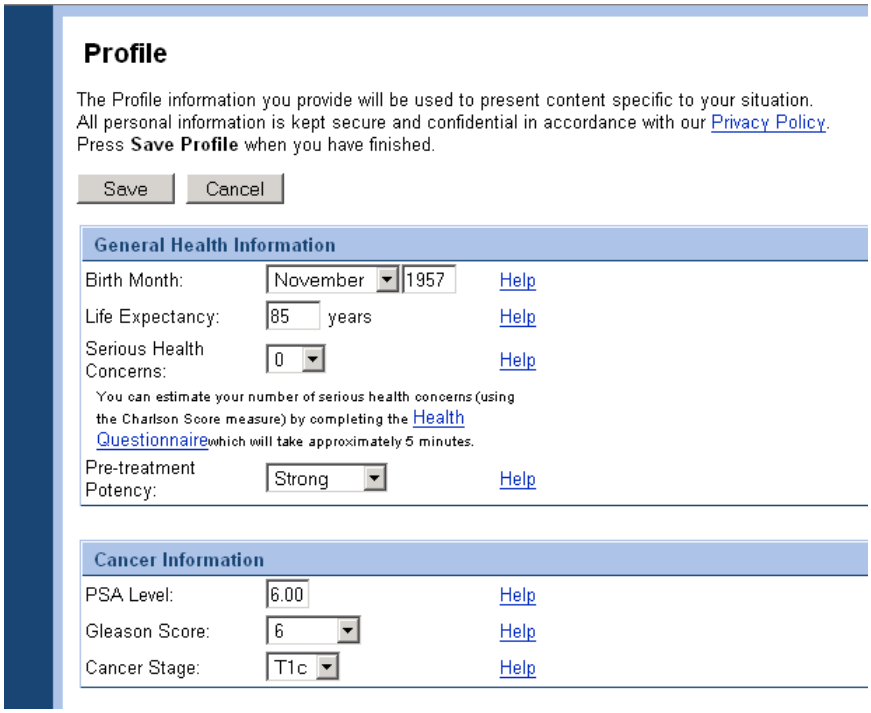

Figure 1: Example of PCaDA.com's patient profile interface

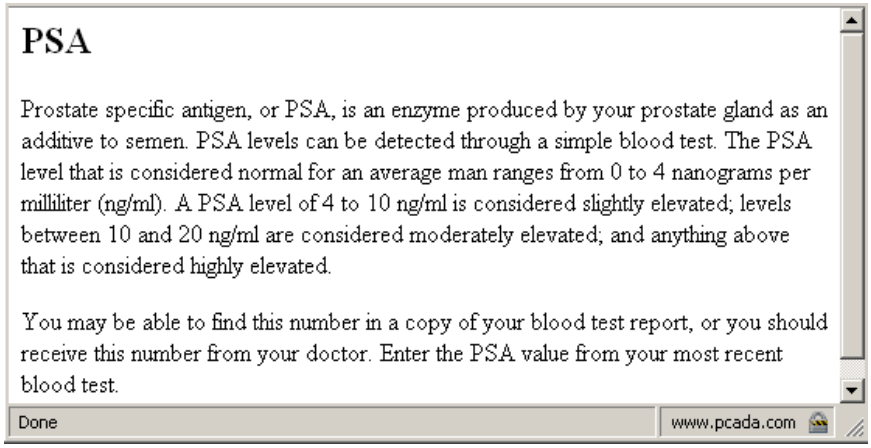

Figure 2: Example of a profile help window

The first uncertainty is the life span of the patient when ignoring the possibility of death from prostate cancer. An example is shown in Figure 3 for a man who is currently 50 years old. The expected value of the patient's life span is called "life expectancy,"

and it can be determined by using any of several publicly available health questionnaires. PCaDA refers users to a questionnaire available via MSN Money (2008). The shape of the curve is determined using actuarial data, which are also widely available. PCaDA uses data obtained online from the United States Social Security Administration (2007). This probability distribution serves as a starting point for analyzing the effects of prostate cancer and treatment.

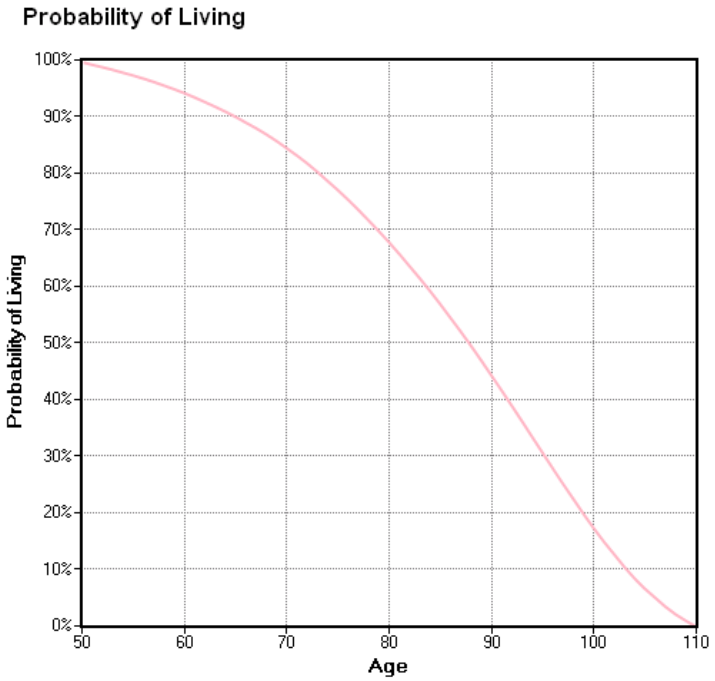

Figure 3: Example of a survival curve before considering the effects of prostate cancer

The next important uncertainty is the probability of death following each of the various treatment alternatives. There is a wealth of information in medical journals to help assess these uncertainties. The individual sources are discussed in the literature review. There are numerous articles that report cure rates from each of the treatment methods discussed in this paper.

These probabilities of death from prostate cancer also depend on a few factors specific to the individual patient. There are three commonly used measures of prostate cancer

severity. For simplicity, these can be combined into a single measure called cancer score. The probabilities of cancer death over time following treatments are parameterized by cancer score. An example of a set of cancer death probability curves for a particular 50-year-old patient is shown in Figure 4. The top curve represents the no treatment case, and the lowest curve is surgery.

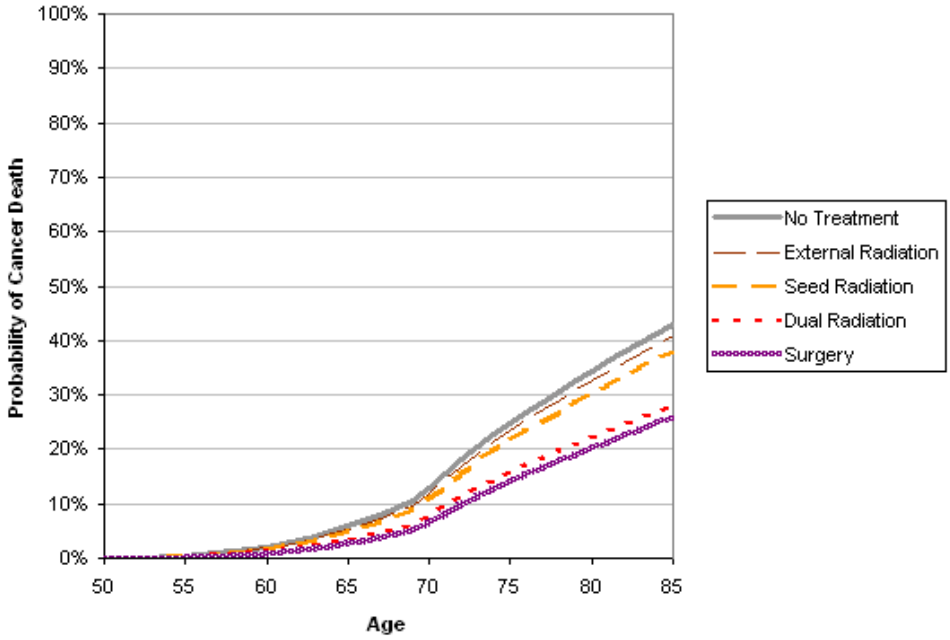

Figure 4: Example curves showing probability of death from prostate cancer given various treatments

The original data provide survival rates by year following each treatment given various patient characteristics. The surgery curve is based on survival data from Han et al. (2003) and Catalona et al. (1999). The radiation curves are based on survival data from Kuban et al. (2003), Zelefsky et al. (2001), and Kupelian et al. (2004). The no treatment data is obtained from Han et al. (2001) and Holmberg et al. (2002). These studies provide not only survival curves, but also the characteristics of the patients, including age and various measures of cancer severity. This allows us to interpolate to

obtain rates of death from prostate cancer as a function of the patient's age, cancer score, and treatment type.

There is also a small probability of death as a result of the treatment itself. Any major surgical procedure involves some risk. It is possible for the patient to die as a direct result from the surgery (literally, on the operating table). However, the more significant danger is that major surgery will result in the exacerbation of some pre-existing condition that will not result in immediate death, but will reduce the life span of the patient. There is a medical concept called the "Charlson score" which summarizes this risk as a single number. It was first developed by Charlson et al. (1987). Patients with high Charlson scores are not considered good candidates for surgery. The patient represented in Figure 4 has a Charlson score of 0, which indicates no serious pre-existing conditions. Positive Charlson scores increase the likelihood of cancer death at the current age due to death directly from surgery, as well as afterward due to the exacerbation of the pre-existing condition(s).

In addition to length of life, the patient should consider the probabilities of incurring any of a number of side effects. Depending on the choice of treatment, the patient may have to deal with impotence, incontinence, and/or toxicity. Impotence is the inability to maintain an erection sufficient for penetration. Incontinence is the inability to control the flow of urine. Toxicity is a general term encompassing various lingering effects of radiation in the body. Impotence and incontinence can occur naturally with age and also as a side effect of the cancer itself. In addition, radiation can cause impotence, and surgery can cause both impotence and incontinence. Toxicity does not occur naturally or as a result of the cancer itself; it is only a side effect of radiation.

An example of a graph showing the probability of impotence for each treatment is shown in Figure 5 for a 50-year-old patient. This graph is somewhat more complex than the previous two. The curve for surgery begins at 100%, because surgery always causes temporary impotence, at the very least. In addition, some of the other curves cross one another. This is due to the fact that there are three underlying causes of impotence: cancer, treatment, and natural aging. The first two causes are affected differently by each treatment. For example, getting no treatment is very unlikely to lead to impotence within the first few years, but is relatively likely to result in impotence due to the cancer itself after 20 or 30 years. The analysis used to generate this graph is a prime example to illustrate why a formal model is necessary to deal with this decision; the underlying factors often interact in a manner far too complex to digest with only a cursory review.

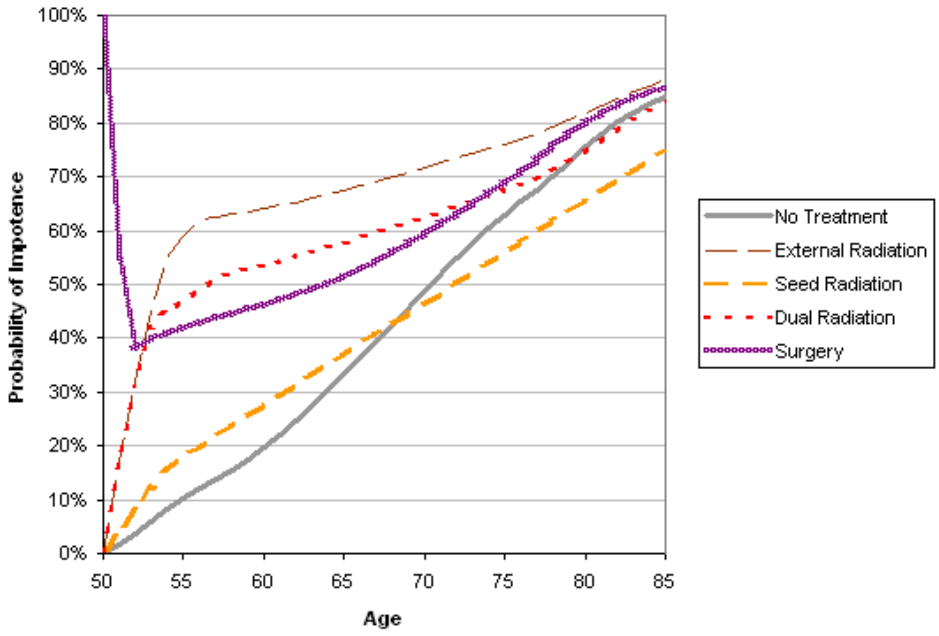

Figure 5: Probability of impotence following various treatments

As mentioned earlier, these probability distributions are determined by analyzing large volumes of data obtained from medical journals. The surgery curves are computed using

data from Roehl et al. (2004) and Schover et al. (2002). The radiation curves are computed using data from Potters et al. (2001), Stock et al. (2001), Zelefsky et al. (2002), and Zelefsky et al. (1999). Johannes et al. (2000) provides data on impotence as a result of natural aging, which affects all of the curves. In addition to probabilities of becoming impotent, these studies also provide characteristics of the patients. As discussed with regard to cancer death, this allows us to interpolate and obtain probabilities of impotence specific to any individual patient.

A graph of this patient's probabilities of incontinence is shown in Figure 6. The computation of the incontinence curves is identical to the method used for impotence, except that it never occurs as a direct result of radiation. The surgery curve is based on data from Catalona et al. (1999) and Eastham et al. (1996). The data for incontinence as a result of natural aging, affecting all five curves, is provided by Malmsten et al. (1997).

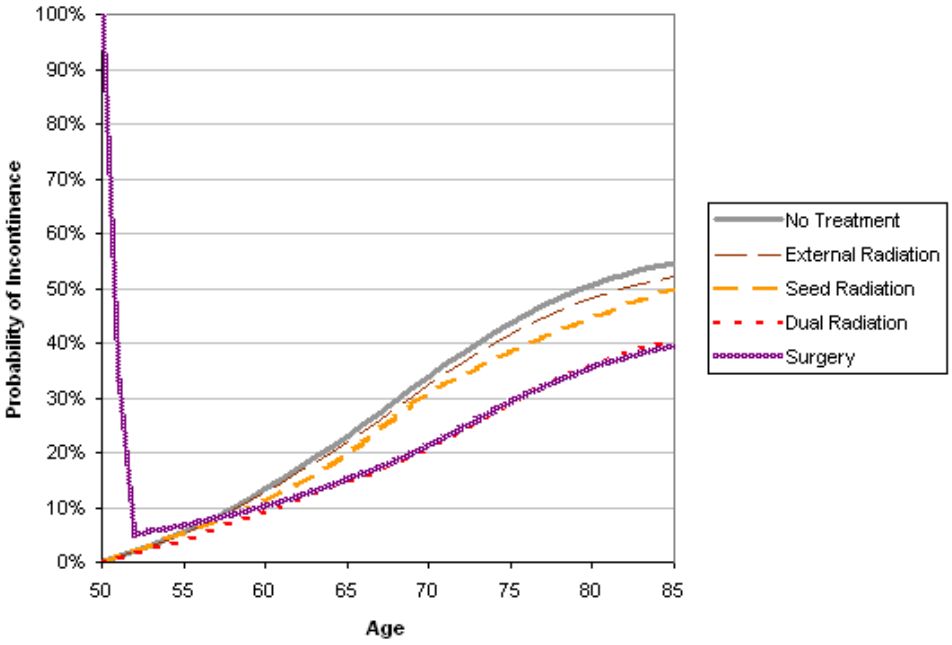

Figure 6: Probability of incontinence following various treatments

A graph of this patient's probabilities of toxicity is shown in Figure 7. Toxicity occurs only as a temporary side effect of radiation, and therefore is not considered when analyzing surgery and no treatment. The external radiation curve is based on data from Zelefsky et al. (2002) and Zelefsky et al. (1999). The seed radiation curve is based on data from Zelefsky et al. (2000), Gelblum and Potters (2000), and Zelefsky et al. (1999). The dual radiation curve is based on data from Gelblum and Potters (2000) and Singh et al. (2000).

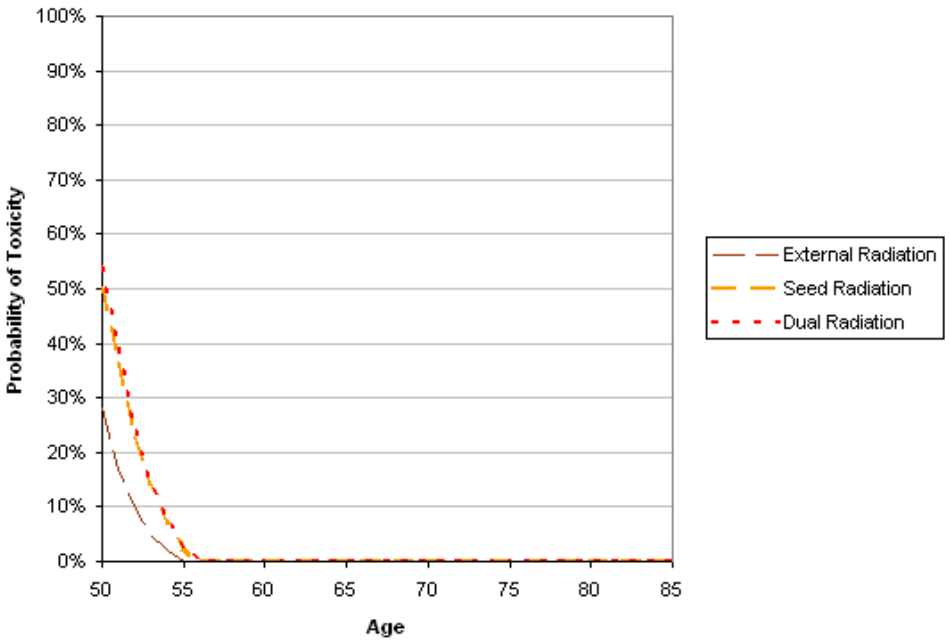

Figure 7: Probability of toxicity following radiation treatments

The next step in developing the model is analyzing the preferences of the user. This is a multiple objective model, since the patient cares not only about maximizing length of life, but also about avoiding each of the three side effects. This challenge is discussed by Barry et al. (1988); they find that patient preferences are often a driving force in determining the best alternative. In addition to the side effects mentioned, it is also very possible that the patient may want to minimize cost, maximize convenience, or consider

any of a number of other possible attributes. However, for the purposes of this model, only four objectives are considered, as these tend to be the factors which are material to the treatment decision. Patients are cautioned to interpret the results not as medical advice, but simply as the output of a tool designed to aid the decision process.

The patient will need to specify his preferences in such a way that allows meaningful comparison between possible outcomes. This is done by establishing relative weights on the attributes. The method used is similar to the concept of quality-adjusted life years (QALYs), which have been discussed in the medical decision making literature, as mentioned earlier. For each side effect, the patient answers the following question: "What percentage of my remaining life would I be willing to give up to avoid this side effect?" That is, the patient determines the value of X ($0 \leq X \leq 1$) such that he is indifferent between n years with the side effect and n(1-X) years without it. This value of X is called the "emotional weight" on this side effect. For example, if blindness reduces a person's quality of life by 20 percent, then that person will value 10 blind years and 8 non-blind years equally. Further explanation is provided on the site for patients who have difficulty in assessing these tradeoffs.

Emotional weights are not the only possible method for determining tradeoffs between attributes. There are many other adaptations of the QALY concept, and some attempts have been made to directly assess preferences over multi-dimensional outcomes. For example, Bremner et al. (2007) apply direct assessments of various states which might be experienced by prostate cancer patients. Emotional weights are an intuitive and robust method in this context, but it is important to realize that there are certainly other valid methods being used.

The main difficulty in using emotional weights is that there is no generally accepted method of eliciting them from patients. PCaDA.com has a fairly straightforward method which allows the user to obtain as much help as necessary. There is a simple interface with "layered" access to content. This makes it easy for the user to follow links to increasingly technical information until he is comfortable with the concepts.

The value of an emotional weight is that it provides a tradeoff between disutility of a side effect and disutility of a loss of life span. Thus, it now makes sense to talk about the disutility of a *possibility* of a side effect. For example, if impotence has a 10% emotional weight, and a treatment increases the probability of impotence by 10% over the patient's life, this is equivalent to reducing the patient's life span by 10%*10% = 1%, in terms of utility. Emotional weights are defined such that this is the case.

The more important point is that now the possibility of each side effect can be expressed in terms of a specific reduction in life span. Therefore, each attribute can be expressed on the same scale, and we can define outcomes in terms of a single variable. The PCaDA term for this variable is "Life Score." Life Score is a weighted average utility obtained from choosing a particular treatment alternative. It takes into account both length and quality of life. The formula for Life Score is shown in Equation (1):

$$\int_{CurAge}^{MaxAge} f\left(LifeSpan = x\right)\left(\int_{CurAge}^{x}\begin{array}{l} P\left(NoDeathFromCancerAtTime = t\right)* \\ \left(1 - P\left(ImpotentAtTime = t\right)* ImpotenceEW\right)* \\ \left(1 - P\left(IncontinentAtTime = t\right)* IncontinenceEW\right)* \\ \left(1 - P\left(ToxicityAtTime = t\right)* ToxicityEW\right)* dt \end{array}\right) dx \quad (1)$$

$f\left(LifeSpan = x\right)$ is the probability density function for the patient's length of life before considering prostate cancer. $P\left(NoDeathFromCancerAtTime = t\right)$ is the probability that

the patient has not died from prostate cancer at time *t*, conditioned on the patient not having died from any other cause at or before time *t*. $P\left(ImpotentAtTime = t\right)$ is the probability that the patient is impotent at time *t* as a result of any of the possible causes of impotence, and $ImpotenceEW$ is the emotional weight assigned to impotence by the patient. If the patient already suffers from impotence, then $ImpotenceEW$ is defined to be zero. The terms for incontinence and toxicity are defined similarly. Essentially, this formula integrates from the patient's current age over all possible life span lengths without prostate cancer, computing the proportion of utility retained for each one.

The Life Score function has both an additive and a multiplicative component. The application of emotional weights is multiplicative; each side effect reduces the patient's utility by a constant factor. However, the aggregation of outcomes over time is additive, as evidenced by the two integrals in the formula. It should be noted that Equation (1) is the theoretical formula; in practice these integrals are actually summations with one data point per year. The differences in the overall Life Score results of the model are negligible.

The next step is to provide an intuitive interpretation of the results. It would actually be more instructive to refer to the result of (1) as "raw Life Score." The maximum possible value is achieved when the model is run without the presence of prostate cancer (the "no cancer case"). The Life Scores which are presented to the user are actually *100**(*Raw Life Score* / *No Cancer Life Score*). This formulation has a rather straightforward interpretation; it is the percentage of Life Score retained from the no cancer case. That is, if a treatment option has a Life Score of 95, then getting this

treatment results in a life with an expected utility of 95% of what it would have been if the person did not have prostate cancer.

Given this definition of Life Score, it is straightforward to compare the desirability of the various treatment options. If surgery has a Life Score of 90, and seed radiation has a Life Score of 88, then the patient should prefer surgery to seed radiation. Figure 8 shows the resulting Life Score following each treatment alternative for the patient described in Figures 3-7, given that his emotional weights are 4%, 4%, and 2% on impotence, incontinence, and toxicity, respectively.

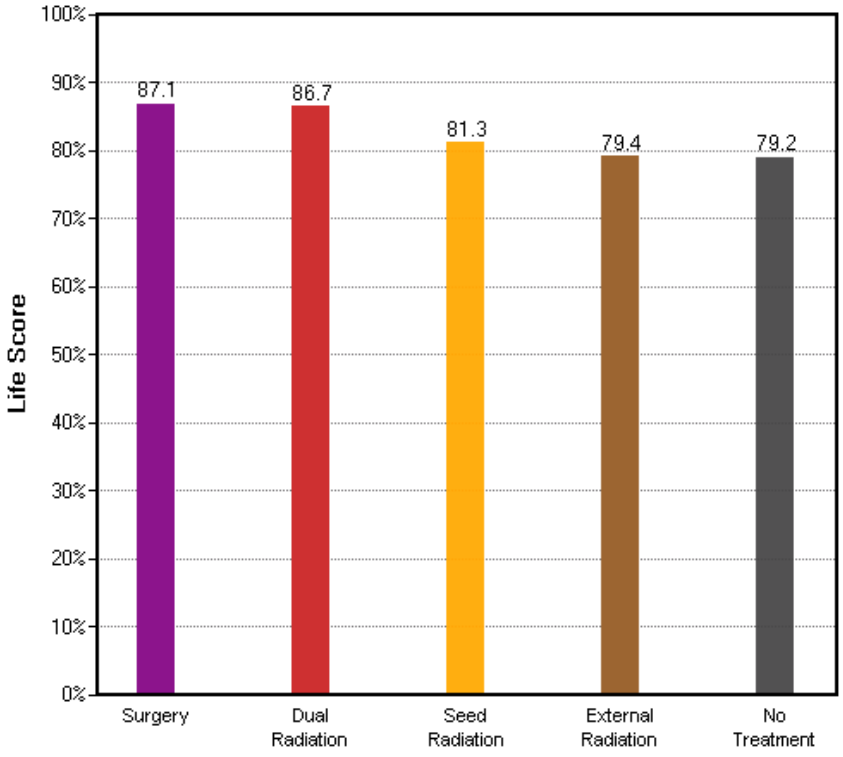

Figure 8: A patient's Life Score for each treatment alternative

On the surface this graph is very simple, and some users of the site may be content to follow the recommendation without further question. However, it would be rather presumptuous to assume that it will suffice for everyone, therefore several intermediate

steps in the calculations are provided. In addition to displaying a final Life Score for each alternative, the model also displays the individual components which contribute to the reductions in Life Score from the ideal "no-cancer" case. This is illustrated for impotence in Figure 9. This graph tells the patient how much of the overall loss in Life Score can be attributed to the increased probability of becoming impotent. For example, the patient's Life Score for surgery is 87.1. Of the 12.9 points of Life Score lost as a result of prostate cancer, 1.1 can be attributed to an increased probability of impotence. This graph is also available for incontinence, toxicity, and cancer death, with identical interpretations.

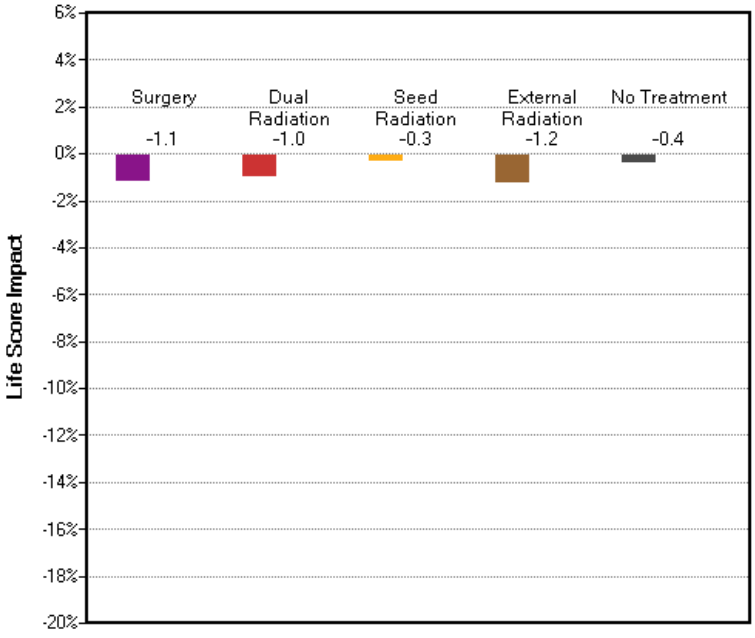

Figure 9: Example Life Score impact of impotence

Providing these graphs to the user adds a mechanism for user feedback to the model. For example, the user might look at Figure 9 and decide that the Life Score calculations are not sufficiently accounting for impotence. He may then realize that he underestimated his emotional weight on impotence, and go back to his profile and change

that parameter. These intermediate results create a feedback cycle that helps ensure the robustness of the model.

Since the analysis is customized to each patient's specific case, it does not make much sense to discuss individual patient results in this paper. However, running the model repeatedly for various types of patient profiles does yield some interesting general results. I will discuss these here, as a few of them are somewhat controversial.

First, surgery will usually result in the highest Life Score for younger men who do not have an extreme aversion to side effects. This is more or less consistent with current medical practice. Seed radiation may occasionally be more desirable if the cancer is detected in a very early stage, and dual radiation (low-dose combination of seed radiation and external radiation) may sometimes be preferred if the patient is exceedingly concerned about side effects. For older patients, the PCaDA model tends to suggest a less aggressive strategy, which means seed radiation if the cancer is very localized, and either external radiation or no treatment otherwise. This difference between young and old patients is widely recognized in the medical world, but the model implies that it is somewhat more extreme than common practice would suggest. Aggressive treatments simply are not very beneficial for older patients, for the morbid (but clearly correct) reason that these patients are likely to die from some other cause before prostate cancer becomes a serious danger. Thus, they would endure additional side effects for a very slim increase in life expectancy.

Possibly the most controversial general result of the PCaDA model is that external radiation is likely being used too often. It can provide a moderate reduction in side effects, but its cure rate is lower than many people believe. This is due to a systematic

censoring and backdating error present in many articles on radiation treatments for prostate cancer. (Censoring involves removing patients from a data set when they stop following up, and backdating involves shifting the recorded time of an occurrence backward to account for delay in observation.) This phenomenon has been observed previously; PCaDA's results simply provide further evidence that radiation cure rates are often overestimated. Detailed analysis of the cure rate error is tangential to this paper, but it is studied and explained thoroughly by Coen et al. (2003) and Vicini et al. (1999).

A small sample of follow-up interviews conducted by PCaDA indicated that a majority of users plan to choose the treatment with the highest Life Score. Among users who did not plan to choose the treatment with the highest Life Score, the most common explanation was the lack of availability or inconvenience of the treatment. For example, dual radiation is currently not available at most clinics in the United States, and some patients preferred to sacrifice a small amount of Life Score for the purposes of cost and convenience. Nearly all users claimed to have been influenced by the results. The most common effect of the model is to steer patients toward less aggressive treatments. A detailed study of patients' actual decisions following the use of this model has not been done, but could be a valuable area for future research.

As of August 2007, PCaDA was receiving an average of 400 hits per week, and had not spent any money on advertising.

Conclusion

This paper illustrates a process for choosing a prostate cancer treatment using the best decision analysis methods possible. The model combines ample historical data with

individual patient characteristics to specify the uncertainties of the model as precisely as possible, and it incorporates the patient's preferences using an adaptation of standard techniques in multi-attribute and medical decision theory. It provides final results in terms of a Life Score, which is conceptually similar to expected utility, along with intermediate results showing the impacts of various pieces of the analysis. From a utility-maximizing perspective, it is superior to the decision processes used by most people in selecting a treatment strategy. Medical decision processes tend to rely on heuristics that do not completely or consistently incorporate all of the relevant information, as discussed by McDonald (1996) and Elstein (1976).

Prostate cancer is a very widespread disease, and thus the potential benefits of such a model are enormous. Patients generally do not have access to all of this data, nor the means to properly incorporate their own preferences into the decision. In many cases, they do not even consider all of the available treatment options. This model has already improved the lives of many people. Acceptance of it as a standard tool for prostate cancer decision making could do so for millions more.

Acknowledgments

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