Erectile Functioning of Men Treated for Prostate Carcinoma

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tion, associated with treatments for prostate carcinoma are often used to guide patient decision-making and develop clinical guidelines. Unfortunately, the published data are largely comprised of case series from single institutions. Meta-analysis is a methodology for combining findings from several studies to produce a better result.

METHODS. A comprehensive literature review and subsequent meta-analysis of the

BACKGROUND. Published reports of complication rates, such as erectile dysfunc-

METHODS. A comprehensive literature review and subsequent meta-analysis of the rates of erectile dysfunction associated with external beam radiotherapy and radical prostatectomy was conducted. A simple logistic regression model was used to combine the data from 40 articles that met selection criteria.

RESULTS. The probability of maintaining erectile functioning after radiotherapy is 0.69. The probability after surgery is 0.42. This difference is significant. Analysis of the effects of variables such as patient age and stage of disease on erectile functioning could not be performed due to inconsistencies across studies and the limited number of studies reporting such variables.

CONCLUSIONS. The published data indicate that men with normal erectile functioning are more likely to retain this function after radiotherapy than after surgery. Attention is drawn to the weaknesses in the reviewed studies in the hope that the clinical trials of emerging treatments, such as cryotherapy, brachytherapy, three-dimensional conformal radiotherapy, and neoadjuvant hormones can be strengthened to reflect more accurately the rate of treatment-associated erectile dysfunction. *Cancer* 1997; 79:538–44. © 1997 American Cancer Society.

KEYWORDS: prostatic neoplasms, prostatectomy, radiotherapy, penile erection, impotence.

ncreasingly larger numbers of men are being faced with the diagnosis of prostate carcinoma. It is estimated that 244,000 men a year receive this diagnosis in the U.S.¹ With greater public demand for screening, this trend is unlikely to change.

When a man receives a diagnosis of early stage prostate carcinoma, he has a choice of two treatments: radical prostatectomy or radical radiotherapy. Both are believed to be equally effective in curing this carcinoma.^{2,3} Health professionals and patients often look to published data on the complication rates of these treatments for guidance in choosing between treatments.

Recently, the published data on complication rates have been used to calculate the trade-off between the potential negative impact of treatment on quality of life and the potential survival benefits of treatment. These calculations have raised doubts as to the benefits of treatment. The suggestion is made that no treatment may, in fact, be the best choice for some men.⁴ Hence, there is a need for accurate estimates of complication rates associated with treatments for pros-

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tate carcinoma, if physicians are to guide patients objectively in their choice between treatments, or in their choice to undergo or not undergo treatment.

A randomized clinical trial would be the best source of data to estimate the relative complication rates of radical radiotherapy and radical prostatectomy. However, such trials have been difficult to mount. Current knowledge is largely based on case series that are typically for a consecutive cohort treated in a single institution with a single treatment method. Other sources of data are recently reported large scale surveys. ^{5,6} Meta-analysis offers a way of combining the results of several studies to provide a better estimate of complication rates than that obtained by referring to a single study or box scores of significant results, and avoids the subjectivity of narrative reviews. ⁷

This study reports the results of a meta-analysis of a comprehensive literature review on the rates of one complication, erectile functioning, which has been shown to be one of the complications of greatest concern to men after treatment for prostate carcinoma. ^{5,6} Apparently, sexual functioning is so important for some men that they would choose a treatment less effective in promoting survival if it were more effective in preserving sexual functioning. ⁸

The literature contains one comparable metaanalysis of the rate of erectile dysfunction in men after prostate carcinoma treatment. Unfortunately, this analysis was performed without respect to the erectile functioning of the men prior to their treatment. By including men who were already experiencing erectile dysfunction prior to treatment, it is impossible to determine the incidence of treatment-induced erectile dysfunction. The current study bears more relevance to the calculation of rates of treatment-associated erectile dysfunction. How many men who were sexually functional before treatment are likely to retain their function? This question is the one that the analysis reported here attempts to answer.

METHODS

A comprehensive literature review was conducted using the Alberta Health Knowledge Network (1994) database, which includes MEDLINE and CANCERLIT. Inclusion criteria for the study included: 1) no articles older than 1970; 2) studies reporting results of external beam radiotherapy, radical prostatectomy, and cryotherapy; 3) studies reporting data on primary, discrete data sets; 4) known pretreatment sexual functioning status; and 5) reports of patients who were not receiving hormone therapy. Articles were reviewed closely to satisfy Criterion 3. For studies in which reports of accumulating data sets are presented, the most recent

article that met the other criteria was selected for inclusion. If the same data set was reported on in more than one article, the most current article that met the study criteria was selected.

All articles were closely scrutinized for the variables of interest. A table was compiled that included the following information on each article: experimental design, type of treatment, number of subjects and their mean age, the patient selection criteria, the definition of normal erectile functioning, times and method of sexual assessment, and the ratio of men with normal erectile functioning before treatment to the number of men with normal erectile functioning after treatment.

Impotence is the term commonly used for impaired erectile functioning in the reviewed articles. Several professional groups have suggested that this term be dropped because it is imprecise and pejorative, in favor of erectile dysfunction. The latter term is used in this article and is defined as the inability to maintain an erection sufficient for intercourse. This is an operational definition only and does not presuppose the etiology of the dysfunction. The authors recognize that sexual functioning is multidimensional, including physical, psychologic, and interpersonal components.

RESULTS

Description of Articles in Study

This analysis is comprised of 40 articles, the main features of which are outlined in Table 1. Of these 40, 15 were reports of radiotherapy, 22 were reports of radical prostatectomy, 1 was a comparison of radiotherapy and radical prostatectomy, and 2 were reports of cryotherapy. The prostatectomy studies were further divided by surgical procedure. Of these, three studies were reports of standard (not nerve-sparing) prostatectomy. In six studies it was not indicated what type of surgical procedure was used. Of the studies in which a nerve-sparing procedure was used, eight did not differentiate between unilateral or bilateral procedures, two were comparisons of unilateral and bilateral procedures, two were comparisons of the nerve-sparing technique in general with standard prostatectomy, and two compared unilateral, bilateral, and standard procedures. Because of the small number of articles on cryotherapy they were dropped from further analysis.

There was a range across the reviewed studies in the rigor of sexual assessment. Eighteen studies used chart reviews, questionnaires were used in 5 studies, interview data in 8 studies, in 2 studies physiologic measures of erectile function were used in addition to interview data, 1 study presented data from a survey

TABLE 1 Summary of Studies Used in Meta-Analysis^a

Study	Treatment	Type of Surgery	No. of Subjects ^b	Age range (yrs) (mean) ^b	Ratio ^c
Bagshaw et al. (1988)	Radiotherapy		914	35-86 (63.4)	375/434
Bahn et al. (1995)	Cryosurgery		130	51-80 (67)	9/27
Banker (1988)	Radiotherapy		100		45/85
Bergman et al. (1984)	Radiotherapy		36	55-73 (66.3)	9/12
Braslis et al. (1993)	Surgery	Not specified	36		3/32
Catalona and Basler (1993)	Surgery	Nerve-sparing	295		173/295
Drago et al. (1992)	Surgery	Nerve-sparing	528	37-75 (64)	100/151
Finkle and Taylor (1981)	Surgery	Standard	16	(61.9)	6/12
Finkle and Williams (1985)	Surgery	Nerve-sparing and standard	41		8/35
Forman et al. (1985)	Radiotherapy		240	51.5-86 (67.5)	60/105
Fowler et al. (1993)	Surgery	Not specified	757		269/689
Fowler et al. (1987)	Surgery	Nerve-sparing and standard	56		16/34
Frazier et al. (1992)	Surgery	Nerve-sparing	173	44-79 (65)	17/22
Goldstein et al. (1984)	Radiotherapy		23	(65)	3/15
Hauri et al. (1989)	Surgery	Nerve-sparing	60		23/47
Helgason et al. (1995)	Radiotherapy	. 0	53		18/35
Jonler et al. (1994)	Surgery	Nerve-sparing	86	49-75 (64)	8/72
Jonler et al. (1994)	Radiotherapy		98	52-74	11/68
Leandri et al. (1992)	Surgery	Nerve-sparing	620	45-84 (68)	59/106
Lim et al. (1995)	Radiotherapy and surgery	Not specified	135		21/46 radiotherapy 2/73 surgery
Leibel et al. (1994)	Radiotherapy		324	52-82	241/280
Loh et al. (1971)	Radiotherapy		36	49-79 (65.5)	3/19
Mameghan et al. (1991)	Radiotherapy		218	45-87	23/42
Mittal (1985)	Radiotherapy		6		4/6
Murphy et al. (1994)	Surgery	Not specified	2122	55-79	153/1059
Onik et al. (1993)	Cryosurgery	•	55		5/14
Pedersen and Herder (1993)	Surgery	Nerve-sparing	182	44-76 (64.2)	24/126
Perez et al. (1988)	Radiotherapy		577		128/210
Pontes et al. (1986)	Surgery	Standard	45		13/35
Quinlan et al. (1991)	Surgery	Nerve-sparing	600		342/503
Rannikko and Salo (1990)	Surgery	Nerve-sparing	68	53-75 (65)	11/29
Ritchie et al. (1989)	Surgery	Nerve-sparing	100		19/98
Shipley et al. (1988)	Radiotherapy	. 0	370		34/54
Sole-Balcells et al. (1992)	Surgery	Not specified	79	50-75 (62.9)	13.33
Spengler (1983)	Surgery	Not specified	32	52-73	12/22
Telang et al. (1992)	Surgery	Nerve-sparing	100	52-74 (66)	35/61
van Heeringen et al. (1988)	Radiotherapy	1 0	18	57-82	9/12
Walsh and Donker (1982)	Surgery	Standard	31	45-68 (60)	5/31
Weldon and Tavel (1988)	Surgery	Nerve-sparing	16	51-73	5/9
Zinreich et al. (1990)	Radiotherapy		27	52-80 (67.7)	4/8

^a References for articles are available from the corresponding author.

of hospitals, and in 1 study the method of sexual assessment was not specified.

Age data such as the mean or range for the entire sample investigated was presented in most studies. The authors' interest was in patients who were known to have normal erectile functioning before treatment, therefore, there were some studies from which preand posttreatment data on erectile functioning was

available for only part of the sample. In many of these cases, the mean age or age range of the subset of interest could not be determined because age figures were given only for the entire sample. Only four studies reported mean ages for patients with normal erectile functioning both prior to and after treatment. Although the mean ages are consistently lower for the group of patients who maintained normal erectile

^b For entire sample.

^c Number with normal erectile functioning after treatment/number with normal erectile functioning before treatment.

functioning than for those who lost erectile functioning, this sample was too small for analysis.

The definitions of erectile functioning also varied across studies, and were not specified in 19 studies. A definition that corresponded with that of the authors was specified in 15 of the studies. Stricter criteria was imposed in four of these studies, extending the definition to include intercourse to either ejaculation or orgasm. Normal erectile functioning was defined in one study as the ability to have a maintainable erection, and as an erection sufficient for ejaculation in one other study. It was defined in terms of scale scores in two studies and by physiologic measures in one study. One study provided a definition of erectile dysfunction rather than a definition of normal erectile function.

In this analysis, the authors entered the data from each study for men reported to have normal erectile function by the definition provided in that study, or men reported to be "potent" for which no definition was provided. "Potent" men were assumed to have normal erectile function. In studies in which results were reported for varying degrees of sexual functioning, such as fully or partially potent, the authors regarded the "partially potent" men as having erectile dysfunctions and used the data for "fully potent" patients only. This was done because it could not be determined that "partially potent" men were capable of intercourse.

In terms of sexual assessment times, the current study is also comprised of a broad range of reports with an absolute range of 3 months to approximately 16 years after treatment. The assessment times reported in 2 studies ranged from 3 to 6 months after treatment, from 6 to 12 months after treatment in 10 studies, and more than 1 year after treatment in 8 studies. A broad range of assessment times, reported in months, of up to 75 months after treatment was reported in 10 of the studies. A similarly broad range, reported in years, was found in an additional 3 studies, with results reported for up to 16 years after treatment. Sexual assessment times were not specified in the remaining seven studies. In studies in which sexual functioning data were presented for more than 1 assessment time, the authors selected the time period that was closest to 1 year after treatment. This allowed for the greatest number of studies to be comparable in terms of follow-up times. A 1-year assessment time is also a commonly accepted length of time to gather stable sexual functioning data.

Data Analysis

A simple logistic regression model was used to examine the effect of treatment method (radiotherapy or prostatectomy) in predicting the probability of normal

erectile functioning after treatment. Logistic regression does not require any distributional assumptions in predicting the probability of success (e.g., normal erectile functioning) as a function of treatment. 11,12 Based on this model, the probability of maintaining normal erectile function after radiotherapy was 0.69 (95% confidence interval [CI], 0.661, 0.709) and was 0.42 (95% CI, 0.400, 0.433) after prostatectomy. The difference between these two probabilities is highly significant (P < 0.0001). These probabilities were arrived at using the logistic regression coefficient of -1.117 (95% CI, 0.287, 0.372) and a constant of 0.780 (95% CI, 1.95, 0.44). The regression coefficient is negative when radiotherapy is coded 0 and surgery is coded 1. More detailed analyses, such as examining the relative effects of different surgical procedures and effects of treatment by age or tumor stage, were not possible because the sample size was insufficient.

DISCUSSION

Erectile dysfunction is a common and aversive complication after treatment for prostate carcinoma. Accurate estimates of this complication rate are important in helping patients select the best treatment. This analysis is an attempt to provide such an estimate based on the existing literature for radiotherapy and radical prostatectomy, the two most common treatments for patients with prostate carcinoma. Subjecting the results of 40 research studies to a meta-analysis, it was found that the probability of maintaining normal erectile function after radiotherapy was significantly higher than after radical prostatectomy, (P = 0.69 and 0.42, respectively).

Wasson et al.⁹ conducted a meta-analysis of treatment outcomes in prostate carcinoma patients. They reported the probability of retaining erectile functioning after radiotherapy to be 0.586 compared with 0.154 after surgery. This compared with the current study findings wherein the probability of maintaining normal erectile function is significantly higher after radiotherapy than after surgery.

Some explanations can be offered for the differences in the authors' estimates compared with those of Wasson et al. First, the same set of studies were not analyzed. Wasson et al. conducted their analysis on a group of studies published between 1966 and 1991 whereas the current set of data is comprised of studies published from 1971 to 1995. This set contained a full 15 studies published since the analysis by Wasson et al., and thus is more likely to reflect current trends. Second, the set of articles analyzed in the current study includes 14 studies that contained at least some data for nerve-sparing radical prostatectomy, 7 of which were published after 1991. These studies gen-

erally vielded higher rates of maintained normal erectile functioning. Wasson et al.'s estimate for surgery (15.4% functional) may have been low because of the recent increase in such reports and may be less reflective of current surgical practice than the current study estimate. Third, in comparing the results from the radiotherapy studies, Wasson et al. reported a lower rate of maintaining normal erectile function (58.6%) than the authors' estimate of 69%. This difference may be at least partly a function of the authors' selecting for analysis only men with normal sexual function prior to treatment. Patients who receive radiotherapy for prostate carcinoma are generally at an age at which there is a high incidence of erectile dysfunction prior to treatment. Because the analysis of Wasson et al. did not exclude men who were already experiencing sexual dysfunction prior to radiotherapy, one would expect their rate of postradiotherapy erectile dysfunction to be higher than the one presented here.

The authors believed that the criterion of pretreatment erectile functioning was the most important inclusion criterion for this study in terms of providing meaningful end comparisons. However, it was also a limitation in that of approximately 600 articles reviewed, only 40 met this criterion. Erectile dysfunctions can be attributed to many causes and unless the pretreatment status is known, there is an implicit assumption that posttreatment dysfunctions are attributed to the prostate carcinoma treatment. This may be an erroneous assumption in many cases, which possibly results in inflated estimates of treatment-induced erectile dysfunction. Thus it should be recognized that the authors may have inadvertently selected out the youngest prostate carcinoma patients for comparison by imposing this criterion. Unfortunately due to the limited data the authors had, it was impossible to test this assumption. However, the authors believe they gained a more accurate picture of one complication, at least for that selected group.

Related to the issue of pretreatment erectile functioning is the issue of definition for erectile function. Helgason et al.¹³ discussed the difficulties that arise due to the lack of a clear and agreed upon definition for erectile functioning and provided examples of the variety of definitions in the literature. There may be a tendency to overestimate normal sexual functioning in the literature due to a lack of rigor regarding definitions. As previously indicated, the broad range of definitions of erectile functioning in those studies that do define it is problematic. This results in comparisons being made between levels of function that are known to differ at the outset. In addition, different degrees of erectile functioning are referred to in many studies. When this is the case, and no operational definition

of erectile function/dysfunction is provided, it is impossible to determine whether or not some patients included in the current study as having normal function were in fact unable to have erections sufficient for intercourse. In the hopes of offsetting the limitations imposed by lack of definitions, the authors selected a strict definition of erectile functioning. In doing so, they may have erred on the side of overestimating erectile dysfunction. Conversely, the authors believe that this compensates for the lack of clear definitions in many studies. As such, they emphasize the importance of defining such variables as normal erectile functioning or erectile dysfunction so that comparisons of this nature can be made with greater confidence. One suggestion is to use the standardized definition for erectile dysfunction set out in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM IV)¹⁴, because it is conceptually and operationally defined, based on empiric work, and readily available. This definition takes into consideration an assessment of the physiologic, psychologic, and interpersonal dimensions of sexual functioning.

Another factor that imposed limits on the authors' ability to combine the results of many previously published studies is the assessment times. The broad range of follow-up times reported makes some comparisons difficult, especially when comparing the results of radiotherapy and prostatectomy. Goldstein et al. 15 and van Heeringen et al. 16 argued that radiationinduced erectile dysfunction gradually develops after treatment and, once present, is virtually irreversible. In contrast, erectile dysfunction that is observed immediately after prostatectomy is associated with a gradual improvement.¹⁷ Given these contrasting patterns, 1 year after treatment appears to be the best compromise for comparisons between these 2 treatment methods. It is generally accepted that after 1 year, either the effects of radiotherapy are expected to have been felt, or a recovery from surgery is expected to have been achieved. An argument can be made for a longer time span but with increasing elapsed time comes an increasing probability of introducing more intervening factors. For example, increasing age is associated with an increased probability of erectile dysfunction.10

In addition to the above limitations with comparisons, the small number of studies limited the authors from conducting many finer grained analyses that they had planned on performing. Middleton et al. ¹⁸ recently conducted a comprehensive literature review of complications after treatment for prostate carcinoma and concluded that the data were insufficient for metaanalysis. Although the authors agree that the data are

sparse and of poor quality, they believe data is sufficiently strong to conduct the presented basic analysis. In the current study, homogeneity of data was ensured by imposing strict inclusion criteria and establishing a common definition of erectile functioning and assessment times. This has allowed the use of a predictive model of analysis as opposed to a descriptive one as reported by Middleton et al.¹⁸ The authors' disappointment was the lack of data with which to perform more detailed analyses. The authors would have preferred to examine the relative effects of treatment by age and disease stage because there are many reasons to believe that these variables would be helpful in predicting outcome.

One final point of discussion is a defense of examination of all the prostatectomy data as a single group, regardless of the surgical procedure. As mentioned earlier, the paucity of studies with data of sufficient quality for an analysis of different surgical procedures prevented the authors from being able to do so. Although it is preferable to differentiate surgical procedures, combining the data for different surgical procedures may still provide a helpful estimate in terms of patient decision-making. The exact surgical procedure sometimes cannot be guaranteed in advance of surgery when the full extent of the tumor and the amount of excision necessary can only be determined during the surgery. In these cases it is not known before surgery that a nerve-sparing procedure will take place or that it will be successful. In this sense, many men cannot ultimately choose to have nerve-sparing surgery. Therefore, the number that reflects radical prostatectomy results in general, is a useful estimate. However, in those cases, in which it is known prior to surgery that the nerves cannot be spared, the authors' combined estimate may not be appropriate. It may suggest a better likelihood of maintaining erectile functioning than can be expected after standard surgery.

CONCLUSIONS

In this analysis it was determined that radiotherapy is superior to radical prostatectomy in terms of a reduced rate of treatment-induced erectile dysfunction. The estimates of erectile dysfunction reported in this article were calculated using a meta-analytic method that combines the results of numerous studies. As such, the authors believe that these estimates are better and can be interpreted with more confidence than the results of any single case series. What distinguishes this analysis from others is that pretreatment erectile functioning was taken into consideration so that the reported outcomes more confidently reflect treatment-induced erectile difficulties.

In this article, some recommendations for improving research methodology were discussed. First is the need to report pretreatment erectile functioning status of patients by age and stage of cancer. It is the pretreatment status that provides a baseline for accurate interpretation of posttreatment complications. Second is the need for a standardized definition of erectile dysfunction. One suggestion is to adopt the definition presented in the DSM IV. 14 A standardized definition allows for better comparisons between studies. For similar reasons, the authors' third recommendation is for a standard follow-up time of 1 year after treatment. The authors believe these recommendations are timely because the field of prostate carcinoma treatment is rapidly developing. In particular, four new procedures are under investigation: cryotherapy, neoadjuvant hormones, brachytherapy, and three-dimensional conformal radiotherapy. If the above recommendations are taken into consideration with emerging work, better quality data will be produced for better patient decision-making and formulation of clinical guide-

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