

Prostate cancer III

Early prostate cancer: clinical decision-making

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Prostate cancer is one of the most common malignant diseases for which health-care intervention is sought worldwide, and in many developed countries it is the most common. Some patients with early-stage prostate cancer, especially those who are elderly and have comorbidities, can be observed without treatment. Surgery (radical prostatectomy) and radiotherapy (external-beam radiotherapy, brachytherapy, or both) are the most widely accepted curative options for patients with early-stage disease who need intervention. All these local treatments have been refined, resulting in comparable cure rates; however, they all have different side-effect profiles. Adjuvant systemic treatments (hormones or chemotherapy), which are effective for advanced-stage disease, might have a greater role in early-stage disease. Selecting the best option for individuals from the available options is challenging—the decision on whether and how to treat is based on many disease and patient factors. Here, we review the major treatment options, discuss their relative advantages and disadvantages, and provide a general approach to management of patients with early-stage prostate cancer.

Prostate cancer is among the most common malignant diseases for which health-care intervention is sought worldwide, and in many developed countries it is the most common non-cutaneous malignant disease.^{1,2} Widespread screening, typically with digital rectal examination and measurement of serum prostate-specific antigen (PSA), means that prostate cancer can be diagnosed at an earlier stage than was previously possible.³ Other reviews in this *Lancet* series address the epidemiological, screening, pathological, and molecular efforts that will affect future diagnosis of prostate cancer. Here, we focus on general management of patients diagnosed with early prostate cancer.

Because screening has meant that more and more patients are presenting with earlier-stage prostate cancer than they were previously, we restrict our review to early-stage prostate cancer. Thus, we assume that metastatic disease, lymph-node positive disease, and locally advanced disease have been ruled out in these patients by physical examination, laboratory studies, and imaging tests such as bone scan,^{4,5} cross-sectional imaging (CT/MRI),^{6,7} and antibody-based imaging (eg, radiolabelled monoclonal antibodies^{8,9}).

Management options for early-stage prostate cancer can be grouped into four broad categories—observation, hormone therapy, surgery, and radiotherapy. Observation is a reasonable alternative for some patients with early disease, usually those who are elderly and have important comorbidities. Hormone therapy, although effective in the adjuvant setting for some patients with early-stage disease, can also be used on its own as an alternative to observation. At present the two main treatments being advocated are surgery and radiotherapy, which have both undergone major changes. Other local methods are effective and are tolerated for early-stage prostate cancer; however, because they have not been as widely accepted (such as cryotherapy¹⁰) or are too new to be assessed (such as high-

intensity focused ultrasound and radiofrequency interstitial tumour ablation^{11,12}), they are not included in this review.

Treatment options

Table 1 shows reported biochemical control results for radical prostatectomy, external-beam radiotherapy, and brachytherapy (with or without external-beam radiotherapy) in several large series. The survival differences in this table should be interpreted with caution since they could be more a reflection of patient selection than of the effectiveness of treatment. Specifically, although all of the series in this table are for early-stage prostate cancer, patients in the external-beam radiotherapy series tend to be older and have more advanced disease (due in part to limitations of clinical staging) than are patients in the corresponding prostatectomy series. Also, the patients reported in many of the brachytherapy series tend to have more favourable outlooks than do those in either the prostatectomy or external-beam radiotherapy series. Finally, different biochemical control definitions are used for the different local control modalities.

Search strategy and selection criteria

We selected the references in this review using the following criteria and methods. In all cases, we searched PubMed, with the search restricted to articles reported in English. For topics in the introduction that were not described in depth in the article, we selected review articles on the given subject from journals that have a high impact factor by merging the search terms “prostate cancer review” with the given subject term (eg, “high intensity focused ultrasound”). In the treatment options section, we selected the largest follow-up series in the highest impact clinical journals available during the PSA era (ie, patient data reported from 1987 onwards using PSA as the clinical endpoint). The keywords “prostate cancer” were merged with, for each appropriate section, “observation”, “radical prostatectomy”, “external beam radiotherapy”, “brachytherapy”, or “hormone therapy”. We used the largest and most recent reports from these individual searches to construct table 1. When comparing the different treatments in the recommendations section, we merged the treatment terms with the word “randomized” or “match paired” (eg, “prostate cancer external beam radiotherapy radical prostatectomy randomized”). We used English and American spellings.

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	Patients	Endpoint	10-year result
Radical retropubic prostatectomy			
Mayo Clinic ¹³	3170	PSA <2 µg/L	52%
Washington University ¹⁴	925	PSA <6 µg/L	61%
Johns Hopkins ¹⁵	2404	PSA <2 µg/L	74%
S Carolina/Baylor ¹⁶	1000	PSA <4 µg/L	75%
External-beam radiotherapy			
MGH ¹⁷	1396	PSA control*	42%
MD Anderson ¹⁸	643	PSA control*	61%†
Fox Chase ¹⁹	408	PSA control‡	59%†
Pooled-institution analysis ²⁰	1218	PSA control‡	68%
Low-dose brachytherapy			
Northwest Prostate			
Institute ²¹	229	PSA control§	70%
Arizona ²²	695	PSA control§	71%¶
Seattle (palladium-103 sources) ²³	233	PSA control‡	83%
Seattle (iodine-125 sources) ²⁴	125	PSA control‡	85%

*Defined as PSA <10 µg/L and absence of two consecutive rises in PSA after nadir. †8-year results. ‡Defined as absence of two consecutive rises in PSA after nadir. §Using consensus definition of biochemical failure as three consecutive PSA rises after nadir. ¶5-year results. ||9-year results.

Table 1: Results for early-stage prostate cancer

Observation

Observation is frequently referred to as watchful waiting. Such a management plan is rarely appropriate for localised malignant disease at anatomical sites other than the prostate. However, since the natural history of prostate cancer is long and many patients diagnosed with prostate cancer are elderly, the decision to offer intervention must be weighed in the context of the patient's life expectancy and existing comorbidities. The decision must also take into account the deleterious effects of treatment as compared with those of tumour growth and progression. Increased awareness of the disease and implementation of screening programmes have introduced a lead-time bias, especially for patients with early-stage disease or on incidental diagnosis (prostate cancer is frequently not diagnosed until autopsy and in these cases is of no clinical significance). Although cancer in the prostate will continue to grow if not treated, the progression, which can in part be predicted by histological grade, must be balanced with the patient's age and life expectancy.

Observation might be appropriate for patients with low-grade cancer and a short life expectancy,^{26–41} but those with intermediate-grade and high-grade tumours have a substantial risk of early local failure if an intervention is not undertaken. The probability of dying from prostate cancer as a function of disease grade, and how this relative probability weighs against age-matched death in the general population has been carefully investigated.³⁷ This report³⁷ and others,^{27,29,30,35} in combination with the patient's PSA history, can assist in individualising the decision to treat the prostate cancer.

Other patients who could be observed are those incidentally diagnosed with prostate cancer at the time of transurethral resection of the prostate (most commonly for benign prostatic hypertrophy) and found to have low-grade, low-volume disease.³⁹

At present, no consensus exists on the patient population to be observed—the decision must rely on the disease status, patient status, and reliability and desire of the patient to proceed with a plan of diligent follow-up. Preliminary efforts have been undertaken^{40,41} to develop criteria on the basis of tumour grade, pretreatment PSA, PSA doubling time, PSA concentration, and number of positive biopsy samples. These ongoing efforts will probably result in different appropriateness criteria for administration of radical treatment in different prostate

cancer subpopulations, since life expectancies for individual subpopulations are different. Recommendations for patients presenting with identical disease factors and comorbidities vary geographically. Health-care providers in the USA frequently recommend potentially curative local treatment, whereas providers in Europe (particularly Scandinavia) often recommend observation.

Radical prostatectomy

Radical prostatectomy has been the standard against which other local treatments are compared. This procedure has been refined, resulting in high cure rates with decreased morbidity in appropriately selected patients. Furthermore, this reduction in morbidity has not resulted in reduced disease control. Radical prostatectomy is a collective term for a family of procedures and can be broadly separated into the retropubic and transperineal approaches. For patients for whom lymph-node sampling is indicated, radical retropubic prostatectomy⁴² has an advantage in that the lymph nodes can be dissected and the prostate removed in a single incision, whereas radical perineal prostatectomy requires separate incisions for the lymph-node dissection and prostatectomy. Minimally invasive techniques such as laparoscopic prostatectomy^{43,44} have not yet achieved widespread use, and their indications and limitations have not been systematically identified. We restrict our discussion to radical retropubic prostatectomy, which is the most widely done and reported surgical treatment of prostate cancer.^{13–16,45–56}

Advantages

Pathological assessment of disease—Surgery allows for en-bloc assessment of extracapsular extension, seminal vesicle invasion, and extension to surrounding structures. Also, the decision to spare nerve bundles unilaterally or bilaterally can often be made during surgery, increasing the probability of potency preservation without sacrificing a complete resection. The presence of positive margins can also be assessed, and these margins, together with other pathological variables can guide adjuvant local therapy or systemic therapy.^{57–59} Pathological assessment of disease results in frequent upstaging. This difference in pathologically-staged disease as compared with clinically-staged disease must be carefully considered when comparing prostatectomy with other methods of treatment.

Biochemical follow-up is less ambiguous for radical prostatectomy than for radiotherapy—PSA is expected to be undetectable after prostatectomy, with any rise after an undetectable PSA nadir being suspicious for local recurrence. This contrasts with radiotherapeutic approaches in which the prostate is in place, the healthy prostate continues to secrete PSA, and benign entities such as prostatitis, trauma, and digital-rectal examination can increase the PSA, requiring the observation of a trend of increases to declare biochemical failure.⁶⁰

The potential for salvage therapy with radiation—Adjuvant radiation, although somewhat morbid after prostatectomy, has been used with success^{25,61} (as measured by biochemical control) for patients for whom high-risk prognostic features warrant immediate adjuvant treatment and for whom a local or biochemical recurrence occurs after prostatectomy. This is by contrast with salvage prostatectomy after radiotherapy, which, although increasingly the subject of study, is often quite technically challenging and morbid due to postradiotherapy fibrosis in the operative setting. Although radiotherapy continues to be assessed after prostatectomy, no survival benefit to this approach has been recorded.

Disadvantages

Urinary incontinence—Because radical prostatectomy requires an anastomosis between the bladder and the urethra distal to the prostate, urinary incontinence can develop.^{62–65} A comprehensive definition of urinary incontinence does not exist, with definitions ranging from the requirement of urinary pads to the occurrence of urinary dribbling during stressful activity. Although results of studies have shown that patients can adapt to adverse outcomes of surgery, patient responses to the effect on quality of life from these adverse outcomes, particularly incontinence, vary widely.⁶⁵ In any event, incidence of incontinence is quite high immediately after surgery and decreases with time, so that 2–5% of patients have severe incontinence⁶³ 6 months or longer after surgery.

Impotence—Potency after treatment (prostatectomy or radiotherapy) is usually defined as the ability to have an erection sufficient for vaginal penetration. Often, a patient can be considered potent after treatment but have impairment as compared with his performance before therapy. Diminished or absent potency can occur after surgery because neurovascular bundles are manipulated or severed.^{62,63,66–71} The true incidence of impotence is difficult to measure accurately because of differences in physician-based and patient-based assessment of potency impairment. New surgical approaches that spare the neurovascular bundle or bundles through unilateral or bilateral nerve-sparing techniques⁴⁵ have reduced impotence rates. The results have been quite variable in the reported series, with potency preservation ranging from 10% to 90% (with an average of 30%). Some are concerned about residual prostate cancer as a result of the nerve-sparing technique; however, to date, the margin positivity and the survival and recurrence rates at 5 years seem to be similar between the conventional and nerve-sparing procedures.⁷²

Operative risk and recovery—Although mortality has decreased from a large proportion in the older series to a negligible rate in the modern series, prostatectomy is a major surgical procedure and requires the patient to be able to tolerate the procedure without substantial risk. Additionally, by comparison with radiation approaches, prostatectomy generally has a longer recovery period with restricted activities and loss of stamina.

External-beam radiotherapy

External-beam radiotherapy involves daily treatment for 7–8 weeks. It has been studied extensively for early-stage prostate cancer,^{17–20,73–81} and, like radical prostatectomy, has undergone a technological revolution, with results of many series showing survival comparable to that of surgery, but with a different side-effect profile. The simple four-field technique evolved to conformal radiotherapy,⁷⁸ which increased the precision by which the high dose conforms to the target volume. This greater precision of delivery allowed for increased doses to the prostate without any increase in complications, resulting in improved cure rates.⁷⁹ Intensity-modulated radiotherapy, which is the newest way to plan and deliver external-beam radiotherapy, facilitates further dose escalation while keeping complications to a minimum.^{80,81}

Advantages

Availability to a wide spectrum of patients with prostate cancer—External beam radiotherapy is non-invasive, has no anaesthesia risk, and can be offered to many patients who would not be able to tolerate either prostatectomy or brachytherapy.

Few urinary toxic effects—Although low-grade urinary side-effects occur frequently during external-beam radiotherapy,^{82–86} high-grade urinary toxicity, both acute and chronic, is lower than that with prostatectomy or brachytherapy. In particular, the incontinence rate is lower than that for prostatectomy, and the urinary retention rate is lower than that for brachytherapy (as discussed below). The pattern of urinary toxic effects also differs, with the uncommon toxic effects of external-beam radiotherapy mainly manifesting as increased urgency, frequency, and nocturia, which can often be well managed with α -adrenergic blockade⁸⁶ or other similar conservative measures.

Potency preservation—Potency preservation rates of external-beam radiotherapy are much higher than those of prostatectomy that do not spare the nerves,^{82–84,87–89} and are much the same or slightly higher than in unilateral or bilateral nerve-sparing prostatectomy (40–50% in the reported series). Although neurovascular bundles receive radiation, the nerves are not physically manipulated or severed as in the case of a prostatectomy, resulting in higher potency preservation. Erectile dysfunction after radiotherapy is often responsive to sildenafil.^{88,89}

Disadvantages

Clinical staging—Although imaging studies^{4–9} can assist in determining extraprostatic spread and spread to bones, many patients are up-staged at the time of prostatectomy.^{57–59} External-beam radiotherapy, which relies on clinical staging, requires foregoing this pathological information which could have allowed for the tailoring of adjuvant locoregional or systemic therapy. Clinical staging will have lower survival rates because higher-stage (eg, node-positive) patients are included who are not detected by the clinical and imaging workup.

Rectal complications—Because the prostate is close to the rectum, a therapeutic dose cannot be delivered to the prostate without also delivering some dose to the rectum. This rectal irradiation can result in early and late rectal complications.^{82,83,90} This difficulty is compounded by organ motion⁹¹—since the prostate position is sensitive to bladder and rectal filling, the radiation planning process is often not adaptive to this prostate motion and a higher than intended radiation dose to the rectum is delivered. Although steps have been taken (such as fiducial seed placement,⁹² ultrasound localisation,⁹³ and intensity-modulated radiation therapy^{80,81}) that reduce rectal complications, the rectal toxicity rates for external-beam radiotherapy remain higher than that for brachytherapy alone, and much higher than the near-negligible rate for prostatectomy. Although rectal bleeding is not uncommon after external-beam radiotherapy, severe rectal bleeding occurs rarely (1–2%^{82,83,90}) and can usually be treated with cauterisation, formalin therapy, or other measures.⁹⁴

Brachytherapy

Brachytherapy, which involves placement of radioactive sources directly into the region of interest, is used in many centres. As a treatment for early-stage prostate cancer, it now achieves disease-free survival comparable with those of radical prostatectomy and external-beam radiotherapy, with a different side-effect profile.

Early efforts with brachytherapy produced disappointing results,⁹⁵ probably because of poor techniques. In the mid-1980s, brachytherapy resurged mainly because of advances in transrectal ultrasound, fluoroscopy, computer-based preplanning, and stabilisation equipment that made radioactive source

placement much more precise, both in low-dose rate^{21–24,96–100} and high-dose rate¹⁰¹ settings. Although both these techniques involve placement of radioactive sources transperineally under transrectal ultrasound guidance, in low-dose rate brachytherapy the radioactive sources (typically low-energy iodine-125 or palladium-103 seeds) are placed permanently, whereas in high-dose rate brachytherapy, the radioactive source (typically high-energy iridium-192) is in place only temporarily. Because long follow-up exists for permanent sources, the discussion will be restricted to low-dose rate brachytherapy.

Advantages

Localised dose distribution—Compared with external-beam radiotherapy, a more localised dose distribution is possible, reducing the dose to surrounding structures. With external-beam radiotherapy the beam needs to traverse normal structures (such as the bladder and rectum) to reach the prostate—with brachytherapy the sources are inserted directly into the prostate, and the overall dose-distribution consequently has a sharp fall-off. This highly conformal dose distribution results in a lower incidence of rectal^{102,103} and neurovascular side-effects (such as impotence)^{104,105} than with external-beam radiotherapy.

Potency preservation—Compared with radical prostatectomy, brachytherapy has better potency preservation,^{104,105} due, as in external-beam radiotherapy, to the absence of physical manipulation or severance of neurovascular bundles. For this reason, as in external-beam radiotherapy, erectile dysfunction is usually responsive to sildenafil.

Available to a large group of patients—Brachytherapy is available to slightly more patients than is prostatectomy—although generally an operating room procedure, brachytherapy is a shorter procedure with a shorter recovery time than prostatectomy.

Disadvantages

Urinary toxic effects—The trauma of needle placement into the prostate (especially a large prostate, which requires many sources) can, in the acute setting,¹⁰⁶ result in prostate oedema and cause urinary hesitancy, frequency, or retention requiring a temporary catheter—these effects can often be prevented or ameliorated by use of α -adrenergic blockade and corticosteroids in the preoperative and postoperative periods. In the chronic setting,¹⁰⁷ there is also a small risk of urinary stricture, resulting in the need for surgical intervention or permanent urinary catheter placement.

Anatomical restrictions—Pubic arch interference (interference of transperineal needle placement due to bony obstruction) can result from a large prostate or from individual patient anatomy.¹⁰⁸ In this situation, hormonal cytorreduction, with its own set of complications (discussed below), can be done to shrink the prostate to make it more amenable to brachytherapy.

Follow-up uncertainties—In addition to the follow-up issues about radiotherapy raised during discussion of prostatectomy follow-up above, brachytherapy has a well-documented PSA rebound (the cause of which is not known) that takes place 1–2 years after the procedure,¹⁰⁹ also making follow-up PSAs difficult to interpret.

Dose distribution inadequacies—Early brachytherapy efforts⁹⁵ were probably unsuccessful because they did not account for the anisotropy (dose asymmetry) of the radioactive seeds. Even with today's treatment planning, the dosimetry can differ greatly between the planned implantation and the implantation actually done, because of seed anisotropy and seed migration. Furthermore,

although the brachytherapy dose distribution is highly conformal (which, as discussed above, has implications for dose reduction to surrounding healthy structures), the dose within the prostate itself can be quite variable. The effect of these potential dosimetric inadequacies remains to be seen—some investigators have suggested that for cases of inadequate dose distributions or for cases of high-risk disease, a small dose of external-beam radiotherapy should be added.^{21–24,96–100} Although adjuvant external-beam radiotherapy in this manner is done quite frequently, the effectiveness and basis for this course of external-beam radiotherapy in improving survival has not yet been shown.⁹⁷

Hormone therapy

The prostate is a hormone-responsive organ, and this observation has been the basis for interventions for prostate cancer that either reduce serum testosterone or block the actions of this hormone.¹¹⁰ Hormone therapy was previously accomplished mainly by orchiectomy, which has now been mostly replaced with chemical castration. Many hormonal agents work at different points along the hormone axis to inhibit production of or block the action of testosterone. The broad classes of agents are oestrogens, progestagens, gonadotropin-releasing hormone analogues, adrenal enzyme synthesis inhibitors, and antiandrogens. A common regimen is combination of an antiandrogen with a gonadotropin-releasing hormone analogue to provide total blockade of androgens. Hormones can be delivered neoadjuvantly (before local therapy), adjuvantly (immediately after local therapy), or for salvage (for biochemical or clinical failure after local therapy). Although hormones can delay a local intervention for prostate cancer and be used as an alternative to observation for selected patients with comorbidities, they must be combined with local intervention to achieve a long-term cure.

Hormones have been used with prostatectomy with limited success.^{111–113} Although some reports have shown an improvement in the margin status at the time of prostatectomy with neoadjuvant hormone therapy, an improvement in survival endpoints for early-stage prostate cancer has not yet been shown.

Hormones improve survival results when combined with radiotherapy, probably because of their different mechanism of action—they can independently destroy prostate cancer and sensitise the tumour to radiation. The benefit of hormone therapy in addition to external-beam radiotherapy in intermediate-stage and locally-advanced disease has been shown in many randomised studies;^{114–117} however, a meta-analysis for these populations (which also included metastatic disease) showed only a nominal benefit.¹¹⁸ The true benefit of hormones in patients with early-stage disease remains to be determined. The outcome of randomised trials are pending, but results of retrospective reviews^{119,120} suggest improvement in selected patients with early-stage disease who have one or more poor prognostic factors (high-grade disease, high PSA, or both). If this improvement is confirmed, hormones will probably be used much more in patients with early-stage disease.

Common side-effects of hormones are hot flushes, loss of libido or erectile function, weight gain, gynaecomastia, liver inflammation, and osteoporosis.¹¹⁰ These side-effects, although usually short-lived and mild for the short-course hormone therapy typically used for early-stage prostate cancer (as opposed to the long-course hormone therapy advocated for advanced-stage disease), must still be balanced against the benefit.

Other systemic agents have an increasing role in metastatic and locally advanced disease¹²¹—however, the role of systemic agents in early-stage disease is still under investigation. Furthermore, the design of trials in this setting must consider the good prognosis of early-stage disease, the efficacy of hormones, and the side-effects of the investigational agents.

Recommendations

The controversies surrounding the decision of how best to manage early-stage prostate cancer are among the most intricate and intensely debated in all of clinical medicine and are unlikely to be resolved quickly. The controversy stems in part from specialty bias,^{122,123} from the fact that few randomised trials comparing treatments have been done, and from the many endpoints used. Survival or disease-free survival (as defined clinically or by PSA), and the many disadvantages described above must all be considered.

The few randomised trials that have been done have been criticised for biases in unbalanced treatment groups and outdated treatment techniques.¹²⁴ Randomised trials are difficult to implement in prostate cancer. The long natural history of early-stage prostate cancer requires many years of follow-up, during which the treatments being compared may have become obsolete. Also, diagnosis of prostate cancer at an increasingly earlier stage due to widespread PSA and digital rectal examination screening efforts carries the risk of introducing lead-time and length biases, and some patients might not require treatment.

Because there is little evidence from randomised trials comparing the different local control modalities, matched-pair analyses and retrospective analyses have been undertaken.^{125–129} In these reports, surgery, external-beam radiotherapy, and brachytherapy (with adjuvant external-beam radiotherapy used when indicated) have been shown to be equivalent treatment options for early-stage prostate cancer in the PSA era. Although the evidence lends support to the equivalent survival outcome of the different local control treatments, clinicians still have to decide whether and how to treat individual patients with prostate cancer. This issue has been approached systematically, but no consensus has been reached.^{130–132} The many factors that must be considered when selecting a management option can broadly be grouped into disease factors and patient factors.

Disease factors

The most commonly assessed disease-related factors include pretreatment PSA, histological grade, and tumour stage (as assessed by digital rectal examination). These three variables have been assessed systematically. In particular, the probability of organ-confined disease, extracapsular extension, seminal vesicle invasion, and lymph-node involvement as a function of the tumour stage, grade, and PSA have been carefully tabulated.⁵⁰ Nomograms have been devised on the probability of control with prostatectomy, external-beam radiotherapy, or brachytherapy, mostly based on these three disease factors.^{50,126}

The value of these variables in guiding treatment lies in assessing the probability of organ-confined disease that might be amenable to surgery or brachytherapy, or whether there is a high probability of seminal-vesicle invasion, extracapsular extension, or lymph-node invasion that dictates the need for adjuvant hormone therapy or external-beam radiotherapy, or both, to a margin around the prostate and seminal vesicles or regional lymph nodes. Although adjuvant external-beam radiotherapy can be

Site	Prostatectomy	External-beam radiotherapy	Brachytherapy	External-beam radiotherapy and brachytherapy
Rectal	+	+++	+	++
Sexual (impotence)	+++	++	+	++
Urinary				
Incontinence	+++	+	+	+
Retention	+	+	+++	+++

Increasing number of ++ indicates increasing complication rates.

Table 2: **Relative complication rates from local control treatments for prostate cancer**

added in this way, the risk of toxic effects, especially bowel and bladder complications, must be taken into consideration.

Patient factors

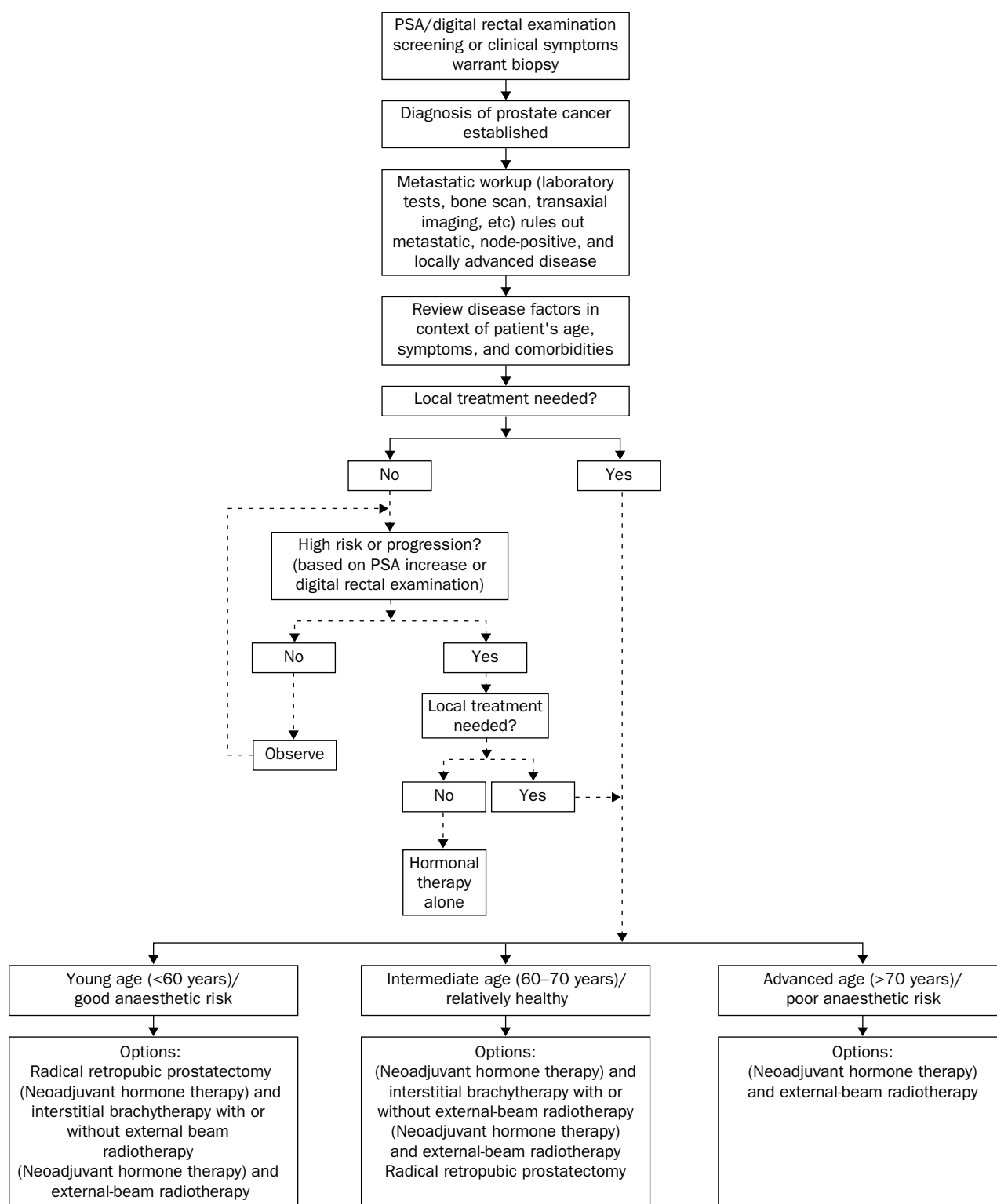
Patient factors relate to the age, comorbidity, erectile function, prostate size, and specific previous medical conditions (especially genitourinary and gastrointestinal problems). These factors can be used to help the patient decide on treatment or observation, and can be discussed in the context of the advantages and disadvantages of each of the individual treatment options. Perhaps the most important factor, however, is the weight¹³³ the individual patient places on the possible major complications (erectile, rectal, and urinary)^{134,135} of the various approaches. These results are summarised in table 2.

General methods

The balancing of disease and patient factors to arrive at a management decision in early-stage prostate cancer depends on the clinician's skill in responding to the wishes and concerns of the individual patient. That involves discussing the probable outcomes and possible complications of the treatment choices objectively and in detail.

The figure is a proposed algorithm for treatment of early-stage disease. After prostate cancer is diagnosed and after diagnostic workup has ruled out advanced or metastatic disease, the key decision is whether any local therapy is needed. If local therapy is not deemed necessary and disease progression is not a substantial risk, a plan of observation (watchful waiting) is undertaken. If disease progression is a risk, or if the disease progresses (based on PSA, digital rectal examination, or radiological workup) during observation, but local therapy is not deemed necessary, hormone therapy alone can be recommended. For patients for whom local therapy is necessary, a review of the disease and patient factors is undertaken, and three major groups are identified (figure). For the patients who are young or have a good anaesthetic risk, the treatment options are radical prostatectomy, brachytherapy (with or without neoadjuvant hormone therapy and with or without external-beam radiotherapy), and external-beam radiotherapy (with or without neoadjuvant hormone therapy). For patients who are of intermediate age and relatively healthy but not ideal candidates for prostatectomy, brachytherapy (with or without neoadjuvant hormone therapy and with or without external-beam radiotherapy) or external-beam radiotherapy (with or without neoadjuvant therapy) are preferred. Finally, for patients who are only able to tolerate non-invasive options, external-beam radiotherapy (with or without neoadjuvant hormone therapy) is preferred.

Controversies abound in management of early-stage prostate cancer, and this algorithm (figure) will change as new techniques and new outcome data become available.



Proposed treatment algorithm for early-stage prostate cancer

Locally advanced disease

Although the primary focus of this report is on early-stage disease, we provide a brief review of locally advanced non-metastatic disease. The definition of locally advanced disease varies, and generally includes patients who have disease penetrating through the prostatic capsule or invading a seminal vesicle on digital rectal examination. Incidence of locally advanced disease varies from population to population and consists of patients who are

either untouched by screening efforts (due to lack of access to medical care or to non-compliance with a prescribed course of screening) or have an unusually aggressive natural history (ie, disease growing rapidly between screening intervals).¹³⁶ Diagnostic workup is similar to that described above for early-stage disease, with the exception that locoregional imaging (ultrasound, CT, MRI)^{6,7} and distant (bone scan, serum alkaline phosphatase, chest radiograph)^{4,5} workups are absolutely

needed to assess the disease status. Some advocate a staging lymphadenectomy before undertaking any local therapy.¹³⁷ Management of locally advanced disease is, as for early-stage, somewhat controversial. Data from randomised trials have shown excellent results with surgery over radiotherapy for selected patients with locally advanced disease;^{137,138} however, for patients who have higher risk disease (by clinical examination, PSA, or grade), radiotherapy is the standard^{136,139} local modality. Additionally, adjuvant or neoadjuvant hormone therapy is regarded standard treatment in addition to radiotherapy for locally advanced disease.^{114–117} Because distant failure is a substantial cause of death, chemotherapy, both in neoadjuvant and adjuvant settings, and in the context of surgery and radiotherapy, continues to be examined.¹⁴⁰

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