Current Status of Neoadjuvant Therapy in Localized Prostate Cancer

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Prostate cancer is the most common cancer diagnosed in men in the United States [1]. With the increasing interest in early diagnosis and treatment of prostate cancer, 75 to 80% of men now present with localized prostate cancer [2]. In an effort to cure localized prostate cancer, the annual number of radical prostatectomies in the United States increased from 2,600 in 1984 to about 16,000 in 1990 [3]. With today's longer life expectancy, the impact of prostate cancer on morbidity and mortality is likely to increase even further within the next few years.

One can distinguish three subtypes among the patients with the clinical diagnosis of localized prostate cancer: approximately 25% of these men require no treatment at all, since their cancer will remain latent and asymptomatic; 40% can be cured with radical surgery alone because their disease is pathologically organ-confined, and the remaining 35% require additional treatment besides radical surgery since they appear to have residual tumor after surgery as a result of tumor extension beyond the prostatic capsule or microscopic metastases to pelvic lymph nodes [4]. Unfortunately, it remains difficult for the clinician to differentiate between these subtypes. Despite new imaging modalities (endorectal MRI) and prostate specific antigen (PSA), PSA density, PSA velocity, and age-specific PSA, there is no valid staging method to reliably classify a newly diagnosed localized prostatic cancer. It is however of utmost importance to distinguish patients with organ confined prostate cancer from patients with locally advanced prostate cancer because the latter have, after radical surgery, a higher risk of developing local recurrence or distant metastases whereas patients with organ confined disease after radical surgery have a high likelihood of disease-free survival [5]. Known poor prognostic signs for progression prior to radical prostatectomy are: high number of positive biopsies, Gleason score > 7 , high initial PSA value, and microscopic nodal disease [5,6-9]. Known poor prognostic signs for progression after radical prostatectomy are:

a high grade malignancy, aneuploidy, tetraploidy, capsular penetration, positive surgical margins, and pathologically confirmed seminal vesicle involvement [5-8,10,11].

It is likely that in future, immunohistochemical staining techniques, e.g., E-cadherin expression, will be used as prognostic indicators to distinguish men who should be offered radical surgery from men in whom treatment can be deferred [12]. Today, it is still impossible to clearly answer the questions whether or not to treat and what are the best therapies to use.

Until recently, the current surgical approach in the management of clinically localized disease was to offer radical prostatectomy to all suitable candidates with clinically non-metastasized stage T_{1b} (A2) or T_2 (B) lesions, (T_{1b} according to the TNM staging system [13]; stage A2 according to the Whitmore staging system [14]) irrespective of the tumor grade. Since clinical staging of localized prostatic cancer is hampered by inadequacy and inaccuracy, leading to understaging in up to 60% of patients, most series of radical prostatectomy patients contain a large number with tumors extending beyond the prostate (pT_3 or C lesions) [15]. This experience showed that radical surgery is feasible in a significant percentage of these patients, and also that the quality of life does not deteriorate and may even be improved when compared to conservatively treated patients [15,16-18].

Thanks to this experience and to advances in surgical techniques, small clinical T_3 tumors are currently frequently considered for radical surgery. The percentage of patients with clinical T_3 , Grade 1 and 2 (Mostofi) prostatic cancer showing progression after radical surgery is comparable to that of patients with clinical T_{0-2} , pN_0 , M_0 , Grade 1-3 tumors after surgery [5].

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Since Huggins and Hodges [19] described the androgen dependency of prostate cancer in 1941, the question of whether preoperative hormone manipulation may enhance surgical curability has also been addressed. Indeed, shortly thereafter, attempts were made to reduce the size of the tumor before radical surgery in order to improve the surgical curability [20–23]. This approach was not very popular because of the irreversibility of bilateral orchiectomy and the toxicity of estrogens.

Interest in preoperative hormonal manipulation has recently been renewed with the availability of reversible luteinizing hormone-releasing hormone (LHRH) analogues and non-steroidal anti-androgens. The combination of these drugs is now used for temporary, combined androgen blockade (CAB). The elimination of androgens of testicular origin is achieved by medical castration using LHRH analogues. The action of adrenal precursors, which are converted to the active androgen dihydrotestosterone (DHT), is neutralized by non-steroidal anti-androgens competing with DHT for binding to the androgen receptor [24]. In fact, CAB causes a 33–50% reduction in prostatic size within 3 months [25–27] whereas the reduction in prostatic size seems to be less pronounced after surgical or medical castration, or treatment with anti-androgens alone [26]. The present approach using CAB could have the advantage of a more complete and more rapid reduction in the size of the tumor than other endocrine (mono-)therapies. It is now used as a 3-month preoperative treatment with the aim of reducing the size of the prostate and the tumor, making it more accessible to surgery. Hopefully, this also positively influences the cure and survival rate. The aim of neoadjuvant therapy is to cause a maximal reduction in prostatic androgen levels to induce maximal atrophy, apoptosis, and death of prostate cancer cells within a short period of time. Thus, combination therapy using a pure anti-androgen in association with LHRH analogues seems to be the most logical approach. The use of a LHRH analogue alone, an anti-androgen alone, or an inhibitor of androgen formation alone seems inappropriate because partial blockade of androgens is likely to induce the development of tumor resistance to androgen blockade [28]. CAB is also used before and during radiation therapy for locally advanced prostatic cancer with the aim of reducing the number of stem cells to be inactivated by radiation therapy [29].

Studies on the role of neoadjuvant hormonal treatment followed by radical prostatectomy in patients with localized prostate cancer should be interpreted with care since most of them are non-controlled and usually involve a small numbers of patients [6,25,

27,28,30–41]. So far, there are few early publications on well controlled clinical studies [28,42–46].

There is no common agreement about the duration of neoadjuvant treatment. Variations are from 2 to 8 months, but neoadjuvant treatment is usually given for 3 months. However, the maximal biochemical and pathological downstaging effects seem to require 8 months of neoadjuvant treatment [47]. There is also no agreement about which medication should be used. LHRH analogue monotherapy is used [34,39,48] sometimes combined, only during the first weeks, with anti-androgens to avoid flare effects [36,45]. Estrogen or anti-androgen monotherapy has also been used [36,39,41,46]. Others have given CAB with LHRH analogues combined with an anti-androgen, be it steroidal (e.g., cyproteroneacetate), or "pure" (flutamide or anandron) [6,25,27,28,31,33,39,44,49]. There are also reports of hormonal therapy combined with chemotherapy using cyclophosphamide, cisplatin or a combination of mitomycin, 5-fluorouracil, and calcium folinate [32,37]. Recently, early results of a well controlled study comparing direct radical prostatectomy vs. estramustine phosphate, followed by radical prostatectomy have been published [42].

The real use and advantages of neoadjuvant treatment of localized prostate cancer are not evident and appreciable today. The data available indicate that as an average, a prostate (and tumor) reduction of 33–50% can be obtained after 3 months of hormonal treatment [25–27]. Some data suggest an improved operability [25,31] and, hence a more radical surgery, others do not find this advantage [27,44].

Pathological stage reduction is mentioned in some studies [6,27,28,34,35,41], others do not report pathological downstaging [36,40], or report mainly clinical downstaging [27,37]. An overview of the data presently available is given in Table I. These downstaging percentages should be interpreted with caution since in surgical series 25% of the patients with a clinical stage T₃ tumor are actually staged as pathological T₂ [5,50].

Downgrading has been described by Monfette et al. [25] and Ferguson et al. [51]. Others do not report downgrading [6,31] or even report undergrading of the pretreatment core needle biopsies [33]. Evidently, the latter could be related to an unrepresentative biopsy of the tumor, which is notoriously heterogeneous and multicentric. Recently, Armas et al. [53] and Ferguson et al. [51] observed a paradoxal increase in Gleason score [52] after neoadjuvant therapy. After neoadjuvant therapy, the observed nuclear tumor grade according to Mostofi [54] was lower and the Gleason score paradoxically higher. These changes can be explained as follows: therapy induced

TABLE I. Downstaging in Clinical Stage T₃ (C) Prostatic Carcinoma After Neoadjuvant Treatment

Reference	Clinical downstaging		Pathological downstaging	
	Patients	Percentage	Patients	Percentage
Flamm et al., 1991 [6]	0/21	0	7/21	29
Morgan and Meyers, 1991 [37]	29/36	81	3/36	8
MacFarlane et al., 1993 [27]	10/12	83	3/12	25
Köllerman et al., 1993 [32]	49/103	48	40/103	39
Schulman, 1994 [31]	9/15	60	4/15	27
Voges et al., 1994 [68]	64/70	91	9/64	14
Narayan et al., 1994 [69]	14/30	47	3/14	21
Debruyne and Witjes, 1994 [60] ^a	13/33	39	6/35	17

^aRandomized study.

shrunk nuclei are less likely to exhibit variability in nuclear and nucleolar size and shape seen in high nuclear grades (Mostofi), and shrunk glands show coalescence and fusion suggestive of less differentiated architectural patterns (higher Gleason score). However, the baseline architectural pattern is not necessarily less differentiated after neoadjuvant treatment. The cells are shrunk or even hydropic degenerated and thereby more closely grouped, resulting in paradoxically higher Gleason scores. Their ability to multiply or spread remains questionable. The apparent dedifferentiation of cancer cells could be the *in vivo* morphologic expression of "apoptosis" induced by androgen deprivation. Hence, the Gleason score does not seem to be a valid scoring system after neoadjuvant treatment. The biological and clinical significance of these histologic changes in androgen-deprived cancer is still uncertain and has to be determined in future studies.

Monfette et al. described absence of identifiable carcinoma in 10 of 34 patients diagnosed by biopsy ($n = 6$) and by transurethral resection of the prostate ($n = 4$) [25]. Also Fair et al. reported that 10% of the patients treated with CAB in a non-study situation had no apparent tumor in the pathologic specimen despite step sectioning of the entire prostate [41]. Several other authors have reported incidental downstaging to pT₀ [21,31,49,55–59]. The early results of our own study, conducted by the European Study Group on neoadjuvant treatment of prostate cancer, show that initially, in four of the 53 patients with clinical T₂ prostatic carcinoma, no tumor could be found in the radical prostatectomy specimen after neoadjuvant CAB. One patient with a clinical T₂ tumor, in whom no tumor could be found in the radical prostatectomy specimen after the first pathological examination using step sectioning of the entire prostate, was reviewed by the local pathologist. Immunohistochemistry (PAP and PSA) revealed a residual fo-

cus of carcinoma. In another patient who was downstaged to pT₀ according to the local pathologist, a small focus of carcinoma was recognized by the review pathologist. These two patients with an initial pathological stage pT₀ appeared to have a pT₁ tumor after pathological re-examination [60].

From a pathological point of view it is difficult to explain how an extracapsular tumor can become organ-confined by simple hormone manipulation. The so-called pathological downstaging can be a consequence of the phenotypic changes of tumor cells which make them difficult to be recognized as persisting cancer cells. The phenotypic changes after total androgen deprivation are: atrophy of the glandular epithelium with a relative increase of the fibromuscular stroma and a decrease in gland density; nuclear pycnosis and intracytoplasmic vacuolation mainly in tumor cells; and squamous metaplasia in the glands and ducts [33,48]. The pathologist should be aware of these phenotypic changes because of their possible misinterpretation and confusion with other atrophic, metaplastic, and proliferative lesions. Special care has to be taken in the pathological interpretation of frozen sections. The atrophic cells can easily be confused with lymphocytes, resulting in false negative histology reports. With the use of the laparoscopic lymph node dissection, a technique that gradually has become more popular, misinterpretations on frozen sections of lymph nodes and resection margins during the surgical procedure will probably be avoided in future when routine paraffin sections are more commonly used and the use of immunostaining in select cases can be considered.

Immunostaining of tumor cells can be helpful in the sometimes difficult diagnosis of prostate cancer after combination therapy. However, reduction in immunostaining of tumor cells and prostate glands for both PSA and prostatic acid phosphatase after

combination therapy can lead to a false-negative diagnosis [61]. The use of monoclonal antibodies against specific cytokeratins is a better, now commonly available, tool that can be very helpful to detect immunohistochemically persisting tumor cells and positive margins [62].

Many studies describe the suppression of tumor-growth as a result of hormonal therapy in prostate cancer. Cell death following androgen ablation is described by Kyprianou et al. [63] and van Steenbrugge [64]. Kyprianou et al. demonstrated that in nude mice, after androgen ablation, human androgen-dependent prostatic cancer cells (PC82) regress due to a sequence of biochemical and morphological events resulting in both the cessation of cell proliferation and the activation of a pathway of programmed cell death (apoptosis). It is likely that a certain percentage of androgen-dependent prostatic cancer cells die as a result of androgen deprivation. Whether the activation of a pathway of apoptosis explains how an extracapsular tumor can become organ confined or explains the mechanism of downstaging to pT₀ as reported by several institutions, remains questionable and is not yet confirmed by clinical or experimental evidence.

What is the current status of neoadjuvant therapy? The actual importance of the question, "Could neoadjuvant therapy really be beneficial?" has been shown published in two conflicting articles in 1993. Oesterling et al. [40] concluded that "preoperative androgen deprivation therapy has little or no benefit for decreasing the extent of tumor or pathological stage; the concept of downstaging is misleading." On the other hand, Fair et al. [41] concluded that "although it is not possible to state currently that any patient has received benefit from neoadjuvant hormonal therapy it is likewise not possible to be dogmatic in the assertion that neoadjuvant therapy is not beneficial." Therefore, it is important that further clinical studies, preferentially randomized trials, should be performed to determine the real value of preoperative hormonal therapy.

Realizing that there is a strong relationship between tumor volume, seminal vesical invasion, the extent of capsular invasion, and metastases as has been clearly shown by McNeal et al. and Stamey et al. [65,66], it is likely that the benefit, if any, lies in a decrease of positive margins and subsequently a lower risk for local recurrence in a subgroup of patients with clinical T_{1,2} tumors resulting in an enhanced local control and possibly also survival. A decrease of positive margins has recently been shown in patients with clinical T₁ and clinical T₂ prostatic cancer in a randomized study by Labrie et al. [28], Van Poppel et al. [30], Soloway et al. [44], Pedersen et al.

[45], and by Goldenberg et al. [46] and in a retrospective study of Häggman et al. [38] but further follow-up is needed to address the effect on local control and survival. A decrease of positive margins in patients with clinical T₃ tumors has not yet been shown, but literature on neoadjuvant treatment in T₃ patients is sparse. Consequently, the benefit of neoadjuvant hormonal treatment in patients with clinical T₃ tumors remains unsure.

Could neoadjuvant CAB have a direct impact on the development of distant metastases during or after radical surgery? At the 1995 American Urological Association meeting Israeli presented the use of a sensitive reverse transcriptase-polymerase chain reaction assay using DNA primers derived from the prostate-specific membrane antigen to detect occult circulating prostatic tumor cells and showed that circulating prostatic tumor cells were detected in 9/10 patients in the control group as compared to 2/12 patients in the neoadjuvantly treated group [67]. These findings indicate that a significantly higher number of patients may be rendered tumor-free, and potentially "cured" by the use of neoadjuvant CAB. The biological significance of these findings has to be investigated in future.

It is hoped that in future more neoadjuvant studies will be well controlled and that time to progression and more importantly survival data, rather than just response rates describing downstaging percentages or improved positive surgical margins percentages, will be reported. Although these response rates are important, they may ultimately not translate into prolonged time to progression and survival with neoadjuvant treatment.

Further prospective well-controlled, randomized, clinical investigations are necessary to provide the still-needed information on both the local effects and survival advantages of neoadjuvant hormonal manipulation in prostatic carcinoma. Many questions remain unanswered, therefore, neoadjuvant therapy is not yet advisable outside clinical research settings.

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