Review

Treatment Strategies for High-Risk Prostate Cancer - Utility of Combination Therapy of Neoadjuvant Therapy and Radical Prostatectomy to Improve Oncologic Outcomes

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Abstract: Prostate cancer (PCa) is most commonly observed in male patients. Although PCa progresses relatively slowly, high-risk PCa is associated with an increased risk of lymph nodes, distant metastases, and PCa-related death. Several guidelines recommend radiation therapy (RT) of the prostate combined with long-term androgen deprivation therapy for high-risk PCa. A comparison of clinical outcomes between radical prostatectomy (RP) and RT for high-risk PCa by propensity score-matched analysis showed that RP had a significantly higher risk of biochemical recurrence than RT. However, the combination of neoadjuvant chemohormonal therapy followed by RP may be more likely to achieve a cure when overall survival is considered the primary endpoint. In this review, we aimed to confirm the oncological outcomes of RP and RT for high-risk PCa and highlight the importance of neoadjuvant therapy followed by RP for high-risk PCa.

Keywords: prostate cancer; high-risk prostate cancer; radical prostatectomy; radiation therapy; neoadjuvant therapy; oncological outcomes

1. Introduction

An estimated 268,490 patients in the United States and 94,748 patients in Japan were expected to be newly diagnosed with prostate cancer (PCa) in 2022 and 2019, respectively [1,2]. Most patients with PCa are older than 65 years, and this disease is most commonly found in male patients [1,2]. PCa progresses relatively slowly, and approximately 85% of patients with prostate cancer are diagnosed with low-risk or intermediate-risk diseases according to several guidelines; therefore, the prognosis for PCa without metastases is recognized as having relatively better oncological outcomes, including better overall survival (OS), cancer-specific survival (CSS), prostate cancer-specific mortality (PCSM), metastatic-free survival (MFS), and biochemical recurrence-free survival (BRFS) [3–7]. However, approximately 15% of patients are diagnosed with high-risk PCa, which has biological features different from those of the above-mentioned cohorts [6]. PCa, especially high-risk PCa, is one of the most heterogeneous oncologically specific diseases and shows clinical heterogeneity across a wide range of clinical variants [8]. In addition to frequent locoregional invasion, these cancers often have micrometastases at the time of diagnosis and are associated with an increased risk of lymph nodes or distant metastases and PCa-related death [8–10]. Therefore, several attempts have been made over the last decades to combine or sequentially administer various therapeutic regimens, such as local and systemic therapies, to control high-risk PCa [9]. Several

guidelines recommend radiation therapy (RT) to the prostate combined with long-term androgen deprivation therapy (ADT) for 2 to 3 years or trimodality therapy combining external-beam radiation RT (EBRT), brachytherapy, and ADT, which has relatively favorable oncological outcomes [3,4,11–13]. Conversely, although the European Association of Urology (EAU) guidelines recommend that radical prostatectomy should be performed in selected patients, a precise answer to the question of who should be classified as a selected patient remains unclear [4].

When considering OS as the primary endpoint, several studies over the last decade reported that half of all patients with high-risk PCa who received RT developed biochemical recurrence (BCR), with approximately 40% dying of PCa, and that ADT plus EBRT did not contribute to the improvement of oncological outcomes [12,13]. With regard to surgical treatment, improved oncological outcomes, such as prolonged OS and CSS with second-line treatment of BCR, have been reported [14–16]. In particular, a Swedish cohort study of more than 3,500 patients followed up for more than 15 years reported better OS in patients with intermediate-risk and high-risk PCa who underwent radical prostatectomy (RP) than in those who received RT, resulting in a hazard ratio (HR) of 1.77 [14]. Furthermore, surgical treatment of PCa with oligometastases improved OS compared with treatment with ADT alone, and surgical treatment of high-grade or high-risk PCa is currently being reconsidered [17–20].

In this review, we aimed to confirm the oncological outcomes of RP and RT for high-risk PCa and highlight the importance of neoadjuvant therapy followed by RP for high-risk PCa to improve oncological outcomes.

2. Comparison of Treatment Efficacy between RP and RT for High-Risk Prostate Cancer

Currently, the European Urological Association guidelines recommend in high-risk patients with PCa who have a life expectancy of ≥10 years, RP with extended pelvic lymph node dissection (ePLND) in selected patients, EBRT with 76–78 Gy, or long-term ADT and brachytherapy (BT) boost [4]. However, no trials that are either completed, ongoing, or planned have compared RP and RT in patients with high-risk PCa [21]. Unfortunately, level 1 evidence comparing mainstream therapies that define the gold standard management for high-risk PCa remains inconclusive [22]. Thus, only retrospective studies may currently provide a better understanding of the differences that can potentially distinguish high-risk PCa after definitive treatment [21].

A comparison of clinical outcomes by propensity score-matched analysis between RP and RT for high-risk PCa showed that RP had a significantly higher risk of BCR than RT ($p < 0.001$) [23]. RT was significantly correlated with a reduced risk of BCR compared to RP (HR 0.16, 95% confidence interval [95% CI] 0.07–0.37, $p < 0.001$) [23]. Kaplan–Meier analysis showed no statistically significant differences in local recurrence-free survival ($p = 0.155$), metastasis-free survival (MFS; $p = 0.250$), or OS ($p = 0.502$), and differences in clinical covariates and treatment modalities did not predict the aforementioned oncological outcomes [23]. A retrospective study that enrolled 4,041 patients undergoing RP classified as having high-risk or very high-risk PCa by the National Comprehensive Cancer Network (NCCN) stratification between 1992 and 2016 demonstrated that 926 patients (50.6%) experienced BCR, with a median time from RP to BCR of 10.8 months for very high-risk PCa and 14.3 months for PCa ($p = 0.002$) [21]. The 5- and 8-year BRFS rates were 47.8% (interquartile range [IQR], 45.3–50.4 months) and 39.6% (IQR, 36.8–42.7 months) for the entire cohort [21]. At the last follow-up period, 234 patients (12.8%) experienced distant metastasis and 107 (6%) died of PCa [21]. The 5- and 8-year MFS rates ranged from 71.5% (IQR, 64.1–79.7%) and 91.2% (IQR, 83.8–88.6%) in very high- and high-risk PCa, respectively [21]. Regarding OS, the 5- and 8-year rates were 85.7% (IQR, 82–89.6%) and 76.1% (IQR, 69.1–83.8%) for very high-risk PCa and 91.5% (IQR, 89.8–93.2%) and 83.7% (IQR, 91–86.5%) for high-risk PCa, respectively [21]. For patients with high-risk PCa who received trimodality therapy, including EBRT, BT, and ADT, the prescribed minimum peripheral dose was 104 Gy for BT [24]. These patients underwent EBRT at 40 Gy in 2 Gy fractions to the prostate and seminal vesicles within 1 month after BT and ADT for 24 months, as described in our previous study [25]. Although six patients (1.8%) had a secondary malignant neoplasm after BT, none of the patients in the study died of PCa [24]. The 5- and 10-year BRFS rates in patients with high-risk PCa were 93.4% and 93.4%,

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respectively [24]. Based on these studies, RT may be the preferred treatment modality for high-risk PCa more often than RP because of the higher incidence of BCR in high-risk PCa than in RT. In our opinion, trimodality therapy should not necessarily be considered a highly recommended grade of therapeutic modality for high-risk PCa, consistent with some guidelines [3,4,24,25]. However, trimodality therapy is an effective treatment modality in that it delivers a sufficient dose to the prostate gland and should be considered as one of the treatment modalities for high-risk PCa [24,25].

The Cleveland Clinic reported the results of a retrospective study evaluating BRFS and PCSM in 2557 patients with high-risk PCa who underwent EBRT, BT, and RP [22]. The 5-and 10-year BRFS rates were 74% (IQR, 70–77%) and 53% (IQR, 48–58%), respectively, in the EBRT group; 74% (IQR, 68–79%) and 52% (IQR, 42–62%), respectively, in the BT group; and 65% (IQR, 61–68%) and 47% (43–52%), respectively, in the RP group [21]. The BCR rate of patients treated with RP was relatively lower than that of their counterparts [22]. The 5-and 10-year PCSM rates were 5.3% (IQR, 3.6–7.1%) and 11.2% (IQR, 8.6–13.9%) in the EBRT group, 3.2% (IQR, 1.2–5.1%) and 3.6% (IQR, 1.5–5.8%) in the BT group, and 2.8% (IQR, 1.7–3.9%) and 6.8% (4.7–8.9%) in the RP group, respectively [22]. EBRT had the highest proportion of PCMS than the other two treatments, contrary to the results for BRFS [22]. A nationwide population-based cohort study based on the Prostate Cancer Data Base Sweden database enrolled 34,515 patients who received RP or RT as primary treatment for PCa, with a median follow-up of 5.37 years (IQR, 3.00–7.81 years) [13]. In all enrolled patients with non-metastatic PCa, treatment with RT was associated with significantly higher PCa-related crude mortality than RP (HR, 3.09; 95% CI, 2.69–3.56) [14]. Especially for intermediate- and high-risk PCa, the sub-distribution HRs were consistently in favor of RP over RT [13]. Propensity score matching similarly confirmed the key finding, which favored RP over RT for PCSM in patients without metastatic PCa, with no significant difference in the metastatic group [14].

The three studies that compared the outcomes of RP and EBRT with respect to PCSM are listed in Table 1. In all studies, EBRT was significantly associated with a higher PCSM rate than was RP.

Table 1. Comparison of prostate cancer-related specific mortality between radical prostatectomy and external beam radiation therapy.

Authors (Year) [Reference]	Enrolled Patients	Treatment Methods (Number)	Median Age (Year, IQR)	Median PSA (ng/mL, IQR)	PCSM	HR
Bandini M et al. (2018) [26]	5500	RP: 2507 RT: 2993	RP: 61.9 (52-67) RT: 68 (62-73)	RP: 7.1 (4.9-11.4) RT: 10.9 (6.3-24.7)	10-year PCSM RP: 8.1% RT: 15.8%	0.45
Chierigo F et al. (2021) [27]	24,407	RP: 9823 RT: 14,594	RP: 64 (59-68) RT: 71 (65-76)	RP: 8 (6-20) RT: 13 (7-27)	5-year PCSM RP: 3.5% RT: 6.0%	0.58
Hoeh B et al. (2022) [28]	4165	RP: 1390 RT: 2775	RP: 61 (56-66) RT: 66 (61-72)	RP: 10 (6-24) RT: 20 (8-36)	5-year PCSM RP: 2.4% RT: 5.2%	0.45

IQR, interquartile range; PSA, prostate-specific antigen; PCSM, prostate cancer-specific mortality; HR, hazard ratio; RP, radical prostatectomy; RT, external beam radiation therapy.

Cierigo et al. [27] reported that propensity score matching resulted in two groups of equal sizes for RP and EBRT, with no statistically significant differences in age, prostate-specific antigen (PSA), biopsy Gleason grade (GG) [29], or clinical T stage [30]. The 5-year PCSM rate was 2.3% (95% CI, 1.9–2.9) for RP and 4.1% (95% CI, 3.4–4.8) for EBRT ($p < 0.001$), with a multivariate competing risk HR of 0.68 in favor of RP ($p < 0.010$) [27]. Similarly, the 5-year PCSM with propensity score matching was 2.3% and 3.9% for RP and EBRT, respectively ($p = 0.003$), with a multivariate competing risk HR of 0.52 ($p = 0.020$) [30]. Thus, in terms of OS or PCSM, these studies suggest that RP may improve oncologic outcomes compared with EBRT in patients with high-risk PCa diagnosed by NCCN stratification.

Importantly, the possibility of secondary carcinogenesis should be carefully considered during RT for young patients with PCa. A systematic review and meta-analysis of available data on the

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association between RT and the development of secondary malignancies indicated that patients treated with RT had an increased risk of bladder cancer (BCa) after multivariate adjustment (adjusted HR, 1.67; 95% confidence interval [CI], 1.55–1.80) [31]. Similarly, pooled multivariate adjusted HRs indicated an increased risk of rectal cancer (RCa) in patients receiving RT (adjusted HR, 1.79; 95% CI, 1.34–2.38) [31]. From the Surveillance, Epidemiology, and End Results (SEER) database of 84,397 patients with PCa who received RP or RT, 1660 individuals (18%) developed pelvic tumors after their last treatment for PCa, of whom 1238 had BCa and 432 had RCa [32]. The 5-year probabilities calculated from the cumulative incidence of pelvic cancer, BCa, and RCa in the entire population were 1.42%, 1.06%, and 0.37%, respectively [32]. The cumulative 5- and 10-year BCa incidence rates ranged from 0.75% (95% CI, 0.64–0.85) and 1.63% (95% CI, 1.45–1.82) to 1.26% (95% CI, 1.15–1.37) and 2.34% (95% CI, 2.16–2.53) in patients receiving RP or RT, respectively ($p < 0.001$) [32]. The cumulative 5- and 10-year RCa incidence rates were 0.32% (95% CI, 0.25–0.39) and 0.73% (95% CI, 0.61–0.85), and 0.36% (95% CI, 0.30–0.41) and 0.69% (95% CI, 0.60–0.79) for RP and RT, respectively ($p = 0.4$) [32]. Zang et al. [33] identified 150,915 patients with PCa aged ≤65 years from the SEER database between 1973 and 2014. The cumulative incidence of secondary lung cancer, BCa, and RCa was higher in patients treated with any form of RT than in those treated with RP [33]. Furthermore, the cumulative incidence of lung cancer and BCa differed between patients treated with RP and all forms of RT five years after PCa diagnosis [33]. RT for younger patients with PCa may require close follow-up, paying attention not only to PCa control, but also to the development of cancer in the organs surrounding the prostate.

3. Extended Pelvic Lymph Node Dissection for High-Risk PCa

According to various guidelines, ePLND is strongly recommended as a surgical treatment for high-risk PCa [3,4]. However, there is currently disagreement as to whether pelvic lymph node dissection (PLND) should be performed in any patient when performing RP for PCa [34]. The benefits of ePLND include improved accuracy in precisely staging PCa [30]. Furthermore, this can help identify patients who require or can omit further adjuvant therapy and can predict oncological outcomes, including BRFS, MFS, and PCSM [35,36]. In a multi-institutional database from four centers including 9742 patients who underwent RP with or without PLND 120 months after RP, there was no statistical correlation between oncologic outcomes, including BRFS, MFS, and PCSM, with and without PLND at the time of RP in patients with intermediate- or high-risk PCa [35]. The 10-year BRFS, MFS, and PCSM rates in patients with or without PLND were 60.4% and 65.6% ($p = 0.007$), 87.0% and 90.0% ($p = 0.06$), and 95.2% and 96.4% ($p = 0.2$), respectively [35]. In multivariable Cox regression models after adjusting for pre-and postoperative tumor characteristics, PLND achieved no independent predictor status for BCR (HR, 1.18; $p = 0.1$, and HR, 1.12; $p = 0.2$, respectively), MFS (HR, 1.50; $p = 0.1$, and HR, 1.17; $p = 0.4$, respectively), or PCSM (HR, 2.26; $p = 0.1$, and HR, 1.45; $p = 0.4$, respectively) [35]. In a single-center randomized trial involving 1440 patients who underwent RP with limited PLND (lPLND) or ePLND, there was no significant difference in the rate of BCR between the two groups (HR, 1.04; 95%CI, 0.93–1.15; $p = 0.5$) [36]. The median number of lymph nodes (LN) removed was 12 (IQR, 8–17) for lPLND and 14 (IQR, 10–20) for ePLND. The corresponding positive rate of LN involvement was 12% for lPLND and 14% for ePLND ($p = 0.3$) [36]. In a prospective, single-center, phase III trial in patients with intermediate- or high-risk clinically localized PCa, 300 patients were registered, of whom 150 were assigned to ePLND and 150 to lPLND [37]. The median BRFS was 61.4 months in the lPLND group and unachieved in the ePLND group (HR, 0.91; 95%CI, 0.63–1.32; $p = 0.6$), and median MFS was also unachieved in both groups (HR, 0.57; 95%CI, 0.17–1.8; $p = 0.3$) [37]. In a subgroup analysis, patients with PCa with GG 3–5 who were assigned ePLND demonstrated favorable BRFS (HR, 0.33; 95% CI, 0.14–0.74; $p = 0.007$) [37]. They concluded that ePLND may have a potential benefit for BRFS in patients with PCa who are diagnosed with GG ≥3, even though PLND may be less significant in PCa with GG ≤2 [37]. In our retrospective, multicenter cohort study of 3195 patients undergoing RARP (MSUG94 Group), we found that PSA, biopsy GG, cT3, and high-risk prostate cancer were significantly higher in the PLND group [31]. Therefore, we investigated the significance of PLND in RARP in 1210 patients with similar backgrounds using propensity score

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matching [34]. The 3-year BRFS rate for all patients was 93.7% in the PLND group and 91.5% in the group without PLND, with no difference between the two groups ($p = 0.855$). Furthermore, there was no difference in the BRFS rate between patients with and without PLND (low-risk, $p = 0.55$; intermediate-risk, $p = 0.771$; high-risk, $p = 0.635$) [34]. Although these results suggest that PLND is not necessary in all patients, its significance in improving oncological outcomes should be reconsidered.

4. Neoadjuvant Therapy prior to RP for High-Risk PCa

The administration of neoadjuvant ADT before RP was associated with reduced pT3, the proportion of positive surgical margins (PSM), and the incidence of LN involvement compared to RP alone [4,38]. Kim et al. also performed a propensity score matching analysis and found that NHT for high-risk PCa did not contribute to BCR or OS (BCR: HR, 1.35 and 0.84, respectively; OS: HR, 1.05 and 0.77, respectively; p = 0.539) [39]. Tosco et al. reported using propensity score-matched analysis of patients with high-risk PCa that there were fewer PCa-related deaths in those who received NHT, attributing this to the effect of the additional postoperative RT [40]. Moreover, a meta-analysis of localized and locally advanced PCa demonstrated that these advantages did not provide a prognostic survival benefit for PCa, including OS and BRFS [41]. Similarly, three cohort studies showed that NHT prior to RP failed to lead to a significant BRFS advantage compared to RP alone (pooled HR, 1.00; 95% CI, 0.78–1.54) [41]. Sun et al. [42] retrospectively analyzed clinical data from 385 patients with high-risk PCa who underwent RP, including 168 patients who underwent neoadjuvant NHT followed by RP and 217 patients who underwent RP alone. Although patients who received neoadjuvant ADT had shorter operative times, decreased volume of blood loss, lower rates of PSM, and higher rates of downstaging GG after RP ($p<0.05$), there were no statistically significant improvements in BCR, BRFS, or perioperative complications [42]. In the entire cohort, initial PSA, biopsy GG, clinical T stage, and use of NHT were significantly correlated with PSM ($p < 0.05$); however, NHT did not improve BCR ($p > 0.05$) [42]. Therefore, NHT for high-risk PCa should not be easily performed for downstaging or PSM reduction because it does not contribute to improved oncologic outcomes. Furthermore, the European Association of Urology has noted that evidence for neoadjuvant ADT is weak, limiting its recommendation for preoperative NHT for PCa [4].

Currently, neoadjuvant combination therapy using ADT and androgen receptor signaling inhibitors (ARSI) is being increasingly performed; however, there have been very few reports on oncological outcomes (Table 2).

Table 2. Overview of pathological outcomes at radical prostatectomy.

Authors (Year) [Reference]	Treatment Methods	Enrolled Patients (N)	pCR (%)	MDR (%)	LNI (%)	PSM (%)	pT3 (%)
Efstathiou E et al. (2019) [43]	ADT+AA	44	NE	NE	34	5	52
	ADT	21			38	14	67
McKay RR et al. (2019) [44]	ADT+AA+Enza	50	10	20	10	18	50
	ADT+Enza	25	8	8	12	12	56
Devos G et al. (2022) [45]	ADT+APA	45	51	38	20	18	49
	ADT	44	27	9	16	18	73
McKay RR et al. (2021) [46]	AA	34	11.8	2.9	17.6	8.8	521.1
	Enza	17	29.4	17.6	11.8	11.8	80.6
	AA+Enza	66	37.9	15.2	9.1	15.2	51.5
Ravi P et al. (2022) [47]	Neo-RP	112	10	12	11	13	55
	RP alone	259	0	NE	15	26	72

pCR, pathological complete response; MDR, minimal residual disease; LNI, lymph node involvement; PSM, positive surgical margin; pT3, pathological T3 disease; ADT, androgen deprivation therapy; AA, abiraterone; Enza, enzalutamide; APA, apalutamide; Neo-RP, neoadjuvant androgen receptor signaling inhibitors and radical prostatectomy; RP, radical prostatectomy; NE, not evaluated.

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Neoadjuvant therapy with ARSI tended to reduce the rates of pathological complete response (pCR) and minimal residual disease (MRD); however, it was not as effective in terms of LN involvement and PSM rates, and pT3 rates tended to be relatively high. McKay et al. [46] reported the pathological and oncological outcomes in 117 patients who received neoadjuvant therapy. A total of 25 patients (21.4%) had MRD, and 11 (9.4%) had a pCR [46]. At the end of the follow-up period, 49 patients (41.9%) had developed BCR, and the 3-year BRFS rate was 59.1% (95%CI, 49.0–67.9 months) [46]. Ravi et al. [47] showed that the 3-year BRFS rate was 59% in patients who received neoadjuvant therapy followed by RP (Neo-RP group) and 15% in those who received RP alone (HR, 0.25; $p < 0.01$). The MFS rates were 96% and 68% in the Neo-RP and RP alone groups, respectively (HR, 0.26; $p < 0.01$) [47]. While neoadjuvant therapy with ARSI may improve oncologic outcomes in high-risk prostate cancer compared with surgery alone, these results currently remain unsatisfactory.

Chemotherapy, such as the use of docetaxel, which is widely used in other solid tumors to improve oncologic outcomes [48], is also administered to patients with metastatic PCa and has been shown to prolong survival in advanced PCa [49]. Several clinical studies have demonstrated that neoadjuvant chemohormonal therapy (NCHT) is well-tolerated and has acceptable treatment benefits [50–53]. A systematic review and meta-analysis of six studies of 1717 patients with PCa found no significant relationship between NCHT before RP and RP alone in terms of LN metastasis ($p = 0.92$), although BRFS and OS were significantly improved when patients were treated with NCHT (HR, 0.54; 95%CI, 0.34–0.85; $p = 0.008$ and HR, 0.67; 95%CI, 0.48–0.94; $p = 0.02$, respectively) [53]. In a single-center, retrospective study, 177 patients with high-risk PCa received the following treatments: docetaxel-based neoadjuvant chemotherapy plus NHT in 60 patients (NCHT group), NHT in 73 (NHT group), and RP alone in 44 (non-NT group) [50]. In the NCHT group, patients received 4–6 cycles of total androgen blockade with systemic chemotherapy using docetaxel [51]. In the NHT group, patients only received 4–6 cycles of total androgen blockade [51]. Following RP, 81% of the NCHT group, 73% of the NHT group, and 48% of the non-NT group had undetectable PSA levels ($p < 0.001$) [50]. Although there were no significant differences between the three groups, no residual tumor was confirmed in surgical specimens in 17.3% of the NCHT group and 8.6% of the NHT group [50]. The median durations of BCR after RP were 19, 13, and 9 months in the NCHT, NHT, and non-NT groups, respectively ($p < 0.001$) [51]. However, the incidence of adverse events caused by anticancer agents, particularly docetaxel, is an issue with NCHT [50,51]. Hematological toxicities were very common during NCHT according to the Clavien–Dido classification [50–52]. Sasaki et al. [51] reported grade 3/4 toxicities, including neutropenia (85%), febrile neutropenia (10%), and oral mucositis (5%). Although hematologic toxicity can be treated with granulocyte colony-stimulating factor, we believe that physical weakness due to adverse events before surgery should be avoided.

In our previous studies, NCHT consisting of a gonadotropin-releasing hormone agonist or antagonist (GnRH) plus low-dose estramustine phosphate (EMP) followed by RP for high-risk PCa improved BRFS and OS [53,54]. However, gynecomastia, an adverse event caused by the estrogenic effects of EMP, occurs in almost all patients, and there is also a risk of developing deep vein thrombosis. Therefore, we currently perform NCHT with GnRH and tegafur-uracil (UFT) for high-risk PCa [55]. Multiple studies have reported the efficacy and safety of UFT-containing regimens for a variety of malignant neoplasms, including lung cancer, breast cancer, gastric cancer, and castration-resistant PCa (CRPC) [56–59]. For CRPC in particular, the usefulness of UFTs has been demonstrated when administered late-line or in combination with other anticancer agents [56–59]. We have treated 101 patients with high-risk prostate cancer using GnRH and UFT. Although the median follow-up was relatively short (17.0 months), the 1- and 2-year BRFS rates were 95.8% and 92.0%, respectively. Grade ≥3 NCHT-related adverse events included liver disorder in seven patients (5.9%), rash with liver disorder in one (0.9%), and anorexia with liver disorder in one (0.9%) according to the Clavien–Dido classification [60]. This regimen may be an option for NCHT in patients at high-risk of PCa because of its simple administration, mild adverse events, and relatively better BRFS.

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5. Future Perspectives

To date, there is no clear evidence that NHT for RP improves prognosis [4,39–43]. Furthermore, NHT should not be performed because of concerns about increased risk of weight gain, emotional changes, cardiovascular disease, diabetes, osteoporosis, and other adverse events [4,38–42]. MacLennan et al [61] emphasize that NHT may currently be administered in an unintentional manner to patients who would not benefit from it. The reason why RP after NHT does not improve oncologic outcomes may be that high-risk PCa is a heterogenous cancer by nature, with cancer cells that do not respond to endocrine therapy. Conversely, previous reports on NHT after RP have suggested that the imaging modalities used for PCa staging, CT and bone scintigraphy, may have missed micrometastases with respect to those with high-risk cases [41,44–48].

Recently, prostate-specific membrane antigen-positron emission tomography (PSMA-PET/CT) has emerged as a game changer in PCa staging [62]. Hofman et al [62] conducted a randomized trial in patients with high-risk PCa undergoing curative treatment with surgery or radiation therapy and reported that PSMA PET/CT was 27% (95% CI, 23-31%) more accurate than conventional imaging (92% vs 65%, $p < 0\ 0001$). If PSMA-PET/CT enables pre-treatment diagnosis of micrometastases that cannot be diagnosed by conventional CT or bone scintigraphy, physicians may be able to efficiently select patients with locally advanced PCa who are truly free of metastases, those with a small number of metastases, and those whose prognosis can be extended with pharmaceutical therapy or surgery. Clinical trials are expected to be conducted to determine whether neoadjuvant therapy for these good candidates, such as ARSI or cytotoxic agents, can be more oncologically effective than conventional ADT and improve the oncological outcomes in patients with locally advanced or high-risk PCa [44–48,53–55].

6. Conclusions

High-risk PCa involves a highly aggressive and heterogeneous tumor that is often difficult to cure with monotherapy. Therefore, it is necessary to develop individualized treatment strategies for each patient and to use a number of different therapeutic approaches. Although radiotherapy is the treatment of choice for high-risk PCa, the combination of NCHT followed by RP may be more likely to achieve a cure when OS is considered as the primary endpoint. We look forward to the accumulation of cases and results of prospective clinical trials in the future.

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Institutional Review Board Statement: The study protocol was approved by the Institutional Re view Board of Gifu University (number: 29-106, 2018-213, 2019-267, 2020-210, 2021-B39, 2021-A050). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Statement: Informed consent has been obtained from patients with low, inter mediate, and high-risk PCa, undergoing RARP for the study under approval number 2021-A50. More information about this trial can be found at https://www.med.gifu-u.ac.jp/visitors/disclosure/docs/2018-212.pdf (accessed January 28, 2023). Other than that, formal consent is not required for retrospective studies. In accordance with the provisions of the Japanese Ethics Committee and Ethics Guidelines, written consent was not required for retrospective and observational research using existing materials and other sources in exchange for the release of research information. The study information was open for the public consumption at https://www.med.gifu-u.ac.jp/visitors/disclosure/docs/29-106.pdf, https://www.med.gifu-u.ac.jp/visitors/disclosure/docs/2018-213.pdf, https://www.med.gifu-u.ac.jp/visitors/disclosure/docs/2019-267.pdf, https://www.med.gifu-u.ac.jp/visitors/disclosure/docs/2020-210.pdf, and https://www.med.gifu-u.ac.jp/visitors/disclosure/docs/2021-B039.pdf (accessed on January 28, 2023).

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical reasons.

Conflicts of Interest: The authors declare no conflicts of interest.

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