ADT in Combination with Radiation Therapy for Clinically Localized Prostate Cancer

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Abstract

External beam radiotherapy (EBRT) is a well-established definitive therapeutic approach for clinically localized prostate cancer (CLPCa). Although CLPCa had been mainly treated with EBRT alone, androgen deprivation therapy (ADT) has been shown to improve not only biochemical control but also survival outcomes when combined with EBRT.

Adding ADT to EBRT using former standard doses (65–70 Gy) significantly improved survival outcomes compared with EBRT alone in patients with intermediate- or high-risk disease. Therefore, ADT is considered to be an essential element in definitive EBRT for most cases of CLPCa.

In terms of intermediate-risk patients, the neoadjuvant combination of ADT for a period of 4–6 months combined with EBRT is recommended. On the other hand, for high- or very-high-risk patients, neoadjuvant ADT for 4–6 months followed by adjuvant ADT for 24–30 months is considered to be the standard treatment for use in combination with EBRT.

However, the optimal duration of ADT in combination with EBRT remains controversial. In addition, the usefulness of ADT is controversial when combined with dose-escalated EBRT. Moreover, ethnic differences in patient sensitivity to ADT have been suggested. Randomized trials are required to clear up these unsolved issues regarding ADT combined with EBRT.

Keywords

Clinically localized prostate cancer · Radiation therapy · Combined androgen deprivation therapy

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12.1 Introduction

The impact of the combination of androgen deprivation therapy (ADT) with radiation therapy for clinically localized prostate cancer (CLPCa) has been largely explored with respect to external beam radiation therapy (EBRT) through the use of randomized trials. However, no prospective randomized trial has been conducted to confirm the impact of ADT on brachytherapy for CLPCa, even though ADT is also often clinically combined with brachytherapy. Therefore, this chapter focuses on EBRT as a radiotherapeutic approach for use in combination with ADT.

Thus far, six randomized trials have demonstrated highly significant improvements in survival with combined ADT and EBRT, compared with EBRT alone (Tables 12.1 and 12.2). Combined short-term neoadjuvant ADT (NA-ADT) ± concurrent ADT demonstrated survival advantages over EBRT alone in patients with intermediate- and high-risk CLPCa (Table 12.1). In addition, long-term adjuvant ADT (A-ADT) resulted in significantly better survival outcomes, mainly in high- or very-high-risk cases, compared with those who were treated with EBRT alone (Table 12.2). The radiation doses used in most of these trials were former standard doses (65–70 Gy).

Other randomized studies also confirmed that dose escalations above the former standard doses to the prostate improve prostate-specific antigen (PSA) control rates [1, 2]. However, the impact of dose escalation on survival has not been demonstrated in phase III trials [3, 4]. On the other hand, combined ADT significantly improves survival, as indicated in this chapter. Therefore, ADT is considered to be an essential component of definitive EBRT for CLPCa.

Evidence of definitive EBRT with ADT in East Asian populations, including the Japanese, is rather sparse. In addition, the timing of the start of salvage ADT (S-ADT) in patients who developed a PSA recurrence, which may affect the prognosis [5–7], was not defined in any of the trials conducted in Western countries. Moreover, the impact of combined ADT and dose-escalated EBRT remains controversial [8].

12.2 EBRT Plus ADT Versus EBRT Alone

12.2.1 Overview of the Combination of ADT with EBRT

EBRT alone was previously the main treatment approach in definitive EBRT for prostate cancer [9]. However, not only biochemically recurrence free, but also survival advantages of combined EBRT with AD T over EBRT alone have been proven by randomized trials conducted mainly in the 1980s and 2000s (Tables 12.1 and 12.2). Therefore, combined EBRT with ADT has become a standard approach for patients with intermediate- or high-risk CLPCa. On the other hand, EBRT alone remains as the standard treatment modality for low-risk cases since excellent biochemical control can be achieved by minimizing severe adverse events with dose-escalated EBRT, and, hence, adverse events associated with ADT can be avoided [10, 11].

Table 12.1 Randomized phase III studies comparing NA-ADT plus EBRT versus EBRT alone

Study	*n*	Clinical stage	RT dose (Gy)	RT field	Arm	PSAF (%)	DM (%)	PCSM (%)	OM (%)	Median FU (years)
RTOG 86-10 [15]	456	Bulky T2-4N0-1M0	65–70	WP	RT alone EBRT + 4M-ADT (NA+C)	80 **65**	47 **35**	36 **23**	66 **57**	13.2 11.9
RTOG 94-08 [16]	1979	T1b-2bN0M0	66.6	WP	RT alone EBRT + 4M-ADT (NA+C)	41 **26**	8 **6**	8 **4**	43 **38**	9.1
TROG 96-01 [17]	818	T2b-4N0M0	66	PSV	RT alone EBRT + 3M-ADT (NA+C) EBRT + 6M-ADT (NA+C)	74 **60** **53**	14 15 **10**	22 19 **11**	43 37 **29**	10.6
Laverdiere [18]	161	T2-3N0M0	64	PSV	EBRT alone EBRT + 3M-ADT (NA) EBRT + 10M-ADT (NA+C+A)	58 **34** **31**	N/A	N/A	N/A	5
PMH 9907 [19][a]	252	T1b-2N0M0	75.6–79.8	PSV	EBRT alone EBRT + 5M-Anti-A (NA+C)	24 17	N/A	N/A	14 18	9.1
D'Amico [20]	206	T1b-2cN0M0	70	PSV	EBRT alone EBRT + 6M-ADT (NA+C+A)	[b]	N/A	14 **4**	39 **26**	7.6

[a]The study was closed early

[b]ADT use for PSAF was significantly lower in the RT+ADT arm

Bold number: significantly different from the control (EBRT alone)

EBRT external beam radiotherapy, *n* number of patients, *PSAF* prostate-specific antigen failure, *DM* distant metastasis, *PCSM* prostate cancer-specific mortality, *OM* overall mortality, *FU* follow-up period, *M* month, *WP* whole pelvis, *P+SV* prostate plus seminal vesicles, *ADT* androgen deprivation therapy, *NA* neoadjuvant, *C* concurrent, *A* adjuvant, *N/A* not available

Table 12.2 Randomized phase III studies comparing A-ADT plus EBRT versus EBRT alone

Study	*n*	Clinical stage	RT dose (Gy)	RT field	Arm	PSAF (%)	DM (%)	PCSM (%)	OM (%)	Median FU (years)
RTOG 85-31 [21]	977	T3N0-1M0	65–70	WP	EBRT alone EBRT + permanent ADT (A)	N/A	39 **24**	22 **16**	61 **51**	11
EORTC 22863 [22]	415	T1-4N0M0	70	WP	EBRT alone EBRT + 36M-ADT (C+A)	N/A	70[a] **49**[a]	30 **10**	60 **42**	9.1
EORTC 22991 [23]	819	T1b-2aN0M0	70,74,78	P+SV (WP)	EBRT alone EBRT + 6M-ADT (C+A)	30 **17**	8 4	4 2	12 9	7.2

[a]Distant metastases or all cause of death

Bold number: significantly different from the control (EBRT alone)

EBRT external beam radiotherapy, *n* number of patients, *PSAF* prostate-specific antigen failure, *DM* distant metastasis, *PCSM* prostate cancer-specific mortality, *OM* overall mortality, *FU* follow-up period, *M* month, *WP* whole pelvis, *P+SV* prostate plus seminal vesicles, *ADT* androgen deprivation therapy, *C* concurrent, *A* adjuvant, *N/A* not available

Table 12.3 Randomized phase III studies comparing different durations of NA-ADT in combination with EBRT

Study	*n*	Clinical stage	RT dose (Gy)	RT field	Arm	PSAF (%)	DM (%)	PCSM (%)	OM (%)	Median FU (years)
TROG 96-01 [17]	818	T2b-4N0M0	66	P+SV	EBRT alone EBRT + 3M-ADT (NA+C) EBRT + 6M-ADT (NA+C)	74 **60** **53**	14 15 **10**	22 19 **11**	43 37 **29**	10.6
Crook [37]	378	T1c-4N0M0	66–67	P+SV WP	EBRT + 3M-ADT (NA) EBRT + 8M-ADT (NA)	42 35	N/A	6 7	19 21	6.6
ICORG 97-01 [38]	276	T1-4N0M0	70	P+SV	EBRT + 4M-ADT (NA) EBRT + 8M-ADT (NA)	34[a] 37[a]	N/A	4 8	10 17	8.5
RTOG 99-01 [39]	1489	T1b-T4N0M0	70.2	P+SV WP	EBRT + 4M-ADT (NA+C) EBRT + 9M-ADT (NA+C)	27 27	6 6	5 4	34 33	9.4

[a]PSAF or all cause of death

Bold number: significantly different from the control (EBRT alone or EBRT plus short-term ADT)

EBRT external beam radiotherapy, *n* number of patients, *PSAF* prostate-specific antigen failure, *DM* distant metastasis, *PCSM* prostate cancer-specific mortality, *OM* overall mortality, *FU* follow-up period, *M* month, *WP* whole pelvis, *P+SV* prostate plus seminal vesicles, *ADT* androgen deprivation therapy, *NA* neoadjuvant, *C* concurrent, *N/A* not available

There are two major approaches to combining ADT with EBRT: short- and long-term ADT. Short-term ADT is usually combined with EBRT as a neoadjuvant ± concurrent setting with durations of 3–10 months (Tables 12.1, 12.3, and 12.4). On the other hand, long-term ADT is mostly used after EBRT adjuvantly (± concurrently) (Table 12.2). Long-term ADT is also combined with short-term NA-ADT, mainly for patients with locally advanced disease [11] (Table 12.4).

12.2.2 NA-ADT Plus EBRT Versus EBRT Alone

Theoretically, the combination of ADT neoadjuvantly with EBRT has the following benefits. First, improved tumor control can be expected because ADT prior to EBRT enhances tumor eradication compared with EBRT alone, as shown in animal experiments [12]. Second, NA-ADT reduces the volume of the prostate by around 30% on average [13, 14], and this is expected to decrease the risk of adverse effects associated with EBRT by allowing a reduced radiation field size to cover the prostate.

Several randomized phase III studies comparing EBRT plus short-term NA-ADT (± concurrent ADT) with EBRT alone have been conducted [15–20] (Table 12.1). In these studies, intermediate- to moderately high-risk T1-T3N0M0 cases were the main targets. As for the radiation fields, both localized (prostate and seminal vesicles) and whole pelvis followed by a local boost approaches were indicated. The radiation doses were the former standard doses (65–70 Gy) in most studies except for the PMH 9907 study [19], where escalated doses (75.6–79.8 Gy) were used. The duration of NA-ADT in these studies varied from 3 to 10 months. In all but the PMH 9907 study, significantly lower PSA recurrence rates were achieved in combined approaches compared with EBRT alone (Table 12.1). In addition, the combined approach of short-term NA-ADT with EBRT significantly improved both prostate cancer-specific mortality (PCSM) and overall mortality in most studies.

In summary, 4–6 months of NA-ADT significantly improves not only biochemical but also survival outcomes in CLPCa treated with EBRT using the former standard doses. On the other hand, the PMH 9907 study (with a dose-escalated setting) failed to show such benefits. However, the PMH 9970 study only used bicalutamide as hormonal therapy, and the study was closed earlier than planned because subsequent evidence suggested that the relative clinical effectiveness of bicalutamide was inferior to that of standard ADT with luteinizing hormone-releasing hormone agonists [19]. Therefore, the impact of short-term ADT on dose-escalated EBRT remains an open question.

12.2.3 A-ADT Plus EBRT Versus EBRT Alone

There have been three randomized trials comparing A-ADT (± concurrent ADT) plus EBRT versus EBRT alone [21–23] (Table 12.2). Two studies combining long-term (3 years or permanent) A-ADT with EBRT using the former standard doses demonstrated a significant improvement in survival by combining A-ADT

Table 12.4 Randomized phase III studies comparing short-term ADT plus EBRT versus intermediate/long-term ADT plus EBRT

Study	*n*	Clinical stage	RT dose (Gy)	RT field	Arm	PSAF (%)	DM (%)	PCSM (%)	OM (%)	Median FU (years)
EORTC 22961 [28]	1113	T1c-4N0-1M0	70	WP	EBRT + 6M-ADT (C+A) EBRT + 36M-ADT (C+A)	N/A	N/A	4.7 **3.2**	19 **15**	6.4
RTOG 92-02 [29]	1554	T2c-4N0M0	65–70	WP	EBRT + 4M-ADT (NA+C) EBRT + 28M-ADT (NA+C+A)	61 **45**	26 **17**	22 **16**	73 **70**	19.6
TROG 03-04 [31]	1071	T2b-4N0M0	66–74 46+HDR	P+SV	EBRT + 6M-ADT (NA+C) EBRT + 18M-ADT (NA+C+A)	34 29	15 14	4.1 7.4	17 19	7.4
DART01/05 GICOR [30]	362	T1c-3bN0M0	76–82	P+SV	EBRT + 4M-ADT (NA+C) EBRT + 28M-ADT (NA+C+A)	19[a] **10**[a]	17[b] **6**[b]	3 0	14 **5**	5.3
Ito [32]	280	T3-4N0M0	72	P+SV	EBRT + 14M-ADT (NA+C+A) EBRT + 60M-ADT (NA+C+A)	36[a, c] 42[a, c]	N/A	N/A	20 25	8.2

[a]PSAF or all cause of death
[b]Distant metastases or all cause of death
[c]Non-inferiority unproven
Bold number: significantly different from the control (short-term ADT plus EBRT)
EBRT external beam radiotherapy, *n* number of patients, *PSAF* prostate-specific antigen failure, *DM* distant metastasis, *PCSM* prostate cancer-specific mortality, *OM* overall mortality, *FU* follow-up period, *M* month, *WP* whole pelvis, *P+SV* prostate plus seminal vesicles, *ADT* androgen deprivation therapy, *NA* neoadjuvant, *C* concurrent, *A* adjuvant, *N/A* not available, *HDR* high-dose-rate brachytherapy boost

with EBRT, compared with EBRT alone [21, 22]. The main targets of these studies were patients with locally advanced (T3-4N0M0) CLPCa. Therefore, long-term (2–3 years) ADT is recommended with EBRT for locally advanced CLPCa [10, 11].

The most recent study combined short-term (6 months) A-ADT with EBRT found no significant difference in survival with a median follow-up period of 7.2 years [23]. When compared with the dramatically positive impact of short-term NA-ADT on survival, short-term ADT may need to be administered neoadjuvantly rather than adjuvantly when combined with EBRT using the former standard doses.

12.3 Impact of EBRT on Primary ADT for Locally Advanced Diseases

Locally advanced prostate cancer was formerly treated with primary ADT alone, especially in Japan. In this situation, lifelong ADT is often selected. The significance of adding local EBRT to primary ADT has been debated. However, randomized phase III studies demonstrated the dramatic impact of adding EBRT to primary ADT for locally advanced cases, in terms of not only PSA control, but also survival (Table 12.5). In both the SPCG-7/SFUO-3 and NCIC CTG PR-3/MRC UK PR07 studies, the PCSM rates were reduced by around half when EBRT was added, compared with the rates in those treated by primary ADT alone [24–27]. Because the radiation doses (65–70 Gy) used in these studies can be safely delivered with three-dimensional conformal radiation therapy, EBRT should be combined with long-term ADT for patients with locally advanced prostate cancer, except for patients unfit for EBRT.

12.4 Impact of the Duration of ADT Combined with EBRT

12.4.1 Duration of Short-Term NA-ADT

Table 12.3 summarizes randomized phase III studies comparing different durations of NA-ADT with definitive EBRT for CLPCa. Because ADT is mainly applied to patients with intermediate-risk or moderately high-risk prostate cancer, the duration of ADT is relatively short (6–9 months) even in long-term arms, compared with the duration of long-term arms (28–60 months) in A-ADT studies (Tables 12.3 and 12.4). Although the 3-month ADT arm in the TROG 96-01 study failed to show survival advantages compared to EBRT alone, while the 6-month ADT arm achieved significant improvements in both PSA control and survival outcomes [17], all other studies failed to demonstrate significant differences, not only in survival but also in the PSA failure rate, between shorter (3–4 months) ADT and longer (8–9 months) ADT arms. Therefore, it seems that an ADT duration of 4–6 months will be sufficient for use in combination with EBRT as NA-ADT. Although the role of short-term NA-ADT in a dose escalation setting is unclear, it appears to be reasonable to

Table 12.5 Randomized phase III studies comparing ADT plus EBRT versus primary ADT alone

Study	*n*	Clinical stage	RT dose (Gy)	RT field	Arm	PSAF (%)	DM (%)	PCSM (%)	OM (%)	Median FU (years)
SPCG-7/SFUO-3 [24, 25]	875	T1b-3N0M0	70 (74–78)	P+SV	Lifelong ADT alone Lifelong ADT plus EBRT	75[a] **26**[a]	N/A	34 **17**	61 **51**	12.2
Mottet [40]	264	T3-4(pT3) N0M0	68–70	WP	36M-ADT alone 36M-ADT + EBRT	85 **35**	11 **3**	14 **7**	28 29	5.6
NCIC CTG PR-3/ MRC UK PR07 [26, 27]	1205	T2-4N0M0	65–69	WP	Lifelong ADT alone Lifelong ADT + EBRT	73 **37**	N/A	22 **11**	51 **45**	8

[a]At 7 years

Bold number: significantly different from the control (primary ADT alone)

EBRT external beam radiotherapy, *n* number of patients, *PSAF* prostate-specific antigen failure, *DM* distant metastasis, *PCSM* prostate cancer-specific mortality, *OM* overall mortality, *FU* follow-up period, *M* month, *WP* pelvis, *P+SV* prostate plus seminal vesicles, *ADT* androgen deprivation therapy, *N/A* not available

combine 4–6 months of NA-ADT in view of the striking impact of NA-ADT on survival combined with former standard doses of EBRT because no survival benefit has been proven in any randomized trial using dose-escalated EBRT alone.

12.4.2 Comparison of Short-Term ADT and Intermediate/Long-Term ADT

Randomized trials comparing short-term (4–6 months) ADT with long-term (28–36 months) ADT in combination with EBRT have been mainly conducted in patients with high- or very-high-risk CLPCa (Table 12.4). In those studies, long-term ADT arms demonstrated significant improvement in survival outcomes compared to those with short-term ADT with EBRT [28–30].

In the TROG 03-04 study, intermediate-term (18 months) ADT failed to demonstrate survival advantages over 6 months of ADT, although it was suggested that intermediate-term ADT plus zoledronic acid was more effective than short-term ADT [31]. On the other hand, Ito et al. [32] reported the results of a non-inferiority study comparing long-term (60 months) ADT and intermediate-term ADT (14 months) followed by intermittent ADT (intermittent arm: restart ADT when the PSA value exceeds 5 ng/mL) when combined with EBRT of 72 Gy in patients with locally advanced (T3-4N0M0) disease. Although non-inferiority of the intermittent arm was not proven, there were no statistically significant differences between the arms with regard to not only overall survival but also PSA recurrence-free survival between the arms. Therefore, no consensus has been achieved regarding the usefulness of intermediate-term ADT in EBRT.

Together with the above findings and the impact of short-term NA-ADT over EBRT alone, the current standard treatment for high- or very-high-risk CLPCa is considered to be 4–6 months of NA-ADT followed by EBRT plus an additional 24–30 months of A-ADT [10, 11].

On the other hand, in the subset analyses of both RTOG 92-02 and DART 01/05 GICOR studies, intermediate-risk groups did not show any significant benefits from long-term ADT compared with short-term ADT [30, 33]. Therefore, short-term NA-ADT remains the standard of care with respect to patients with intermediate-risk CLPCa [10, 11].

12.5 Optimal Duration of ADT in Combination with EBRT

There is broad consensus that ADT should not be combined with EBRT in patients with low-risk disease, who can expect to be safely cured by high-dose EBRT alone (in more than 90% of cases) [10, 11]. With respect to the intermediate-risk group, 4–6 months of ADT seems to be optimal, as discussed previously (12.4.2.).

On the other hand, the optimal duration of ADT for high- or very-high-risk groups has yet to be confirmed. As described in Section 12.4.2., the current standard treatment for high- or very-high-risk CLPCa is considered to be 4–6 months of

NA-ADT followed by EBRT plus an additional 24–30 months of A-ADT. However, it has been suggested that the timing of the start of S-ADT could significantly affect survival outcomes in patients who developed PSA recurrence after EBRT [5–7]. In those studies, the survival probabilities were significantly better in patients who were managed by the early initiation (at PSA ≤10–20 ng/mL) of S-ADT after the recurrence of PSA. However, none of the studies comparing EBRT alone and EBRT plus ADT, or short-term ADT plus EBRT and long-term ADT plus EBRT, specified the timing of the start of S-ADT.

We treated 120 consecutive cases with T3-4N0M0 disease (about 40% of whom were classified as very high-risk based on the 2017 NCCN classification system) with high-dose (78 Gy in 39 fractions) intensity-modulated radiation therapy combined with an NA-ADT duration of 6 months under an early salvage policy [34]. After completing IMRT, all patients were followed up without the addition of any adjuvant therapy, including A-ADT. S-ADT was started when the PSA values exceeded 4 ng/mL. Although long-term A-ADT was not used, the 8-year prostate cancer-specific and overall survival rates were 96.6% and 89.1%, respectively. Despite the very-high-risk nature of the patients, the PCSM rate was only 3.4% at 8 years. Therefore, future prospective trials should test whether significant survival advantages are still observed in patients treated with long-term ADT plus EBRT compared with those who were treated with short-term NA-ADT plus high-dose EBRT under an early initiation policy of S-ADT after PSA recurrence.

12.6 Ethnic Differences in Sensitivity to ADT

Japanese patients treated with primary ADT have less than half the adjusted PCSM of those in the USA, according to a comparison of registered data between the Japanese Cancer of the Prostate registry database and USA Cancer of the Prostate Strategic Research Endeavor registry [35]. This suggests that Japanese patients, and probably East Asian populations, have better sensitivity to primary ADT than patients in the USA [36]. This finding may also be applicable to sensitivity to S-ADT. Therefore, the outcomes obtained from studies comparing short-term ADT and long-term ADT with EBRT conducted in Western populations should be validated in studies conducted using East Asian populations.

Conclusions

When definitively treating CLPCa with EBRT using former standard doses, ADT should be combined with EBRT, except in low-risk cases. For intermediate-risk cases, the combination of NA-ADT (± concurrent ADT) for a duration of 4–6 months is the current standard treatment approach for definitive EBRT. On the other hand, an NA-ADT (± concurrent ADT) duration of 4–6 months plus A-ADT of 24–30 months is recommended in combination with EBRT for patients with high- or very-high-risk CLPCa. However, these findings should be validated for Japanese and East Asian populations under an early initiation policy of S-ADT, due to the suggestion that there are ethnic differences in sensitivity to

ADT between Japanese and Western populations. In addition, the impact of ADT is controversial when escalated doses are used for EBRT.

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