Original Article

A comparison of androgen deprivation therapy versus surgical castration for patients with advanced prostatic carcinoma

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Aim: To examine the outcomes of patients with advanced prostate carcinoma who underwent medical or surgical castration.

Methods: A hundred twenty one consecutive cases of patients with advanced prostate carcinoma who underwent medical or surgical castration between 2001 and 2006 were retrospectively reviewed. Associations between clinical outcomes and prognostic scoring factors were determined based on the Reijke study. In the surgical and medical castration groups, the impact on the prostate-specific antigen (PSA) normalization rate, the rebound rate and the disease-free survival rate were evaluated. The mean follow-up was 36.1 months.

Results: In the initial 12 months, there were no statistical differences in the PSA normalization rate and the PSA rebound rate between the two groups. However, the PSA rebound rate after the 12th month (20.90% vs 40.74%, $P=0.0175$) and the 18th month PSA normalization rate (59.70% vs 37.04%, $P=0.0217$) differed significantly between the two groups, and these differences were maintained to the end of the study. When comparing patients grouped according to Reijke prognosis scores, there was no difference between medical and surgical castration for the good prognosis group. However, among the patients given a poor prognosis, surgical castration was superior in terms of the PSA normalization rate, the PSA rebound rate, the tumor progression-free survival rate ($P<0.001$) and the overall survival rate ($P<0.001$).

Conclusion: Advanced prostate carcinoma patients with poor pretreatment prognosis scores should undergo surgical castration rather than medical castration for better PSA rebound rates and overall survival.

Keywords: androgen; surgical castration; prostate neoplasm; metastasis; prognosis; medical castration; prostate-specific antigen; luteinizing hormone-releasing hormone (LHRH)

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Introduction

Prostate carcinoma is the most common nonskin malignancy among men. Age is acknowledged as one of the risk factors for prostate carcinoma. With prostate-specific antigen (PSA)-based screening and postoperative follow-up being widely used^[1–3], the incidence of prostate carcinoma has increased. Androgen deprivation therapy (ADT) is a well-established treatment for advanced and metastatic prostate carcinoma, which began with Huggins's observations on advanced and metastatic prostate carcinoma^[4]. Although ADT improves survival for undergoing hormone therapy, biochemical recurrence after ADT remains a long-term problem to be

solved. The optimal time to initiate hormone therapy for patients with a regular PSA follow-up is still under investigation^[3, 5, 6]. As the modern pharmaceutical industry advanced, a luteinizing hormone-releasing hormone (LHRH) agonist with monthly dosing became available. From that point on, surgical castration was largely replaced by medical castration with an LHRH agonist to reduce the psychological impact of orchiectomy to the patients and to preserve reversibility^[7, 8]. Then, maximal androgen blockade (MAB) was proposed to address the androgens of adrenal origin^[9]. Many trials followed comparing MAB and monotherapy^[10–12]. However, because of the high cost of LHRH agonist and the limited medical reimbursement system, surgical castration has again become more prevalent^[13, 14]. There are several reports comparing the castration level and the sustainability of surgical and medical castration^[7, 15, 16]. However, there are few reports comparing the prognosis between these two groups.

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In this study, we compared the clinical effectiveness of surgical and medical castration with respect to patient outcomes. We also identified clinical outcomes and PSA response features that predicted favorable treatment outcomes for prostate carcinoma after ADT.

Materials and methods

Patient selection

After obtaining institutional review board approval for a retrospective study of the medical records from January 2001 to March 2006, we identified all patients who had advanced prostate carcinoma. Patients with localized prostate carcinoma received definitive therapy, such as radical surgery or radiotherapy. Patients whose clinical staging was greater than tumor stage T3, T4, or metastatic disease, received hormone therapy. In this study, we included these patients receiving hormone therapy but excluded patients on radiotherapy or chemotherapy for prostate carcinoma. However, there were some patients on palliative radiotherapy for spinal or other bone metastases.

The exclusion criteria for this study were concurrent malignancy, previous surgical, radiotherapy or hormonal therapy for prostate carcinoma, poor renal and hepatic function, and a life expectancy of less than 3 months. All of the patients enrolled had a baseline PSA test, chest X-ray films, pelvic magnetic resonance imaging, and whole-body bone scans as baseline data.

From January 2001 to March 2006, we identified 121 patients with advanced prostate carcinoma (defined as stage III or stage IV carcinoma) with complete medical records. MAB included either surgical castration plus antiandrogen therapy with cyproterone (100 mg twice daily), flutamide (250 mg three times per day), or bicalutamide (50 mg daily) or medical castration consisting of LHRH agonist hormone therapy (goserelin 3.6 mg monthly or leuporelin 14 mg monthly) plus antiandrogen therapy. The patients who received medical castration received antiandrogen 2 weeks in advance for testosterone flare-up prevention^[17]. All of the prostate tumors were pathologically staged according to the 1997 TNM classification.

Reijke^[18] developed a prognostic scoring system for patients with advanced prostate carcinoma receiving hormone therapy. The prognostic scoring system is characterized by (a) >5 sites of bone metastasis, (b) hydronephrosis, (c) pain requiring analgesics, and (d) alkaline phosphatase >2 times the upper limit of the normal range. A prognostic score is determined by counting the parameters present and obtaining a five-level score (0–4 points). Collapsing the prognostic score, we divided patients into subgroups according to their prognostic score: the good prognosis group (scores 0 and 1) and the poor prognosis group (scores 2, 3, and 4). We further divided the surgical castration (group 1) and medical castration (group 2) patients into good and poor prognostic groups based on Reijke's classification. The four groups were defined as the following: (1) G1g: surgical castration with a good prognosis score, (2) G1p: surgical castration with a poor prognosis

score, (3) G2g: medical castration with a good prognosis score, and (4) G2p: medical castration with a poor prognosis score. We evaluated these enrollment criteria in association with subsequent disease progression and treatment patterns to clarify the most appropriate therapy for metastatic prostate carcinoma. After initiating the hormone therapy, patients were monitored regularly with a PSA checkup every 3 months.

Statistical analysis

SPSS 15.0 for Windows [SPSS INC., CHICAGO, IL60616] was used to analyze the collected data. The PSA normalization rate and the PSA rebound rate were examined using the Chi-squared test. The tumor progression-free survival rate and the overall survival rate were calculated using the Kaplan-Meier method.

Results

We identified 121 patients with complete medical records. There were 67 patients in group 1 (surgical castration) and 54 patients in group 2 (medical castration). Table 1 shows the patient distribution and prostate carcinoma characteristics (initial PSA, Gleason score, tumor staging, and metastasis). The bone metastasis rate was higher in the medical castration group, and it reached statistical significance. However, in Reijke's criteria with four independent prognosis factors for advanced prostate carcinoma, there was no difference between these two groups.

The cancer-specific survival rates for patients within group 1 and 2 differed significantly ($P < 0.001$) (Figure 1). Patients in the surgical castration group demonstrated better survival than the medical castration group.

Figure 1. Cancer-specific survival based on overall good and poor prognosis groups.

PSA normalization rate

The PSA normalization rates by study group are shown in Table 2. We defined the PSA normalization rate as the percentage of patients with a PSA level returning to normal (<4 ng/mL) and staying normal. The PSA normalization

Table 1. Patient characteristics of the advanced prostate cancer.

	Group 1: Orchiectomy + Anti-androgen	Group 2: LHRH Agonist + Anti-androgen	P value
Number	67	54	
Age (mean)	74.13 (59–89)	72.94 (50–88)	0.3676
Initial PSA level (median)	202.82 (2.56–13851.20)	297.72 (19.14–7422.83)	0.3234
Gleason score			
2–6	9	2	
7	13	10	
7–10	45	42	
TNM stage			
Stage III	17.91% (12/67)	5.56% (3/54)	
Stage IV	82.09% (55/67)	94.44% (51/54)	0.0763
Metastasis			
Bone metastasis	58.21% (39/67)	81.48% (44/54)	0.0109
Lung metastasis	1	3	
Liver metastasis	0	3	
Reijke prognosis criteria			
Good	45 (67.16%)	34 (62.96%)	
Poor	22 (32.84%)	20 (37.04%)	0.7714
Anti-androgen			
Steroid	56.9%	37.25%	
Non-steroid	43.1%	62.75%	

Table 2. Match comparison of patients undergoing ADT at PSA normalization rate.

	Group 1	Group 2	P-value	Group 1g	Group 2g	P-value	Group 1p	Group 2p	P-value
3 month	55.22% (37/67)	44.44% (24/54)	0.3192	55.56% (25/45)	47.06% (16/34)	0.6024	54.55% (12/22)	40.00% (8/20)	0.3743
6 month	71.64% (48/67)	53.70% (29/54)	0.0645	75.56% (34/45)	58.82% (20/34)	0.1806	63.64% (14/22)	45.00% (9/20)	0.3521
9 month	68.66% (46/67)	55.56% (30/54)	0.1960	75.56% (34/45)	55.88% (19/34)	0.1094	54.55% (12/22)	55.00% (11/20)	1
12 month	62.69% (42/67)	42.59% (23/54)	0.0434	71.11% (32/45)	47.06% (16/34)	0.0530	45.45% (10/22)	35.00% (7/20)	0.5403
15 month	61.19% (41/67)	42.59% (23/54)	0.0637	66.67% (30/45)	47.06% (16/34)	0.1281	50.00% (11/22)	35.00% (7/20)	0.3665
18 month	59.70% (40/67)	37.04% (20/54)	0.0217	66.67% (30/45)	47.06% (16/34)	0.1281	45.45% (10/22)	20.00% (4/20)	0.0375
21 month	61.19% (41/67)	35.19% (19/54)	0.0078	64.44% (29/45)	44.12% (15/34)	0.1159	54.55% (12/22)	20.00% (4/20)	0.0289
24 month	55.22% (37/67)	31.48% (17/54)	0.0152	64.44% (29/45)	41.17% (14/34)	0.0676	36.36% (8/22)	15.00% (3/20)	0.0465

PSA normalization is defined as PSA level <4 ng/mL

Group 1: Orchiectomy+anti-androgen. Group 2: LHRH agonist+anti-androgen. G1g: surgical castration group with good prognosis score. G1p: surgical castration group with poor prognosis score. G2g: medical castration group with good prognosis score. G2p: medical castration group with poor prognosis score.

rate peaked in the 6th and 9th months in the surgical and the medical castration group, respectively. The PSA normaliza-

tion rate then decreased with time; in the 18th month, there was a difference between these two groups ($P=0.0217$). When

we further divided groups 1 and 2 into four subgroups by Reijke's^[19] prognostic factors, patients with good prognosis scores, regardless of the castration method, showed no significant difference in PSA normalization during the 2 years of follow-up ($P=0.0676$). However, in the poor prognosis patient group, patients in the surgical castration group (G1p) had significantly better PSA normalization rates than those in the medical castration group (G2p) ($P=0.0465$). This difference, which occurred after the 18th month, remained to the end of the study.

PSA rebound rate

After ADT, follow-up was performed every 3 months for the first 2 years. The first detected PSA increase after steady state for all available PSA measurements at least 3 months apart were analyzed for PSA rebound. PSA rebound was defined as a PSA level ≥ 4 ng/mL or greater than the previous measurement. Table 3 summarizes the PSA rebound rate. The PSA rebound rate was lower in group 1 (surgical castration) than group 2 (medical castration); the significant difference occurred 12 months after castration ($P=0.0175$). In the good prognosis group, there was no significant difference in the PSA rebound rate between surgical and medical castration until the 21st month. In contrast, in the poor prognosis group, the PSA rebound rate was significantly lower in group 1 (surgical castration) after 15 months than in group 2 (medical castration) ($P=0.0286$).

Tumor progression-free survival rate

After stratifying the patients in groups 1 and 2 according to the Reijke scoring system, the cancer survival for patients within the four prognostic groups (G1g, G1p, G2g, and G2p) was analyzed. Tumor progression was defined as any one of the following situations: (1) PSA rebound, (2) increased prog-

nosis score, (3) death, (4) imaging or clinical evidence of tumor progression. In the good prognosis group, the curves of tumor progression-free survival were similar between surgical and medical castration ($P=0.001$). However, in the poor prognosis group, patients in the surgical castration (G1p) group survived significantly longer than those in the medical castration group (G2p) ($P<0.001$, Figure 2).

Figure 2. Tumor progression-free survival rate by group.

Overall survival rate

The overall survival of patients in the four groups is shown in Figure 3. The overall survival rate in the good prognosis group did not differ significantly by castration method. However, among patients with a poor prognosis, those in the surgical castration group survived significantly longer than patients in the medical castration group ($P<0.001$).

Discussion

The concept of treating metastatic prostate carcinoma started with Huggins's observation in 1941^[4]. After that, hormone

Table 3. Match comparison of patients undergoing ADT at PSA rebounding rate.

	Group 1	Group 2	P-value	Group 1g	Group 2g	P-value	Group 1p	Group 2p	P-value
6 month	8.96% (6/67)	12.96% (7/54)	0.6800	4.44% (2/45)	8.82% (3/34)	0.7435	18.18% (4/22)	15.00% (3/20)	1
9 month	16.42% (11/67)	27.78% (15/54)	0.1971	13.33% (6/45)	29.41% (10/34)	0.1394	22.72% (5/22)	25.00% (5/20)	1
12 month	20.90% (14/67)	40.74% (22/54)	0.0175	17.78% (8/45)	35.29% (12/34)	0.1307	27.27% (6/22)	50.00% (10/20)	0.2040
15 month	22.39% (15/67)	48.15% (26/54)	0.0054	20.00% (9/45)	41.18% (14/34)	0.0717	27.27% (6/22)	65.00% (12/20)	0.0286
18 month	23.88% (16/67)	53.70% (29/54)	0.0014	22.22% (10/45)	44.12% (15/34)	0.0676	27.27% (6/22)	70.00% (14/20)	0.0124
21 month	23.88% (16/67)	57.41% (31/54)	0.0004	22.22% (10/45)	47.06% (16/34)	0.0371	27.27% (6/22)	75.00% (15/20)	0.0048
24 month	25.37% (17/67)	57.41% (31/54)	0.0007	22.22% (10/45)	47.06% (16/34)	0.0371	31.82% (7/22)	75.00% (15/20)	0.0068

PSA rebound was defined as that PSA level become higher than the previous checked data.

Group 1: Orchiectomy+anti-androgen; Group 2: LHRH agonist+anti-androgen; G1g: surgical castration group with good prognosis score; G1p: surgical castration group with poor prognosis score; G2g: medical castration group with good prognosis score; G2p: medical castration group with poor prognosis score.

Figure 3. The overall survival rates by group.

therapy became the mainstay of treatment for men with advanced and metastatic prostate carcinoma. The initial regimen of androgen deprivation therapy included bilateral orchiectomy, estrogen therapy, or both. However, these therapies had a greatly negative impact on quality of life, not to mention the occurrence of lethal cardiac events^[20, 21]. The discovery of synthetic luteinizing hormone-releasing hormone agonists reduced the cardiac toxicity and the other side effects of androgen deprivation therapy. Then, in 1983 Labrie *et al*^[9] conducted a new trial for the total elimination of androgen from both the testes and adrenal glands. They reported a small series of patients with advanced prostate carcinoma managed with an LHRH analogue combined with an oral antiandrogen. The results showed an impressive improvement in survival rate, and this success led to numerous studies exploring this concept. In addition, with the longer duration of LHRH dosage intervals and the reduced negative impact to patients' self-image and cosmetic appearance^[7, 8], LHRH agonist therapy became more popular than surgical castration^[22, 23].

Because medical castration is reversible and has less of a psychiatric impact than surgical castration, several new trials have been conducted in different clinical situations. These trials showed that patients with localized prostate carcinoma received no benefit from primary androgen deprivation therapy^[24, 25]; on the contrary, patients with metastatic prostate carcinoma showed a survival benefit with androgen deprivation therapy^[26, 27]. Additionally, these trials provided evidence supporting androgen deprivation therapy for a survival benefit among patients who underwent radical prostatectomy with positive lymph node resection^[28, 29] and among those with locally advanced prostate carcinoma after radiotherapy^[30, 31].

The medical insurance system has become more prevalent and influential in recent decades. Medical expenses surge with administration of more new drugs and the use of new and delicate medical instruments. Restriction of medical expenses became inevitable and is an important factor in physicians' decision-making processes. As a result, the number of surgical castrations increased again^[13, 14]. This study provides evidence supporting surgical castration rather than medical

castration with LHRH, especially among patients with poor prognoses. We also showed that there was little survival benefit among patients with good prognosis scores, regardless of the method of castration. In Samson's analysis of patients with complete androgen blockade or monotherapy with LHRH, they also concluded that there was no survival benefit between complete androgen blockade and monotherapy with LHRH in patients with a good prognosis^[10]. As a result, in the poor prognosis group (>5 sites of bone metastasis, hydronephrosis, pain requiring analgesics, alkaline phosphatase >2 times the upper limit of the normal range), bilateral orchiectomy should be performed for a better survival benefit. The reason why surgical castration is superior to medical castration with LHRH is not clear. According to Morgentaler's saturation model, prostate carcinoma requires a fairly low testosterone concentration for the carcinoma to flourish^[32]. There are some studies indicating that LHRH therapy does not achieve as low of a testosterone level as does bilateral orchiectomy^[33–36]. This might be one of the reasons why surgical castration had better outcomes for advanced prostate carcinoma, especially in the poor prognosis group. Another reason that might explain this difference is the sustainability of testosterone suppression. Bilateral orchiectomy would definitely cease the production of testosterone. Owing to different pharmacokinetics from person to person, the LHRH agonist might not be able to remain effective for one full month in every single person. Then, during readministration of the LHRH agonist, testosterone flares up and this causes so-called acute-on-chronic responses^[36]. In our present study, antiandrogen was used in the medical castration group, but repeated flare-up episodes might also lead to a poor result.

In this study, ADT for the treatment of advanced prostate carcinoma improved tumor progression-free survival and biochemical failure rates after 12 months for patients in the surgical castration group. When we compared Reijke scores among the patients, surgical castration for patients with poor prognostic scores resulted in better disease-free survival and PSA normalization rates. The survival advantage suggests that surgical castration is beneficial in patients with poor prognosis scores, although further studies are needed to identify which patients would derive the most benefit from hormone therapy, particularly when balanced against the potential adverse cardiovascular effects of long-term ADT.

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Author contribution

Ke-hung TSUI designed research; Ke-hung TSUI, Phei-lang CHANG performed research; Yu-hsiang LIN and Chien-lun CHEN contributed new analytical tools and reagents; Chen Pang HOU analyzed data; Yu-hsiang LIN wrote the paper.

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