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Trends of prostate cancer treatment in Ehime Prefecture, Japan: analysis of a hospital-based cancer registry

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Abstract

Background We previously conducted a retrospective Japanese cohort study of patients who underwent radical prostatectomy (RP) between January 2010 and December 2020 in Ehime Prefecture. This study revealed an increase in the number of RP, but other treatment trends remained unclear. In the current study, we examined prostate cancer treatment in Ehime Prefecture using the hospital-based cancer registry of all designated cancer care hospitals and community cancer care hospitals belonging to the Council of Ehime Cancer Care Hospitals.

Methods Trends of prostate cancer were compared by year according to stage and treatment using data from the hospital-based cancer registry between 2011 and 2020.

Results The number of patients with stage 1 disease increased over time, but the proportion of patients with stage 1 disease among all patients decreased from 65.2% in 2012 to 56.9% in 2020. The number of patients with stage 2 disease also increased, but the proportion of such patients among all patients remained constant. Meanwhile, the proportions of patients with stage 3 or 4 disease increased significantly over time, while that of patients undergoing RP increased from 29.2% in 2011 to 45.7% in 2020 ($P < 0.001$). The proportion of patients receiving radiotherapy (RT) decreased from 25.8% in 2011 to 17.2% in 2020. The use of hormone therapy (HT) remained unchanged, and the proportion of patients undergoing observation fell from 11.0% in 2011 to 7.0% in 2020. A higher proportion of patients with stage 3 cancer received HT, and RT was more frequently used in stage 3 cancer than in stage 1–2 cancer. The use of HT increased with age.

Conclusions The data highlighted differences in prostate cancer stages and treatment over time. This information could be shared with both urologists and radiologists to improve treatment.

Keywords Prostate cancer, Hospital-based cancer registry, Treatment, Annual trend, Ehime Prefecture

Background

Prostate cancer was the third most common cancer in men in Japan in 2010 but the most common cancer in 2017 and 2020 [1]. Radical prostatectomy (RP) and radiotherapy (RT) are the typical treatments for localized prostate cancer, whereas hormone therapy (HT) is commonly used for metastatic prostate cancer. Multidisciplinary treatment is also considered for locally advanced prostate cancer. RP has shifted from open procedures to minimally invasive surgeries such as robot-assisted surgery. In Japan, robot-assisted RP (RARP) gained insurance

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coverage in 2012, and its use subsequently spread rapidly [2]. In addition, RT has also undergone major changes with the advent of brachytherapy and the widespread use of intensity-modulated RT (IMRT). Furthermore, RT has progressed, with image-guided RT and hypofractionated RT gaining popularity [3]. HT is generally used as an initial treatment for metastatic hormone-sensitive prostate cancer, but it is not promoted as an individual treatment for localized cancer. Meanwhile, the concept of metastasis-directed therapy (MDT) has emerged, and radical RT of the prostate under HT, including metastases, is currently possible even if metastases are present at the time of initial treatment [4–6]. However, few reports have examined these treatment changes.

To ensure accurate cancer registration, the Japanese Ministry of Health, Labour and Welfare established hospital-based cancer registries (HBCRs) [7]. The National Cancer Center in Japan collects data from the HBCRs of cancer care hospitals categorized by the national government as designated cancer care hospitals (DCCHs). The Council of Ehime Cancer Care Hospitals (ECCHs) has collected HBCR data from each DCCH since 2011 and from each community cancer care hospital (CCCH) since 2016 [8]. We previously examined the Medical Investigation Cancer Network (MICAN) study, a retrospective Japanese cohort study of patients who underwent RP between January 2010 and December 2020 in Ehime Prefecture [9]. This study revealed an increase in the number of RP, but other treatment trends remain unclear. In the current study, we used HBCR data in Ehime Prefecture to examine trends of prostate cancer stage and treatment.

Methods

HBCR is a system that collects new cases undergoing diagnosis or treatment at an individual hospital every year. The HBCR includes identifying and demographic information, diagnostic information, the first course of treatment, and follow-up information. Follow-up data are available in the fifth year after registration. However, follow-up data were not transferred in this study. These first treatment cases were registered for any treatment planned and performed at the facility for at least 5 months after the date of diagnosis or at the first visit in the year of the first treatment. Cases diagnosed in 2020 were submitted for registration between August and September 2021. Therefore, any treatment performed before registration was registered as the first treatment. Treatment was coded as surgical, laparoscopic surgery, endoscopic surgery, radiation, chemotherapy, hormonal, other, or no treatment. The HBCR in Ehime Prefecture was started in 2011. CCCHs were not included in the registry until 2016. At present, there are seven DCCHs and eight CCCHs in Ehime Prefecture. Almost all cases

of RP and RT in this prefecture are performed in DCCHs and CCCHs.

Well-trained cancer registrars at each hospital conduct registration according to standard criteria. Training sessions are held regularly at ECCH to improve the skill levels of registrars. Patients newly diagnosed with prostate cancer who received initial treatment at a DCCH or CCCH in Ehime Prefecture were eligible, and the prostate cancer patients were extracted using ICD-O-3 diagnosis code C61 from 2011 to 2020 if they were first treated at the DCCHs or CCCHs. In Ehime Prefecture, approximately 10% of cases in the hospital-based cancer registry were diagnosed and not treated. These cases were excluded from the current study. In this study, the data were divided into the following categories: surgical treatment ± hormones (RP), radiation therapy ± hormones (RT), hormone therapy (HT), other treatment including chemotherapy (other), and no treatment (observation). In this study, we reviewed changes in the stage distribution and treatment modalities. Treatment was compared and defined as RP, RT, HT, and observation. Observation was the no-treatment group, which, in the case of prostate cancer, included active surveillance (AS) and watchful waiting (WW). Because the performance status (PS) and Gleason score were not included in the HBCR data, the AS group could not be accurately identified. Therefore, the observation group included patients who underwent AS or WW, in addition to patients who were not eligible for treatment because of poor PS. RP and RT included combined HT, and other treatment included chemotherapy combined with HT.

Cancer stages were classified using the 7th edition of the TNM classification until 2017 and the 8th edition from 2018, but the 6th edition was used in 2011. The stage classification in the 6th edition differs significantly from the current classification, particularly regarding stage 1 (T1 and Gleason score 2–4). Therefore, we did not include the 2011 data when stages 1 and 2 were analyzed separately, but these data were added to the analysis of the combined stage 1 and 2 data. Although the TNM 8th edition has been used since 2018, the stages were not changed from the TNM 7th edition.

According to the Statistics Bureau of Japan, the population in Ehime Prefecture reached 1.43 million in 2010 (47.0% males and 23.0% of the population aged 65 and older), declining to 1.33 million in 2020 (47.4% males and 28.7% of the population aged 65 and older). We examined the 10-year treatment trends using HBCR data. The Cochran–Armitage trend test was used to assess the annual trends by age and stage. Statistical analyses were performed using Stata, version 18.0 (StataCorp, College Station, TX, USA).

This study was reviewed and approved by the Ethics Committee at our institution (2023–531).

Results

Figure 1 presents the age and stage distribution. The number of new cases increased from approximately 700 in 2011 to 900 in 2020. In particular, the proportion of patients older than 75 increased from 32.1% in 2011 to 38.9% in 2020 ($P < 0.001$; Fig. 1a). The number of patients with stage 1 disease increased, but the proportion of such patients among all patients decreased from 65.2% in 2012 to 56.9% in 2020 ($P < 0.001$). The number of patients with stage 2 disease also increased over time, but the proportion of such patients remained constant. Meanwhile, the proportions of patients with stage 3 ($P < 0.001$) and 4 disease ($P = 0.0026$) increased significantly over time. In particular, the proportion of patients with stage 3 cancer jumped from 4.9% in 2018 to more than 10% in 2019, before decreasing slightly to 8.9% in 2020 (Fig. 1b). Trends in RP, RT, HT, and observation are presented in Fig. 2. The proportion of patients undergoing RP increased from 29.2% in 2011 to 45.7% in 2020 ($P < 0.001$). However, the number of patients undergoing RT remained similar over time, but the proportion of RT-treated patients decreased from 25.8% in 2011 to 17.2% in 2020 ($P < 0.001$). The proportion of patients undergoing HT remained unchanged at 27%–30%, and the proportion of patients undergoing observation decreased from 11.0% in 2011 to 7.0% in 2020 ($P = 0.019$), although the number of such patients remained constant (Fig. 2). Regarding treatment by stage, the use of RP continued to increase for stages 1 and 2, reaching 55.0% in 2020

($P < 0.001$). Conversely, the proportion of patients undergoing RT declined from 29.0% in 2011 to 11.5% in 2018 ($P < 0.001$). The use of HT and observation did not change over time at a constant rate (Fig. 3a). The proportion of patients with stage 3 cancer who received RP significantly increased from 7.9% to 39.0% ($P < 0.001$). The proportion of patients who received RT was higher in stage 3 than in stages 1–2, and the proportion increased over time, albeit without significance, from 15.8% to 27.3% ($P = 0.464$). Meanwhile, the use of HT in stage 3 decreased from 63.2% to 32.5% ($P < 0.001$) (Fig. 3b). Meanwhile, most patients with stage 4 disease received HT, and the rate did not significantly change over time (Fig. 3c).

Cancer stages and treatments were separately investigated in patients aged ≤ 75 and > 75 years. The proportion of patients with stage 1 disease significantly decreased over time in patients aged ≤ 75 ($P < 0.001$), whereas those with the other stages increased over time (stage 2: $P = 0.050$; stage 3: $P < 0.001$; stage 4: $P = 0.005$). Among patients aged > 75 years, the proportion with stage 1 disease decreased ($P = 0.002$), whereas that of patients with stage 3 disease increased ($P < 0.001$; Fig. 4a, b). Regarding treatment, the use of RP increased in both groups, whereas that of RT decreased ($P < 0.001$). The rate of the increase in RP use was greater for those older than 75 years (from 5.3% to 24.0%). The proportion of patients undergoing RT more strongly decreased for patients older than 75 years (from 26.4% to 16.9%) than for those aged ≤ 75 years (from 25.6% to 17.4%). The use of HT and observation was constant in both groups, and HT was overwhelmingly more common in patients older than 75 years than in those aged ≤ 75 years (Fig. 4c, d).

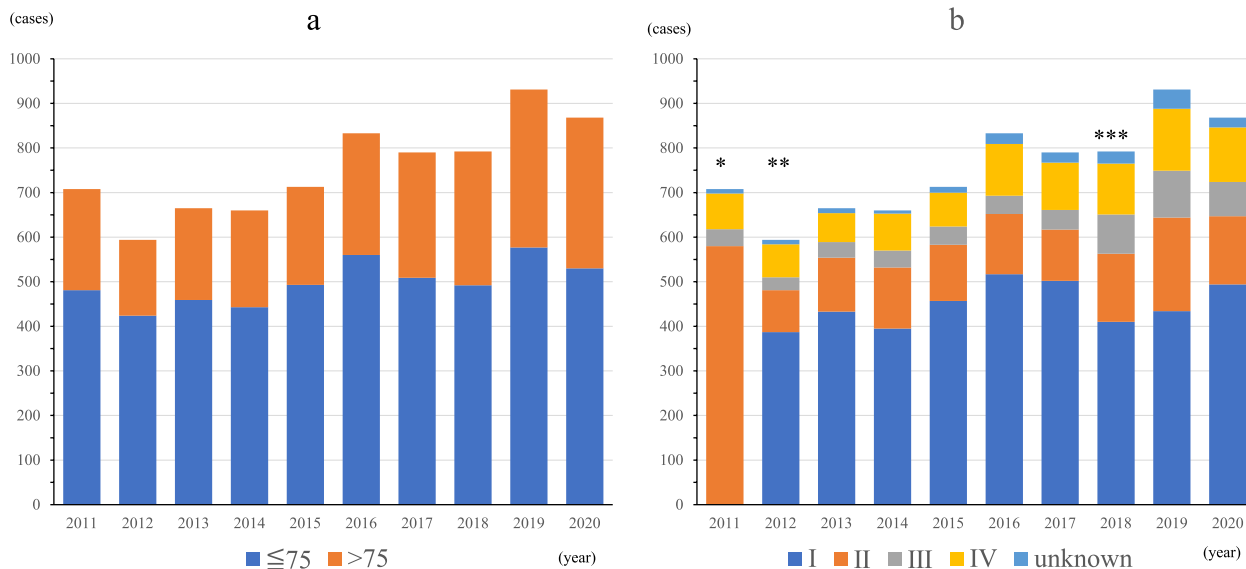


Fig. 1 Trends of age and cancer stage over time. **a** Age distribution; **b** stage distribution. *TNM 6th edition, **TNM 7th edition, ***TNM 8th edition

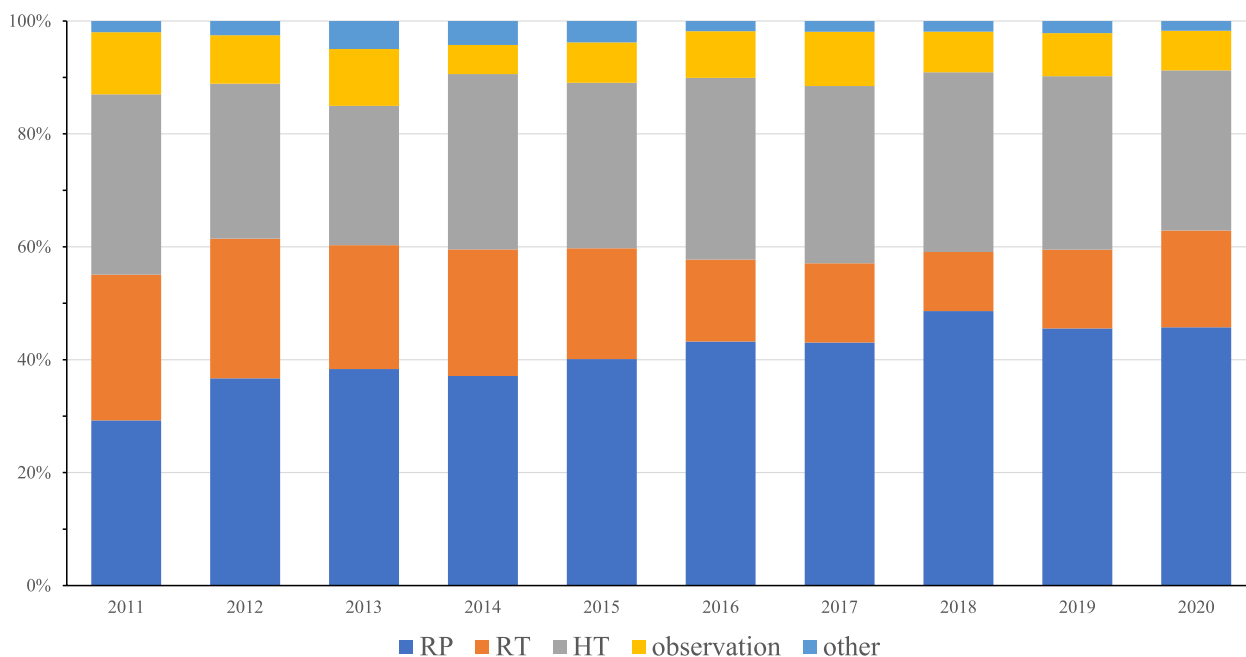


Fig. 2 Trends of treatment over time. RP and RT include neoadjuvant and adjuvant HT, and HT includes concomitant chemotherapy. Observation includes AS and WW. RP, radical prostatectomy; RT, radiotherapy; HT, hormone therapy; AS, active surveillance; WW, watchful waiting

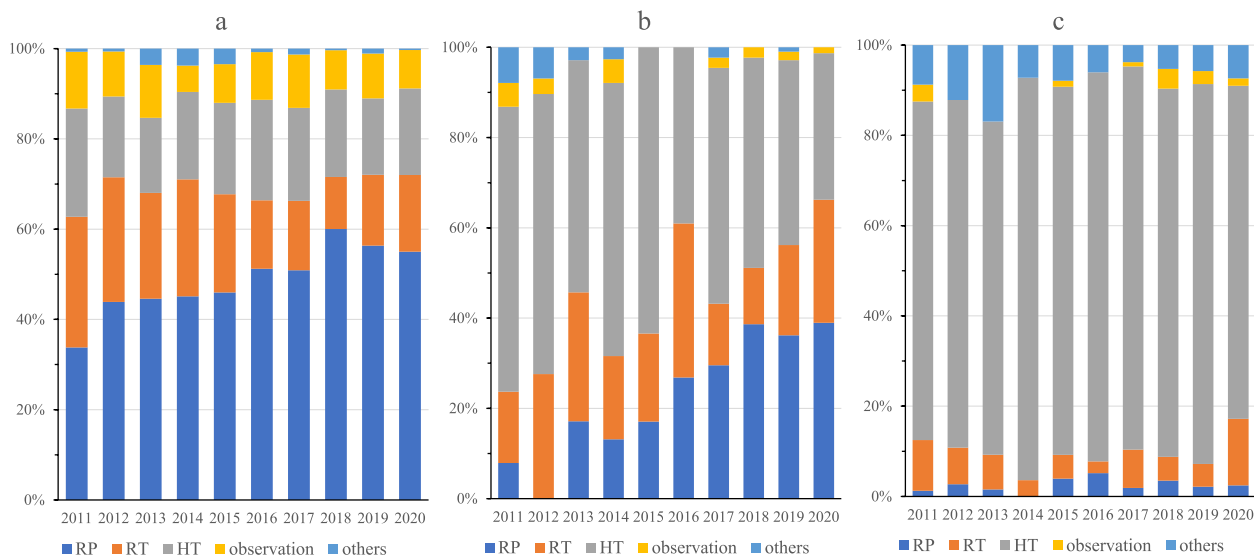


Fig. 3 Trends of treatment by year and stage. **a** Stages 1–2. **b** Stage 3. **c** Stage IV. RP and RT include neoadjuvant and adjuvant HT, and HT includes concomitant chemotherapy. Observation includes AS and WW. RP, radical prostatectomy; RT, radiotherapy; HT, hormone therapy; AS, active surveillance; WW, watchful waiting

Concerning treatment by stage in each age group, no difference was observed by age in stages 1–2, with the use of RP increasing and that of RT decreasing in both groups ($P < 0.001$). Although the proportion of patients undergoing HT did not increase over time, it was the most common treatment in patients older than 75 years (Fig. 5a, b). The use of surgery markedly increased in patients

aged > 75 years with stage 3 disease ($P < 0.001$), whereas the proportion of patients receiving HT significantly declined ($P < 0.001$). The proportion of patients who received RT was higher for those aged > 75 years than in those aged ≤ 75 years, but the rate did not significantly change over time in either group. In patients older than 75 years, the rate of RP increased from 0% to 12.2%, but

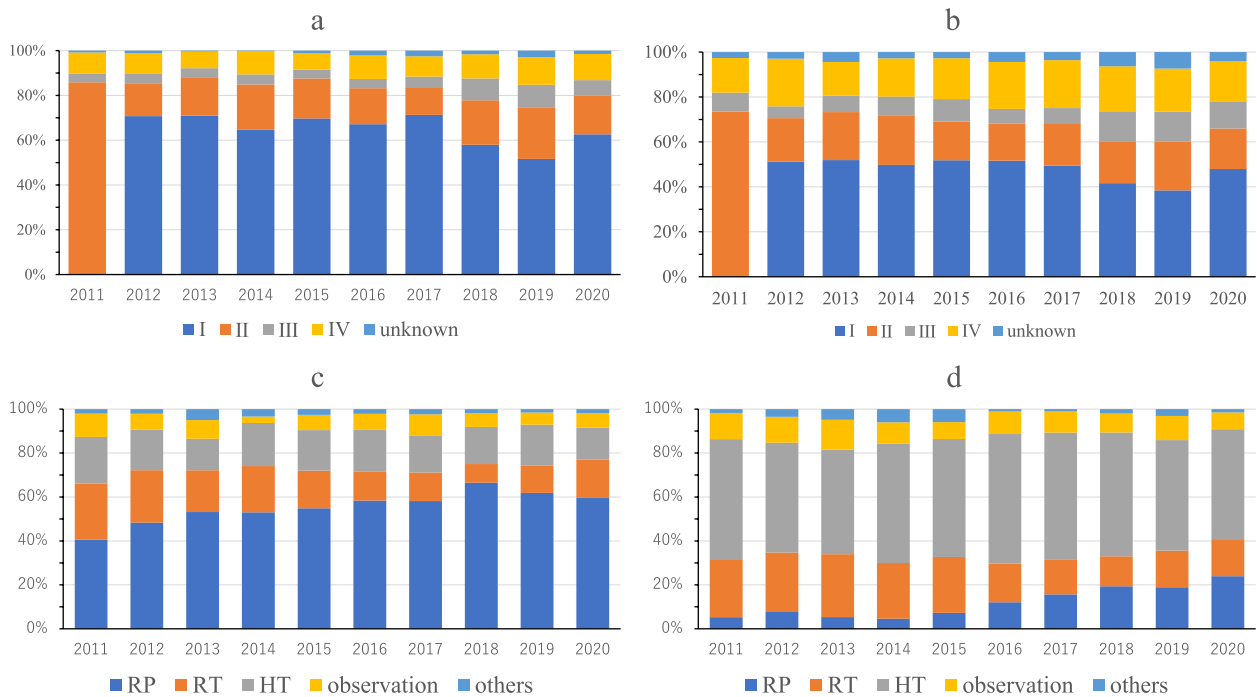


Fig. 4 Trends of clinical stage and treatment by age. **a** Stage distribution in patients aged ≤ 75 years. **b** Stage distribution in patients aged > 75 years. **c** Distribution of treatment in patients aged ≤ 75 years; **d** distribution of treatment in patients aged > 75 years



Fig. 5 Distribution of treatment by stage in younger and older patients. **a** Patients aged ≤ 75 years with stage 1–2 disease. **b** Patients aged > 75 years with stage 1–2 disease. **c** Patients aged ≤ 75 years with stage 3 disease. **d** Patients aged > 75 years with stage 3 disease

numerically fewer patients underwent RP over time. HT was the most common treatment in patients older than 75 years (Fig. 5c, d).

Discussion

To our knowledge, this is the first report of treatment trends for prostate cancer using HBCR data in Ehime Prefecture. In this prefecture, the number of patients with prostate cancer has increased over time. In Ehime, the population is decreasing, but prostate cancer is increasing along with the aging rate. In our previous report on the MICAN study, biopsy and surgery cases were all older [9]. Over the study period, the proportion of patients with stage 1 cancer decreased, whereas that of patients with stage 3–4 cancer increased. The proportion of patients who underwent RP increased over time, whereas that for RT decreased. RP was selected in more than 50% of cases up to stage 2. Meanwhile, the proportion of patients treated with RT decreased, whereas that of patients assigned to HT and observation remained unchanged. In stage 3 cancer, the proportion of patients who underwent RP significantly increased, whereas that of patients who underwent RT increased without significance. Conversely, the proportion of patients who received HT decreased in stage 3. HT was more frequently used in patients older than 75 years than in younger patients, and the proportion of patients who underwent RP significantly increased in older patients. Many younger patients tended to select RP.

Treatments for prostate cancer, including RP, RT, HT, and observation (including AS), are selected according to the disease stage and risk classification. For localized prostate cancer, randomized controlled trials illustrated that survival is similar for RP, RT, and observation [9–11]. Conversely, urinary incontinence is more common for RP, and RT is associated with worsening gastrointestinal symptoms after treatment [12, 13]. In terms of quality of life, observation might be better than RP and RT. Therefore, shared decision-making is needed for treatment decisions based on age and lifestyle.

Bergh et al. found that the number of patients undergoing RP increased sevenfold between 2000 and 2015 [14]. They concluded that the increased use of surgery was attributable to increases in the number of prostate cancer cases and the number of localized cancers that are amenable to RP [14]. The number of patients with prostate cancer increased over time in Ehime Prefecture, resulting in higher numbers of surgeries and cases of localized prostate cancer. Another reason for the increased use of RP was the availability of minimally invasive surgery, especially robotic-assisted surgery, permitting surgery in patients aged ≥ 75 years. Several investigators reported an increase in the number of surgeries and surgical age

during their study periods [15, 16]. In Ehime, the number of surgeries performed in patients older than 75 years significantly increased. Moreover, improvement in urinary incontinence, a postoperative complication, is another factor contributing to the increased use of surgery. RARP has been available in Ehime Prefecture since 2012, being available in four facilities in 2014 and six facilities in 2018 [9].

In Ehime, the MICAN study identified an increase in the number of surgeries [9]. However, details regarding RT use were not provided. Using HBCR data, a decrease in RT use was noted. However, the reason for this decrease is unclear. It is clear that the relative decrease in the use of RT is attributable to the increased use of surgery. More people opted for RP in both the ≤ 75 and > 75 years age groups. RT, especially IMRT, gained popularity in the 2000s according to some reports [17–19]. However, there are no recent reports on the trends in RT. The number of patients undergoing RT has increased, but RP is the more common treatment option, leading to an overall decrease in the proportion of patients undergoing RT.

Although the trends by year are unknown, Cooperberg et al. reported trends in initial treatment using CaPSURE data [20]. In their study covering the period through 2008, AS, RP, external RT, brachytherapy, and HT were selected in 6.8%, 49.9%, 11.6%, 13.3%, and 14.4% of patients, respectively, which were relatively similar to the findings in the present study. In addition, Gray et al. reported treatment trends from 2004 to 2012 by risk classification [21]. Among low-risk patients, the proportion of patients undergoing observation increased from 9.2% to 21.3%, and the proportion of patients undergoing RP increased from 29.5% to 51.1%. Conversely, the proportion of patients receiving external RT decreased from 24.3% to 14.5%, and that for brachytherapy decreased from 31.7% to 11.1%. The trends were the same in the intermediate- and high-risk groups. Their results similarly revealed an increase in RP use and a decrease in RT use. However, their data are more than 10 years old, and it is unclear whether they reflect the current situation.

Regarding observation, AS has become the standard of care for low-risk and very low-risk patients, and its use is increasing [22–24]. In the present study, it was not possible to distinguish between AS and WW, but most of the observed patients with stage 1 disease were considered to be undergoing AS. Cooperberg et al. reported that the rate of AS in the low-risk group jumped from 6.7% in 1990–1994 to 40.4% in 2010–2013 using CaPSURE data [20]. However, only 10% of patients were undergoing observation, and its use did not differ by age or stage in our study. AS protocols have been presented in large studies such as PRIAS, and their validity has been

proven [22–24]. Randomized controlled trials identified no difference in survival rates among RP, RT, and AS [9–11], although some reports recorded better survival rates for RP [25, 26]. In a national survey in Japan, 90.5% of respondents said they would recommend AS for low-risk disease [27]. However, the rates of AS were 21% in 2010 and 32.5% in 2015 [28, 29]. In Ehime, many patients tended to undergo RP even in stage 1, and AS was not selected. The reason for the lack of an increase is not clear, but it is assumed that, as with the decrease in RT usage, many patients prefer RP. In general, patients in rural areas tend to choose RP over RT and observation.

With the increase in the number of patients with cancer, the use of HT appears to be increasing, but the trend has been unclear until this study. In stage 4, HT is the mainstay of treatment, but recently, MDT has also been used. In our report, radical therapy with MDT was performed in some patients with stage 4 disease. However, the number of patients with stage 4 disease is increasing. We must reduce the number of stage 4 cases through early detection.

In older patients, the initial treatment is determined by health status as opposed to age [30]. Under National Comprehensive Cancer Network guidelines, RP is recommended for patients with an expected life expectancy of 10 years or more. In Japan, the expected life expectancy for 75-year-old patients is 10 years as of 2020. As life expectancy has increased, increasing numbers of older people can tolerate RP. Additionally, the spread of minimally invasive surgery is also a major factor. Although RARP, which is currently the mainstay of surgery, has the limitation of a low head position, perioperative results and blood loss have been greatly improved [31, 32]. Currently, more than 90% of patients who had RP in Ehime Prefecture are undergoing RARP, and RP is also being performed in patients older than 75 years [33]. Conversely, it is unclear why the proportions of older patients assigned to RT and observation have not increased. Because the actual numbers themselves have not changed, their decreased proportional usage appears to be related to the prominent increase in surgical treatment. RT is reported to carry a better prognosis in older patients, and thus, it is important to select treatments based on patients' preferences and lifestyles [34].

This study had several limitations. First, only published data were used in this study, it was not possible to verify the data at each facility, and detailed background information such as age were unknown. However, the high registration rate indicates that the results are reliable. In general, HBCRs catalog approximately 70% of all cases, but Ehime has a collection rate exceeding 90% because of the efforts of the registrant and ECCH guidance [8, 35]. Second, the HBCR might not record cancer treatment

data beyond 5 months after the initial treatment. For instance, it is common to start RT after 6 months of HT; therefore, RT could be omitted from the registry. In Ehime, treatment planned at the time of initial diagnosis is registered, and RT is almost fully covered. This verification conducted on our hospital's cases showed that all RT treatments were included (data not shown). Additionally, because all surgeries and RTs are performed at DCCHs and CCCHs in Ehime, the HBCR is sufficient. Radical therapy (RP or RT) after AS might be performed more than 1 year after initial treatment, and consequently, these treatments are not recorded in the HBCR. However, the initial treatment in these cases was observation, and subsequent radical therapy does not usually need to be included in the initial treatment. Third, although prognostic data are essential for cancer treatment, only data at the time of enrollment were analyzed in this study. Prognostic analysis will be necessary in the future. Finally, we only analyzed data within Ehime Prefecture. We do not know if the results are reflective of nationwide trends. The national HBCR has been compiled, permitting comparisons between local and national data. However, such a comparison is an issue for future research. As with the advent of RARP, new treatment methods may change the treatment system significantly in the future. In addition, guidelines will be revised with the advent of new diagnostic methods, including prostate-specific membrane antigen positron emission tomography. Current guidelines recommend prostate biopsy after explaining the risks and benefits [36]. Regularly updating the HBCR may help us to keep up with these changes.

Conclusions

By utilizing data from the HBCR, trends in prostate cancer treatment in Ehime Prefecture were clarified in this study. We hope to make effective use of these data by sharing them with urologists and radiologists in various fields.

Abbreviations

RP	Radical prostatectomy
RT	Radiotherapy
HT	Hormone therapy
RARP	Robot-assisted radical prostatectomy
IMRT	Intensity-modulated radiotherapy
MDT	Metastasis-directed therapy
HBCR	Hospital-based cancer registry
DCCH	Designated cancer care hospital
ECCH	Ehime cancer care hospital
CCCH	Community cancer care hospital
PS	Performance status
AS	Active surveillance
WW	Watchful waiting

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Clinical trial number

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. NY and NT performed material preparation, data collection, and analysis. KH wrote the first draft of the manuscript. All authors have read and approved the manuscript.

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Data availability

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

In this study, we used data from the hospital-based cancer registry, most of which were already publicly available. Some additional analyses were performed based on the approval of the institutional review board of NHO Shikoku Cancer Center (No: CO 2023–531) and were conducted in accordance with the Declaration of Helsinki. On the retrospective nature of the study, the need for written informed consent was waived by the institutional review board of NHO Shikoku Cancer Center.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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