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Original article

The Role of Radiotherapy in Prostate Cancer

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Abstract

Prostate cancer is one of the most common cancers in western countries. The treatment of prostate cancer comprises surgery, radiotherapy, hormonal therapy, chemotherapy, active surveillance and watchful waiting. Radiation therapy has the role of radical, adjuvant and palliative treatment in prostate cancer. With new technologies in imaging and treatment procedures, radio-therapeutic approaches can increase the dose to the target and reduce it to normal tissues. Gastrointestinal and genitourinary toxicities are the most common symptoms during treatment. For late toxicities, not only gastrointestinal and genitourinary toxicities are of to concern, but also sexual function. **Chiang Mai Medical Journal 2011; 50(1):11-21.**

Keywords: prostate cancer, treatment, radiation therapy

Prostate cancer is one of the most common tumors in western countries. In 2008, about 180,000 men in the United States were diagnosed with the disease.[1]

Localized prostate cancer is divided into three risk groups depending of Prostatic specific antigen (PSA), Gleason score (GS) and stage. All parameters are shown in Table 1.

TREATMENT OPTIONS OF PROSTATE CANCER

In grouping prostate cancer, the physician can divide the treatment options according to risk, as shown in Table 2.[2]

Local treatment is composed of surgery (radical) and radiotherapy (External beam radiotherapy: EBRT and/or Brachytherapy: BT). Systemic treatment is hormonal therapy (LHRH agonist or antiandrogen) or systemic chemotherapy.

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Table 1. NCCN risk group of prostate cancer

Risk groups	Stage	Gleason score	PSA
Low risk group	T1-T2a	<6	<10 ng/mL
Intermediate risk group	T2b-T2c	7	10-20 ng/mL
High risk group	T3a	8 to 10	>20 ng/mL
Advanced group	T3b-T4	any	any
Metastasis	N+ or M1	any	any

Table 2. Treatment options in Prostate cancer[2]

Risk group	Treatment options
Low-risk group	Watchful waiting Active surveillance Radical prostatectomy EBRT(Intensity-modulated Radiotherapy:IMRT) BT (Permanent prostate implantation:PPI)
Intermediate-risk group	Active surveillance Radical prostatectomy EBRT (3D-CRT or IMRT) EBRT with BT for boost treatment Short-term hormonal therapy (4-6 months) were consider in unfavourable group (>50% positive core biopsy, >50% of length of core, PSA velocity >2 ng/mL/yr)
High-risk group	EBRT (3DCRT or IMRT) EBRT with BT for boost treatments Long-term hormonal therapy (2-3 years) is suggested.
Node positive disease	Hormonal therapy+/-radiotherapy
Metastasis disease	Palliation

Role of radiotherapy in the treatment of prostate cancer

Radiotherapy consists of external beam radiotherapy (EBRT) and brachytherapy (BT). Both of these can be used as monotherapy or combinaed with each other. Radiotherapy can be used as radical treatment (EBRT or BT or both of them), adjuvant treatment after radical prostatectomy (EBRT) and palliative treatment (EBRT). Radiotherapy has been developed for a long time in giving the dose directly to the target lesion (prostate gland, seminal vesicles and lymph nodes). The treatment options of radiotherapy are described as follows:

1. Radical treatment: In the radical treatment aspect, radiotherapy has the benefit of treating localized prostate cancer from a low-risk to high-risk group. In a low-risk group, treatment of EBRT or BT alone (permanent prostate implantation) can be applied with the same outcome. For intermediate to high-risk groups, EBRT alone or a combination of EBRT and BT are used to

yield good results. The combination of hormonal therapy and radiotherapy improves survival rate according to the literature.[3-4]

1.1 External beam radiotherapy (EBRT) By using a cobalt machine, linear accelerators or charged particle treatment, and ionizing radiations (which are generated from this machine) are irradiated to treat the lesions from many directions, with the goal of treating them within the body.

1.1.1 Conventional radiotherapy EBRT has been used for a long time to treat prostate cancer. With conventional simulation, a dose of 66 Gy in 33 fractions is prescribed. In the low risk group, only the prostate gland is treated. Regarding the intermediate to high risk group, multiple phase treatment is planned to treat the pelvic lymph node with a dose of 46Gy and a total dose of 66-70Gy to the prostate gland and seminal vesicles. (Fig. 1)[5]

1.1.2 Three-dimensional radiotherapy: The new technologies of medical imaging (CT, MRI or US) help to identify the target volumes and organs at risk (rectum, bladder, head of femurs and penile bulb). The beam can be placed and adjusted appropriately to the target volume. (Fig. 2) The results of conventional studies showed that when a dose from 66 Gy escalate to over 70 Gy, it yields a comparable relapse-free survival rate to other treatment. When compared to radical prostatectomy (RP), radiotherapy in localized prostate cancer showed a 74% overall survival rate and 76-99% distant metastasis-free survival rate.[6] In studies of dose escalation from Pollack et al., Peeters et al., and Zeitman et al., the biochemical control of disease improved with a higher dose.[7-9] From these studies, a dose of 78 Gy was accepted as the standard current dose.

1.1.3 Intensity-modulated radiotherapy (IMRT): New technologies using dynamic means of beam modification, usually through moving leaves of a multi-leaf collimator, enable varying doses across a treatment volume to be delivered, with the prospect of even higher-dose escalation to small sub-volumes and greater avoidance of normal structures.[10]

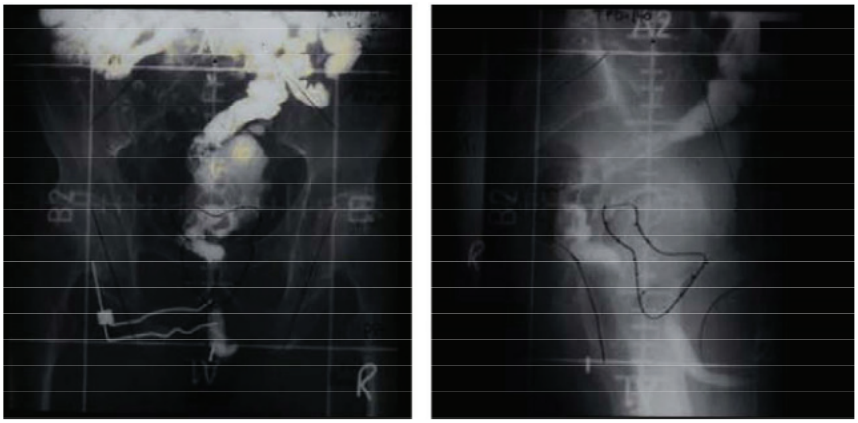

Figure 1. The simulation films of high-risk prostate cancer.
From Lawton CAF, Michalski J, El-naqa I, et al. RTOG GU radiation oncologists reach consensus on pelvic lymph nodes volume for high-risk prostate cancer. Int. J. Radiation Oncology Biol. Phys. 2009; 74: 383–387.

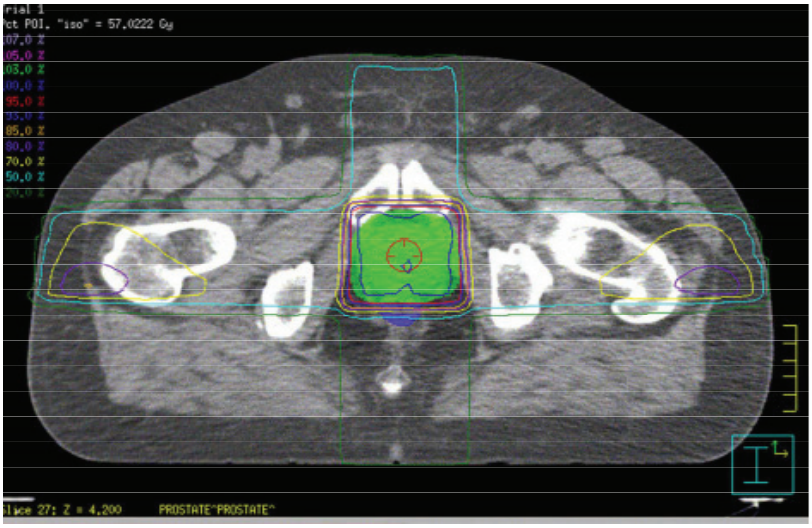

Figure 2. Axial CT imaging of three-dimensional conformal radiotherapy in prostate cancer with the four-field box technique. The red line (95% isodose) covered the prostate gland (green).
(from Moule RN, Hoskin P. Non-surgical treatment of localised prostate cancer. Surgical Oncology 2009; 18: 255-267).

This has proved to improve dose distribution in the target (prostate gland) area and reduce the volume of the rectal and bladder wall receiving high-dose radiotherapy (75 Gy).[11]

With the benefit of IMRT, dose escalation might be possible with good results. With a dose of 86.4 Gy, bNED was 71-86%, while other studies showed a 5 yr-relapse free survival of 72-94% and 8 year actuarial survival of 84-100% (bNED 67-89% after 81 Gy).[12-14]

1.1.4 Further development of EBRT: With the knowledge of radiobiology, the alpha/beta ratio of prostate cancer is 1.5:3.5, which is different from the usual concept of normal tumor tissue (alpha/beta =10). The low α/β ratio of prostate cancer shows the benefit of hypofractionation (large dose > 2 Gy per fraction) in prostate cancer. However, a large dose per fraction can cause an increase in late effects. To assess the efficacy of hypofractionation in prostate cancer, conventional or hypo-fractionated high-dose intensity-modulated radiotherapy for prostate cancer (CHHIP) trials continue to enroll patients and wait for results. This study randomized patients into three arms: 74 Gy in 37 fractions, 2 Gy per fraction, over 7.5 weeks; 57 Gy in 19 fractions, 3 Gy per fraction, over 4 weeks; and 60 Gy in 20 fractions, 3 Gy per fraction over 4 weeks.[10] Furthermore, the use of charged particles (eg. Proton, carbon-ion) is increasing for prostate carcinoma, due to the benefit of dose distribution (Braag's peak), which has had promising results.[15-16]

1.2 Brachytherapy

Brachytherapy comes from the Greek word, 'short'. It is the process of treatment that takes the radioisotope close to or inside the lesion via many types of

applicators (needles, thread and so on). In the past, prostate brachytherapy started with a transabdominal approach. Until 1983, Holmes had developed the transperineal implantation with trans-rectal ultrasound guidance with less morbidity.[17] Interstitial brachytherapy with a transperineal approach is nowadays one of the standard procedures and treatment for localized prostate cancer. It can be used as monotherapy in a low-risk group and to boost therapy in intermediate to high risk groups. The use of seed implantation (permanent implants) or High-dose-rate implantation (temporary implants- iridium) is widespread in prostate with different indications. The details are as follows.

1.2.1 Permanent prostatic implants (PPI): By using transrectal ultrasound guidance, transperineal implantation of ultralow-dose-rate radioisotope (I-125, Pd-103) into the prostate gland is feasible. (Fig. 3) PPI is used in the mono-therapeutic treatment of low-risk localized prostate cancer and as a boost therapy (with EBRT) in intermediate-to high-risk groups. A good candidate for PPI should have PSA < 10 ng/mL, GS of less than 7, stage T1c-2b, IPSS score of 0-8, prostate volume < 40 grams, Qmax > 15 mL/s, no residual volume of urine and no previous transurethral resection of the prostate (TURP). Patients who have a recent TURP, IPSS score > 20, presence of metastasis and life expectancy < 5 years are contraindicated.[18] The prescribed doses of PPI are different, based on the radioisotope.[19] For Iodine-125 (28 KeV; T1/2 60 days), the dose of 144 Gy and 110 Gy are prescribed for radical and boost treatment, respectively. For palladium-103(21KeV; T1/2 17 days), the dose of 125Gy and 100 Gy are prescribed for radical and boost treatment, respectively. The results of PPI are shown in Table 3.[20] Good results can be yielded in the low-risk subgroup, with biochemical free survival rate of about 82-98%.

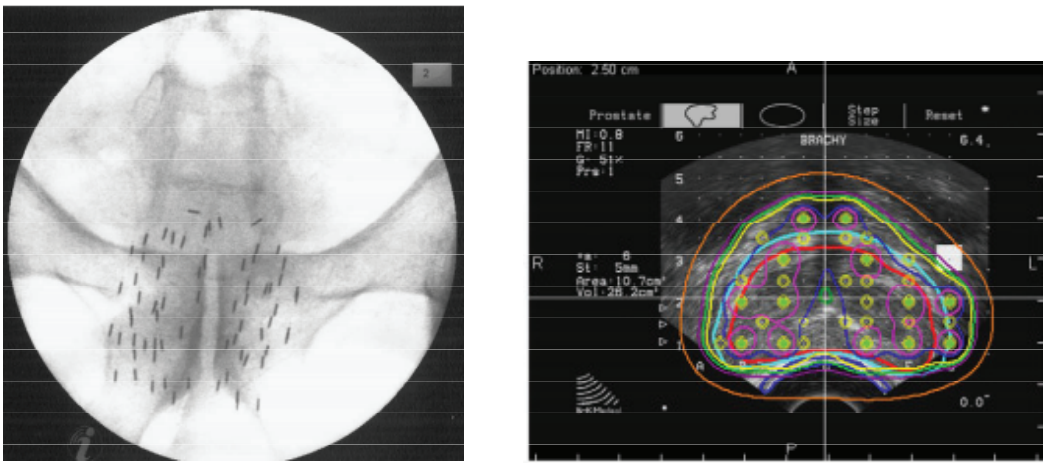

Figure 3. Permanent prostatic implantation in patients with localized (low-risk group) prostate cancer a) fluoroscopy showing the position of seeds b) the axial ultrasound imaging showing the prostate gland (red), 100% isodose (yellow) and seed position (green). (from Moule RN, Hoskin PJ. Non-surgical treatment of localised prostate cancer. Surgical Oncology 2009; 18: 255-267).

Table 3. Results of permanent prostatic implantation according to risk groups.

Risk group	Median follow-up (month)	% of bio-chemical free re-currence
Low-risk group	29-84	82-98
Intermediate risk group	30-96	63-95
High risk group	30-102	24-93

1.2.2 Temporary implantation (HDR) HDR brachytherapy is used to boost treatment in intermediate to high risk prostate cancer. It was first developed in the 1980s by Galalae *et al*, Borghede *et al*, and Mate *et al*,[21-23] by ultrasound guidance when PPI, or stainless or plastic needles are inserted into the prostate gland via the perineum. (Fig. 4) Patients with stage T1b-T3b, any GS, or any initial PSA without metastasis are accepted, and the dosages of 6-10 Gy are prescribed for the whole prostate gland (or 15-20 Gy to the peripheral zone).[24]

The results of HDR implantation are shown in Table 4.[20] With the benefit of HDR in terms of safety for coworkers and caregivers, its usage as mono-therapy in low-risk group prostate cancer has been studied. The biochemical relapse-free survival rate can yield 94-100% in this modality, however, there was less data to conclude this benefit.[25-26]

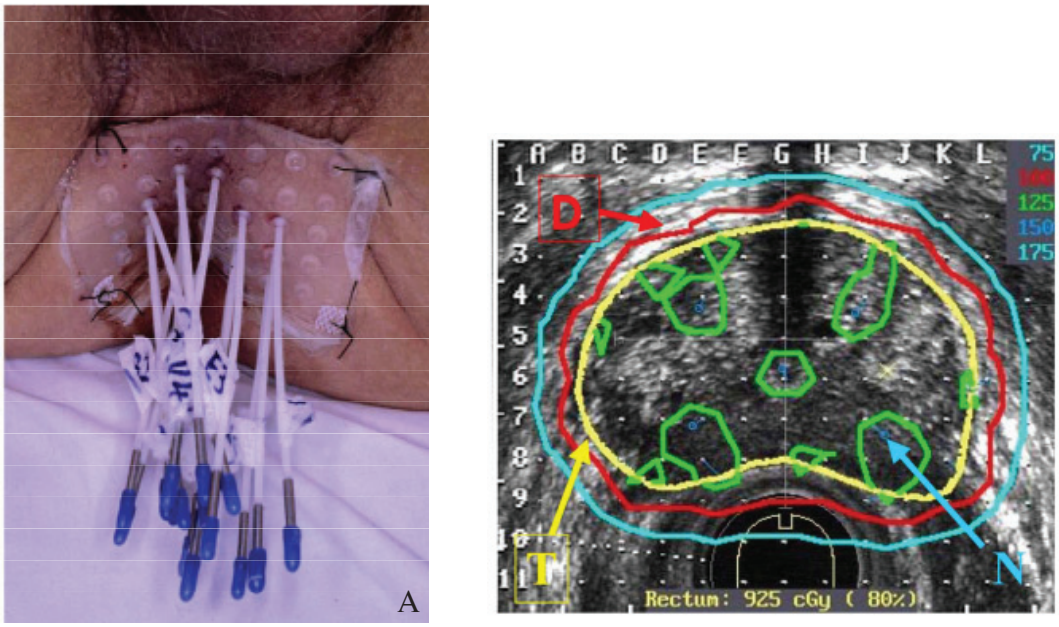

Figure 4. High-dose-rate interstitial brachytherapy for prostate cancer (intermediate-to high-risk group) a) transperineal plastic catheter implantations; (from Moule RN, Hoskin PJ. Non-surgical treatment of localised prostate cancer. Surgical Oncology 2009; 18: 255-267). b) axial ultrasound imaging showing the prostate gland (yellow). The prescribed dose (100%), shown by the red line, correlated with needles (light blue points) (from: Kovacs G, Pötter R, Loch T, et al. GEC/ESTRO/EAU recommendations on temporary brachytherapy using stepping sources for localized prostate cancer. Radiother Oncol 2005; 74: 137-148)

Table 4. Results of HDR boost treatment according to risk groups.

Risk group	% of biochemical free recurrence
Low-risk group	93-100%
Intermediate risk group	82-100%
High risk group	62-97%

2. Adjuvant treatment

Indication of recent adjuvant radiation therapy was T3 at least, with positive surgical margin and extracapsular extension from a pathological report. The dose of 60-64Gy at the surgical bed was recommended. A supporting study from EORTC 22911, SWOG 8794 and a German study showed the benefit of adjuvant radiotherapy in terms of biochemical disease-free survival (bNED) improvement.[27-29] Interestingly, adjuvant radiotherapy yielded an improvement of overall survival rate in a SWOG study.[28] All the reports are shown in Table 5.

3. Palliative treatment

The most common problems of prostate cancer in palliative settings were bone metastasis, spinal cord compression and local symptoms (pain of lesion, dysuria, hematuria). The most common symptom of bone metastasis is pain, which can be controlled with analgesics and bisphosphonates. Radiation therapy can treat localized prostate bone pain, due to metastasis, effectively with an improvement in 50-80% and complete relief in about 20-50% of patients. However, dose and fractionation have not been defined clearly for decades. The local irradiation of a problematic site can relieve the symptoms.[30] The dose of 30 Gy in 10 fractions or 20 Gy in 5 fractions was use with good palliation results and acceptably late complication. Nowadays, a single dose of 8 Gy can be used with the same response rate as the standard regimen in terms of pain relief and analgesic use. However, the rate of re-treatment was higher in single fraction.[31-33]

Table 5. Supportive studies of adjuvant radiotherapy in prostate cancer patients with radical prostatectomy and pathological results showing a high chance of recurrence

Study/parameters	EORTC22911	SWOG8794	ARO 96-02 and AUO AP 09/95
Criteria	ECE, SVI,+ve margin	ECE, SVI, +ve margin, without lymphadenopathy	ECE, SVI with or without +ve margin
Number of patients	1,005	431	307
Time interval from surgery to RT	<16 wks	<18wks	8-12 wks
Dose of RT	60 Gy/ 30fx	60-64 Gy/30-32 fx	60 Gy/30 fx
Results	bNED 74% vs. 52.6%	bNED 38% vs. 23% 15 yrs OS 47% vs. 37%	bNED 21% improvement

In malignant spinal cord compression, urgent treatment is needed. Radiotherapy and decompressive surgery are the treatment modalities mostly used. Surgical decompression can be performed in cases of rapid progression, radioresistant histology or no response after irradiation. Rades et al, reported a retrospective study of 1,304 patients with metastatic spinal cord compression. They found that the functional outcome was independent when comparing the five fractionation schedules (1*8, 5*4, 10*3,15*2.5 and 20*2 Gy). More protracted schedules were related to fewer in-field recurrences. and lower re-treatment rates.[34]

For radiotherapy in malignant spinal cord compression by prostate cancer, the 2*8 Gy was no different to the split course schedule (3*5 Gy plus 5*3 Gy), with a response to treatment of 85% in the split-course cohort and 76% in the short-course one.[35] The functional outcome after radiotherapy was affected significantly by the time to develop motor deficits before radiotherapy and the number of vertebra involved. For patients with good prognosis, protracted schedules (e.g. 10 fractions of 3 Gy) should be applied to achieve better local control.

Local invasion of prostate cancer can cause symptoms like perineal discomfort, urethral obstruction, pain and bleeding. Local irradiation is a non-invasive treatment to reduce the symptoms described above. Hypofractionation is accepted to relief patient symptoms according to the extent of disease mand patient status. The fractionation and dose of irradiation are debatable, but they have to be adjusted to the situation of the patient. From the study of Perez et al, local palliative irradiation offers relief of symptoms in most patients with hematuria, up to 80% withurinary outflow obstruction and 50-70% with pain secondary to disease advancement.[36]

Radiation toxicities in radiotherapeutic treatment

The most common toxicities were gastrointestinal toxicity, genitourinary toxicity and impotence. Normally, acute radiation occurs at the second week of radiation and resolves itself about one month after treatment. The most common acute side effects during EBRT are genitourinary toxicities (nocturia, dysuria, urgency and frequency), which occur in most irradiated patients. Diarrhea is the second most common symptom, with 25-75% of patients suffering from its. The conclusions of acute RT side effects are shown in Table 6.[1] In late complications of EBRT, less than 4% of patients developed urinary stricture after EBRT. Five to ten percent of pateints had rectal bleeding according to technique, volume and dose of irradiations.

Table 6. Acute side effects of the treatment for prostate cancer with EBRT.

Side effects	Onset of time	Incidence	Treatment
Dysuria, urgency, frequency, nocturia	1-2 wks	Most	NSAID, alpha-blockers, pyridium
Urinary retention	1 wk	Rare	Catheter
Diarrhea	1-2 wks	25-75%	Diet, antidiarrheals
Rectal irritation, pain , bleeding	2-6 wks	10-20%	Sitz baths, rectal steroid
Fatigue	>3wks	Most	Reassurance

In brachytherapy treatment, perioperative brachytherapy complications consisted of pain, dysuria, urinary retention, hematuria, and urinary frequency. Obstructive symptoms can occur in about 10% of patients and are resolved within 6-12 months after implantation. Urinary retention can be resolved within 3 days, and the risk of retention depends on AUA score (less than 10: 2-9% versus more than 20: 25-30%).[1] Urinary incontinece, sticture and necrosis can occur in 1-3% of patients. One to five percent of patients can develop rectal injury with brachytherapy. In the case of impotence from radiation therapy, a retrospective study by Robinson *et al*, showed a post-treatment impotence rate of 24%, 40%, 45%, 66%, 75% and 87% after Brachytherapy alone, EBRT plut BT, EBRT alone, nerve-sparing RP, non-nerve sparing RP and cryosurgery, respectively.[37]

CONCLUSION

Radiotherapy plays a role in prostate cancer as radical, post-operative and palliative treatment. Treatment with radiotherapy can cause gastrointestinal and genitourinary toxicities and impotence, but with new technologies, the toxicities can be reduced to an acceptable rate.

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บทบาทของรังสีรักษาในมะเร็งต่อมลูกหมาก

เอกสิทธิ ธราวิจิตรกุล, พ.บ., วิชาญ หล่อวิทยา, พ.บ., วิมล สุขถมยา, พ.บ. และ อิ่มใจ ชิตาพนารักษ์, พ.บ.

หน่วยรังสีรักษาและมะเร็งวิทยา ภาควิชารังสีวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

บทคัดย่อ

มะเร็งต่อมลูกหมากเป็นมะเร็งที่พบบ่อยในประชากรเพศชาย การรักษามะเร็งต่อมลูกหมากประกอบด้วยการผ่าตัด รังสีรักษา ฮอร์โมนบำบัด เคมีบำบัด และการเฝ้าระวังโรค รังสีรักษามีบทบาทในการรักษามะเร็งต่อมลูกหมากในส่วนของการให้รังสีรักษาอย่างเดียว เพื่อควบคุมรอยโรค, ป้องกันการกลับเป็นใหม่ของรอยโรคหลังผ่าตัด และเพื่อบรรเทาอาการในระยะลุกลามหรือแพร่กระจาย รังสีรักษาในมะเร็งต่อมลูกหมากได้พัฒนาขึ้น เนื่องจากมีพัฒนาการของภาพทางการแพทย์ และเทคนิคในการรักษาทำให้ในปัจจุบัน สามารถให้รังสีได้เฉพาะเจาะจงต่อรอยโรคมากยิ่งขึ้น และเนื้อเยื่อปกติได้รับรังสีที่น้อยลง ผู้ป่วยที่ได้รับรังสีรักษาส่วนใหญ่จะมีผลข้างเคียงในส่วนของระบบทางเดินปัสสาวะและทางเดินอาหาร ซึ่งสามารถลดลงได้เนื่องจากเทคโนโลยีในการให้รังสีที่ดีขึ้น **เชียงใหม่เวชสาร 2554;50(1):11-21.**

คำสำคัญ: มะเร็งต่อมลูกหมาก การรักษา รังสีรักษา