HUMAN TUMOR RADIORESISTANCE BIOLOGICAL INFORMATION DERIVED FROM CLINICAL DATA FOR TREATMENT STRATEGY

Takehito SASAKI

Abstract: Multivariate regression analysis based on various clinical factors has provided useful information to predict tumor clearance probability and patient prognosis. However, this type of approache alone has an apparent limitation in providing information required for changing the treatment strategy, because the biological roles of clinical factors involved in tumor radioresistance are complicated and unknown. In this review, importance of clinical data on the precise tumor volume and the dose required for the local control has been emphasized, because these data are directly related to both the in situ cellular radioresistance and the size of target cell population. Using a biological model tumor system with these clinical data, it was shown that human tumor radioresistance is likely determined by a small number of target cells with in situ radioresistance in tumor tissue. Thus, the problems shown below targeted to this cell population need to be further investigated. Namely: Mechanism of radioresistance acquired in a hypoxic environment. Topographical distribution of target cell population in a tumor tissue. Research and development for new laboratory tests to diagnose molecular characteristics of the target cell population.

Key words: Human tumor, Radioresistance, Spheroid, Hypoxia, IGF-IR

要旨:様々な臨床的要因の多変量回帰分析法は腫瘍の消失確率や患者の予後を予測するのに有用な情報を提供してきた.しかし,このような方法は治療戦略をどのように変更するかについて要求される情報の提供には,これらの臨床要因の腫瘍放射線抵抗性に関与する生物学的役割が複雑で,しかも細部はまだ未知であるために,限りがある.この総説では,正確な腫瘍体積と局所制御に必要な放射線線量の重要性を強調した.これらの因子は直接的に標的腫瘍細胞の腫瘍組織in situの放射線抵抗性とその数に関係しているからである.これらのデータを基に,われわれの考案した生物学的モデルによる解析から,ヒト腫瘍の放射線抵抗性は少数の抵抗性標的腫瘍細胞によって決まると考えられた.今後の研究では,この抵抗性標的細胞について, 低酸素状況下で獲得される放射線抵抗性機構, 抵抗性標的細胞の腫瘍組織内分布, 抵抗性標的細胞の分子レベルの性状を診断する新しい検査方法の開発,が重要と考えられる.

進行非小細胞肺癌に対する予防的リンパ領域照射(elective nodal irradiation: ENI)を省いた照射野(involved-field)による加速多分割照射の初期治療成績

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THE PRELIMINARY RESULTS OF ACCELERATED HYPERFRACTIONATED RADIOTHERAPY WITH INVOLVED-FIELD OMITTED ELECTIVE NODAL IRRADIATION (ENI) FOR INOPERABLE ADVANCED NON-SMALL CELL LUNG CANCER

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Abstract: Purpose: To evaluate the preliminary results of accelerated hyperfractionated radiotherapy with involved-field omitted elective nodal irradiation (ENI) for inoperable advanced non-small cell lung cancer. Materials and Methods: Ten patients with inoperable advanced non-small cell lung cancer were treated with accelerated hyperfractionated radiotherapy with involved-field omitted ENI between November 2001 and November 2003. The clinical stage for one patient was stage IIB, 3 patients were stage IIIA, and 6 patients was stage IIIB. Chemotherapy was performed 8 patients (sequential: 1 patient, concurrent: 7 patients). The involved-field consisted of the primary tumor and nodes with a short-axis diameter more than 1 cm on CT scans. Total dose was 72 Gy and 74.6 Gy in 2 patients treated with radiation therapy alone, 75 Gy in 1 patient treated with sequential chemotherapy, 66 Gy in 6 patients and 72 Gy in 1 patient treated with concurrent chemotherapy. Follow up periods were between 2 and 25 months (median: 14 months).

Results: Local recurrences developed in 3 patients with the two year local control rate at 49.4%. Out-field regional recurrence developed in one patient, the two years regional control rate was 88.9%. Two years cause specific and overall survival rate was 47.4%. Adverse events were evaluated NTC-CTC ver.3.0. Three patients in 8 patients treated with chemotherapy developed grade 3 neutropenia. Two and 1 patient developed grade 2 and 3 pneumonitis, respectively. Nobody developed more than grade 2 esophagitis.

Conclusions: Accelerated hyperfractionated radiotherapy with involved-field omitted ENI was feasible with limited toxicity.

Key words: Accelerated hyperfractionated radiotherapy, Involved-field, Elective nodal irradiation, Non-small cell lung cancer

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要旨:【目的】局所制御の向上を目的とした切除不能進行非小細胞肺癌に対する予防的リンパ領域照射(elective nodal irradiation: ENI)を省いた照射野(involved-field)による加速多分割照射の初期治療成績について検討する.

【対象と方法】対象は2001年11月から2003年11月まで治療を行った切除不能進行非小細胞癌10例であった.年齢は51~80才(中央値75才), 臨床病期はIIB期1例,IIIA期3例,IIIB期6例であった.化学療法は原則として同時併用とし,8例に施行した.照射野は原発巣とCT上短径1 cm以上の腫大リンパ節を肉眼的腫瘍体積とし,これに呼吸性移動及びセットアップエラーを加味した安全域を加えた領域を含むものとした.総線量は放射線単独で治療を行った2例で72 Gyと74.6 Gy,化学療法逐次併用した1例で75 Gy,化学療法同時併用で治療を行った6例で66 Gy,1例で72 Gyであった.原則として1回1.5 Gyを1日2回照射する加速多分割照射で行った.観察期間は2~25ヶ月(中央値14ヶ月)であった.

【結果】10例中3例で局所再発を認め、2年局所制御率は49.4%であった.照射野外の領域リンパ節再発は1例のみで、2年領域制御率は88.9%であった.2年原病生存率は47.4%であった.有害事象は、化学療法同時併用で治療した7例中3例でGrade 3(NCI-CTC ver. 3.0)の好中球減少を認め、Grade 2、3の肺臓炎をそれぞれ2、1例に認めたが、いずれも軽快した.Grade 2以上の食道炎は認めなかった.

【結語】Involved-fieldによる加速多分割照射は化学療法同時併用例でも,比較的安全に施行可能であった.しかし,今後は化学療法同時併用又は放射線治療単独における至適線量の確立していく必要があると思われた.

前立腺癌に対する外部照射と1日2回の高線量率組織内照射の 初期成績の検討

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EXTERNAL IRRADIATION AND INTERSTITIAL BRACHYTHERAPY TWICE PER DAY FOR PROSTATE CANCER INITIAL RESULTS

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Abstract: Purpose: To evaluate the effectiveness and safety of the combination of external irradiation and interstitial brachytherapy twice per day for prostate cancer.

Materials and Methods: The cases were 42 patients with prostate cancer (4 cases in Stage A, 14 in Stage B, 20 in Stage C and 4 in Stage D) who underwent external irradiation of 50 Gy to the prostate gland including 30 Gy to the pelvis and interstitial brachytherapy of 5.5 Gy \times 2/day in 4 cases, 7.0 Gy \times 2/day in 2 cases and 7.5 Gy \times 2/day in 36 cases. The average age was 77.5 (range 61 to 89) years old.

Results: Prostate specific antigen (PSA) values after the combinated radiation therapy dropped in each case. Three cases with PSA failure were noted during the average observation term of 12 months. No cases with stage A, B or less than Gleason score 6 were associated with PSA failure. Biochemically no evidence of disease (bNED) survival curve showed significant PSA failure in the cases with PSA values of 30 ng/ml than in those with PSA values of <30 ng/ml. Transient rectal bleeding (2.3%), diarrhea (7%) and perianal pain (4.7%) as adverse effects of radiation treatment were noted.

Conclusion: Initial results of external irradiation and interstitial brachytherapy twice a day are promising especially for aged cases with early prostate cancer. However, longer-term observation is needed to evaluate the real effectiveness and the adverse effect of this combinated radiation therapy.

Key words: Prostate cancer, Brachytherapy, Radiation therapy

要旨:【目的】前立腺癌症例に対して外部照射と1日2回の組織内照射を行いその有用性と安全性について検討した.

【対象と方法】平均年齢77.5歳の前立腺癌患者42例(Stage A,4例,Stage B,14例,Stage C,20例,Stage D,4例)に前立腺局所に外部照射50 Gy(Stage C,Dでは小骨盤40 Gyを含む)照射後に小線源組織内照射を行った.組織内照射は5.5 Gy×2回 / 日を4例,7.0×2回 / 日を2例,7.5 Gy×2回 / 日を36例に各々行った.

【結果と結論】併用療法後のPSA値の測定を行い,全例にPSA値の下降をみた.平均12ヶ月の観察期間中に3例にPSA failureをみた.Stage A, B, あるいはGleason score 6以下の例ではPSA failureをみなかった.術前PSA値30 ng/ml以上と未満例でbNED survival curveに有意差をみた.副作用として一時的な直腸出血(2.3%),下痢(7%),会陰部痛(4.7%)をみた.

外照部射と1日2回の組織内照射の初期成績から,本併用療法は安全で高齢者にも耐え得る軽度の侵襲で有用な治療効果を挙げうるものと期待されるが,正確な評価のためにはさらなる長期間の経過観察を必要とする.

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下咽頭癌に対する化学・放射線療法の治療成績

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RADICAL RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY FOR HYPOPHARYNGEAL CARCINOMA

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Abstract: We took a routine conservative approach for hypopharyngeal carcinoma. This retrospective study analyzes the outcome of treatment with this policy. Between 1993 and 2002, 36 patients with hypopharyngeal carcinoma received radiotherapy with or without chemotherapy at our institution. Doses ranged from 60 Gy to 72 Gy given to the involved fields. Fourteen patients received CDDP and 5FU, either inductive or concurrent with radiotherapy. The overall five-year survival was 38% and the two-year local control rate was 69%. The local control rate was dependent on the size of primary tumor. Two-year local control rates were 60% with radiotherapy alone and 88% with chemoradiotherapy. Neck dissections combined with radiotherapy were all successful for 12 patients with N1-2. In 14 patients with N0, 3 patients were salvaged successfully after nodal recurrence. Ultimate conservation rate of laryngo-pharynx was 67%. This non-surgical therapy provided survival comparable with that achieved with the standard approach of surgery and postoperative radiotherapy.

Key words: Hypopharyngeal carcinoma, Radiotherapy, Chemoradiotherapy, Salvage surgery

要旨:過去10年間,36名の下咽頭癌患者に対して放射線治療を第一選択とする治療方針を採った.化学療法を14名に併用し,頸部郭清は12名に施行した.36名全体の5年生存率は38%,2年局所制御率は69%であった.T1,2,3,4の2年局所制御率は各々89%,89%,75%,16%であった.また,局所制御は腫瘍サイズに依存していた.治療法別の2年局所制御率は放射線単独で60%,化学放射線療法で88%であった(P=0.1167).局所再発した9名中,2名に救済手術が施行された.N1~2に対して郭清と照射を併用した12名は全例領域再発を認めなかった.N0であった14名中,頸部リンパ節の後発転移が3名に生じたが,いずれも救済可能であった.最終的な咽喉頭温存率は67%であった.照射技術の改善と化学療法の併用により,放射線治療は手術に遜色ない結果が得られる可能性が示唆された.

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上咽頭癌に対する放射線治療成績 MRIにおける節外浸潤所見が遠隔転移に及ぼす影響

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TREATMENT OUTCOME OF NASOPHARYNX CANCER: DOSE PRESENCE OF MR FINDINGS OF EXTRACAPSULAR SPREAD IN CERVICAL NODE METASTASIS INFLUENCE DISTANT METASTASIS?

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(Received 8 March 2004, accepted 20 May 2004)

Abstract: Purpose: Evaluation of our treatment outcome of nasopharynx cancer for a neoadjuvant chemotherapy followed by radiation was performed. In addition, we reviewed whether presence of findings of extracapsular spread (ECS) in cervical node metastasis in MRI influenced treatment outcomes.

Material and methods: Twenty-eight patients with nasopharynx cancer without distant metastasis were treated with radical chemoradiation between 1991 and 2002 at Kurume University Hospital. They were UICC 1997 stage II-IV (stage II: 5 patients, stage III: 10 patients, stage IV: 13 patients). Patients ranged in age from 16-71 years, with a median of 56 years, and included 22 men and 6 women. We administered 1-3 courses of systemic chemotherapy before radiotherapy. Follow-up period was at least 6 months from the beginning of radiation therapy. We performed MRI before treatment for all cases. Metastatic lymphnode, that showed the presence of a perinodal high signal intensity area on STIR sequence or presence of a diameter greater than 3 centimeters in the longest axis, were defined as ECS.

Results: Four patients developed distant metastasis after initial therapy, and at 3-years the distant failure free rate was 75%. The three-year overall survial rate and failure free rate were 59% and 55%, respectively. In MRI, metastatic cervical lymphnodes were deteced 21 (75%) among the 28 patients, and the findings of ECS were noted for 11 cases (52%) of these 21 patients. None of the patients without the findings of ECS developed distant metastasis. In chisquare analysis, a significant relationship was noted between the findings of ECS and distant metastasis.

Conclusion: The neoadjuvant chemotherapy followed by radiation for nasopharynx cancer did not lead to satisfactory treatment outcomes. It seems that the findings of ECS in MRI might be a important factor to develop distant metastasis.

Key words: Nasopharyngeal cancer, Chemoradiation, MRI, Extracapsular spread

要旨:【目的】化学放射線療法が施行された上咽頭癌の治療成績を評価する.またMRI上,節外浸潤を呈する転移リンパ節の存在が治療成績に影響する因子となりうるか検討する.

【対象と方法】1991年1月から2002年6月までに放射線化学療法が施行され,半年以上の経過(中央値24ヶ月)が追えた上咽頭癌症例28例(II期5例,III期10例,IV期13例)を対象とした.男性22例,女性6例で,年齢は16才~71才(中央値56才)であった. 照射は通常分割法で頭蓋底部から鎖骨上窩までを含め,原発巣には50 Gy~72 Gy(中央値65 Gy)を照射した.なお抗癌剤は放射線治療に先行して1~3コース施行した.治療前の頭頸部MRIは全例に施行し,STIR法で転移リンパ節周囲の高信号領域の存在と長径30 mmを越えるリンパ節を節外浸潤有りと定義し,この所見が遠隔転移の発現に影響するかを検証した.

【結果】累積生存率,無再発率,遠隔臓器無再発率は3年でそれぞれ59%,55%,75%であった.MRI上,転移リンパ節は21例 (75%)に認められ,うち節外浸潤は11症例(52%)にみられた.節外浸潤所見がない症例では全例で遠隔転移がみられなかったが,同所見を有する4症例に遠隔転移を認めた.

【結語】上咽頭癌に対する抗癌剤先行の化学放射線療法は満足できる治療成績を導かなかった.MRIにおける節外浸潤所見は遠隔転移を増加させる予後因子になりうると思われる.

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ウェッジファクターについてのアンケート調査結果

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QUESTIONNAIRE SURVEY RESULT ON THE WEDGE FACTOR

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(Received 13 November 2003, accepted 23 February 2004)

Abstract: In April 2001, an over dose irradiation accident happened in Tokyo. In August 2002, we investigated the wedge factor which became the cause of the over dose irradiation accident. The investigation centered around the wedge factor and the measuring method used TPR 20 and 10 beams. The monitored dose units were calculated and then reconfirmed. The investigation was conducted to 78 institutions in the Kinki region. The answers were received from 61 institutions, and covered 78 equipments units, 40 types (while 6 were unidentified) and 135 beams. Measured acceleration energy varied within 1.0 MV at nominal energy of 4 MV, and varied within 2.8 MV at nominal energy of 10 MV. With regard to the MU calculation, the institutions over 60% of use RTP. The over half of institutions responses reconfirmed calculation results by the measurement. However, several institutions (13%) make no reconfirmation. Fifty-seven percent of institutions measured the wedge factor by calibration depth. Ninety-seven percent of institutions measure the wedge factor by 10 × 10 cm in a radiation field. All wedge factors were classified in tables according to manufacturers or energies.

Key words: Wedge factor, TPR20, 10, Calculation method, Reconfirmation, Questionnaire survey

要旨:2001年4月,東京で過照射事故が起こった.2002年8月,我々は,過照射事故の原因となったウェッジファクターの調査を行った.調査内容は,ウェッジファクターとその測定方法,各ビームのTPR20,10,線量モニタ単位の計算方法と計算結果の再確認の方法である.調査は近畿圏の78施設に対して実施した.この結果,61の施設,78の装置,40の形式(不明6)そして135のビームについて回答を得た.測定された加速エネルギーについて,公称エネルギー4 MVにおいては1.0 MVの範囲でばらついていた.また,公称エネルギー10 MVにおいては2.8 MVの範囲でばらついていた.MUの計算については,60%以上の病院がRTPを用いていた.半数を超える数の施設が,測定により計算結果の再確認をしている.しかし,「再確認はしていない」と答えた施設もあった.ウェッジファクターは,57%の施設が校正深で測定している.また,97%の施設が10×10 cmの照射野で測定している.全てのウェッジファクターは,メーカー別,エネルギー別に,分類し,比較のための表とした.

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外部照射(X線)治療の線量に関する品質保証(QA)についての アンケート調査結果(1)1

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A QUESTIONNAIRE SURVEY OF QUALITY ASSURANCE (QA) FOR AN EXTERNAL RADIOTHERAPY FACILITY IN JAPAN

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Abstract: A nationwide survey was performed to investigate quality assurance (QA) for photon external radiotherapy. It was carried out by mailing questionnaires to 737 radiotherapy facilities. Six hundred and twenty eight questionnaires were returned, and 603 answers (including 38 answers from 60Co facilities) were available for analysis. At 565 X-ray treatment facilities, only 68 facilities (12%) treated more than 40 patients per day. The 356 facilities (63%) treated less than 20 patients per day. In this survey we examined following itemes: 1) number of radiation oncologists and radiotherapy technologists (RTT) each facility, 2) individuals responsible for QA, 3) ratio of conducting periodic check for basic QA items, and 4) Ratio of verifying monitor unit (MU) calculation. This survey shows that QA is not satisfactory at most of Japanese radiotherapy facilities.

Key words: Quality assurance (QA), Questionnaire survey, Radiotherapy staff

要旨:全国の放射線治療施設を対象に外部放射線治療のQA(quality assurance)に対する調査を行った.アンケート用紙は737の 放射線治療施設に送付した.628施設より返送があり,コバルト放射線治療施設38を含む603施設からの返送を解析した.X線を 放射線治療に使用している施設565施設のうち、1日40人以上の治療を行っている施設は68施設で、全施設中の12%に過ぎなかっ た.1日の治療人数が20人以下の施設は356施設で全施設の63%であった.このアンケートでは以下の点も調査した.1)各施設で の放射線腫瘍医,放射線技師の数.2)QA担当者.3)基本的なQAを行っている割合.4)モニタ・ユニット計算の確認をしている 割合、この調査で、日本の放射線治療のQAは十分に行われていないことが明らかとなった、

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限局性前立腺癌に対するIr-192 thin wireを用いた 低線量率小線源治療における技術的工夫

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A TECHNICAL DEVICE IN LOW DOSE RATE BRACHYTHERAPY WITH IR-192 THIN WIRE FOR LOCALIZED PROSTATIC CARCINOMA

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Abstract: Purpose: Ir-192 thin wires were used in our hospital since December 1997 for low dose rate brachytherapy for prostatic carcinoma. Since February 2000, we used the therapeutic planning system which created a pattern of dose distribution from a transrectal echogram, however, there were difficulties associated with this treatment which we tried to improve. However, a technical problem with the Ir-192 low dose rate brachytherapy became obvious. Improvements to the method have been tried since October 2001, and are reported here.

Method: We performed brachytherapy for localized prostatic carcinoma on 105 patients from February 2000 to February 2003. We defined the period from February 2000 to September 2001 as the early phase (47 cases). The period from October 2001 to February 2003 was defined as the late phase in which technical improvements were introduced (58 cases). We compared the late phase with the early phase. The early phase treatment procedure is as follows. We did centesis with a plastic needle for the prostate gland using transrectal ultrasound as a guide through the aperture of a template by a transperineal approach. The position of the paracentesis needle was checked by CT and also obtained a pattern of dose distribution in 2 dimensions from the maximal profile of the prostate gland. This was analysed and dose rate calculated and radiation source halt time. We set the clinical target volume around the circumferential part of the prostate gland. We inserted radiation source in a pallium needle and then fixed them in situ. However, the next points were modified. 1) We changed the posture of a patient into extended lithotomy. 2) We invested the position of the transrectal ultrasound probe in a part of infraversion / dorsum. 3) A metal marker was inserted into the apex of the prostate gland and was maintained. 4) We contrasted the urethra by means of transrectal ultrasound. 5) The calculated dose distribution from the transrectal ultrasound for therapeutic planning could be obtained in 3 dimensions. The dose volume histogram was calculated in relation to the prostate, urethra and rectum from which we decided the dose rate. Each technical improvement was evaluated.

Result: 1) The loading of the needle, which avoided the pubic arch by taking the extended lithotomy was enabled. 2) Visualization enabled a good amount of the border area of the prostate gland by positioning of the transrectal ultrasound probe moving towards the dorsum. 3) We inserted a metal marker at the gland apex part in order to aim the radiation source displacement and maintain it. 4) It became easy to identify the urethra by contrasting it. 5) We devised a configuration of paracentesis needle. It became technically clear that the dosage to the urethra and the rectum could be decreased by these improvements.

Conclusion: We evaluated the problem of brachytherapy for localized prostatic carcinoma with a low dose rate Ir-192 thin wire. We introduced technical improvements to improve treatment. This has provided a reference point for further technical improvements for brachytherapy for prostatic carcinoma.

Key words: 192-iridium, Brachytherapy, Prostatic carcinoma

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要旨:【目的】我々は,当院で1997年12月からIr-192 thin wireを使用して前立腺癌に対する低線量率小線源治療をしていた.2000年2月から経直腸エコー像から線量分布図を作成する治療計画システムを使用して,治療に取り組んでいた.しかし,Ir-192低線量率小線源療法にて技術的な問題が明瞭になった.我々は2001年10月から改良を試みたので,それを報告する.

【方法】我々は,当院で2000年2月から2003年2月まで,限局性前立腺癌患者105例に対して小線源療法を実施した.我々は技術的改良をほどこした2001年10月から2003年2月までを後期と定義した(症例58例).2000年2月から2001年9月まで前期と定義した(症例47例).後期を前期と比較した.前期の治療手順は次の通りである.我々は経会陰的アプローチでテンプレートの孔を通して,経直腸超音波ガイド下にて,前立腺に対してプラスチック針の穿刺をする.CTで穿刺針の位置を確かめて,前立腺の最大断面での二次元的線量分布図を得た.それを分析し,線量率を決定して,線源停留時間を算出した.我々はclinical target volumeを前立腺の周縁部に設定した.外套針に線源を挿入して,それらを固定した.しかし,我々は次の点を変更した.1)患者の体位を拡大砕石位にした.2)経直腸超音波プローブを低位/背側にした.3)前立腺の尖部に金属マーカーを挿入留置した.4)経直腸超音波的に尿道を造影した.5)三次元的に治療計画装置で経直腸超音波から線量分布を作成した.我々は前立腺,尿道と直腸に関連したdose volume histogramを算出した.そこで,線量率を決定した.我々は各々の技術的改良をチェックした.

【結果】1) 拡大砕石位をとることによって恥骨弓を避けた穿刺が可能になった.2) 経直腸超音波プローブの位置を背側へ移動させることによって,前立腺の辺縁領域を十分に描出可能にした.3) 線源移動の目安を作るために前立腺尖部に金属マーカーを挿入留置した.4) 造影することにより尿道を同定することが容易になった.5) 穿刺針の配置を工夫した.この技術的に改良によって,尿道と直腸への投与線量を減少させることが明らかになった.

【結論】我々は低線量率Ir-192 thin wireを用いた限局性前立腺癌に対する小線源療法の問題を挙げた、これに対して技術的な改良を試みた、これは、将来の前立腺癌に対する小線源療法の技術的な改良のために参考となるものと考える。