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Σεβαστουπόλεως 76 – 115 26 Αθήνα
Τηλ.: 210 69 82 950, Fax: 210 6994258,
e-mail: eis-iatriki@otenet.gr

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76 Sevastoupoleos street – GR-115 26 Athens
Tel.: +30 210 69 82 950, Fax: +30 210 6994258,
e-mail: eis-iatriki@otenet.gr

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380 Mesogeion Ave. – GR-153 41 Agia Paraskevi
Tel.: +30 210 60 00 643, Fax: +30 210 6002295
e-mail: techn@hol.gr

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PREFACE

Dear Colleagues,

After the 12th Hellenic Surgical Oncology Congress and the Hellenic Society of Surgical Oncology Board Elections, a new Administrative Board was formed. The new Board has set numerous goals for the following two years. Firstly, taking into consideration the work and experience of the previous Boards, we aim to pursue the establishment of a legal frame for the practice of Surgical Oncology in Greece. Moreover, regarding this journal, supervised by a new Editorial Board, we will work towards its indexing in PubMed, which requires the Members' support, with the submission of articles. Finally, the new Board will attempt to organize scientific congresses and seminars throughout Greece, enhancing the Society's approach to Surgical, Medical and Radiation Oncologists around the country. With everyone's support and cooperation, we hope to live up to previous experience and have a productive term of office.

With kind regards,

John Spiliotis, MD, PhD

Director & Chairman, 1st Department of Surgical Oncology,
Metaxa Cancer Hospital, Piraeus, Greece
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of the Hellenic Society of Surgical Oncology

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EDITORIAL

Survival improvement in patients with intermediate thickness melanoma and occult lymph node metastases by sentinel lymph node biopsy

E. de Bree

Melanoma and Sarcoma Unit, Department of Surgical Oncology, Medical School of Crete University Hospital, Heraklion, Greece

INTRODUCTION

The staging and treatment of clinically non-involved regional lymph nodes in patients with melanoma has remained controversial for a prolonged period of time. Indisputably, clinically involved regional lymph nodes are treated with radical lymph node dissection. However, the issue how to proceed in the case of clinically negative regional lymph nodes has been a subject of controversy: observation and lymph node dissection in the case of development of clinically involved lymph nodes versus sentinel node biopsy and early lymph node dissection in the case of involvement of the sentinel lymph node. Although sentinel node biopsy is routinely performed worldwide, in melanoma patients without clinically evidence of metastases to regional lymph node and distant sites,[1-4] its benefit has been disputed by some melanoma experts.[5] Its effect on locoregional disease control is obvious, but increase of disease specific survival has not been demonstrated yet. In thin melanomas (Breslow thickness ≤1.0 mm) the risk of occult lymph node metastases is so low and in thick melanomas (Breslow thickness >4 mm) the risk of distant (micro)metastases is so high that in these cases, staging with sentinel node biopsy has usually been considered redundant. Hence, the sentinel node biopsy procedure may be beneficial, especially in case pertain to intermediate thickness melanoma.

THE FINAL RESULTS OF THE FIRST MULTICENTER SELECTIVE LYMPHADENECTOMY TRIAL (MSLT-1)

Recently, the long term results of the first Multicenter Selective Lymphadenectomy Trial (MSLT-1),[6] in which melanoma patients without evident lymph node and systemic metastases were randomized between management based on sentinel node biopsy (60% of the included patients) and

Correspondence address:
Eelco de Bree, MD, Department of Surgical Oncology, University Hospital, P.O. Box 1352, GR-71110 Heraklion, Greece, Tel.: +30-2810-392056 / 392382, Fax: +30-2810-392382, e-mail: debree@med.uoc.gr

observation (40% of the included patients) have been reported. In the observation-arm, patients underwent wide local excision and observation of the regional lymph nodes, with lymph node dissection only when lymph node metastases became clinically evident. In the sentinel lymph node biopsy-arm, wide local excision was followed by sentinel node biopsy, with immediate lymph node dissection when involvement of a sentinel lymph node was found. In total, the results of the 2001 patients included in this study were analysed, with special focus on the intermediate thickness (in this trial defined as Breslow thickness 1.2 – 3.5 mm) and thick melanomas (Breslow thickness >3.5 mm). After previously reported interval analyses, t the final results after a 10-year follow-up period were finally presented. The incidence of lymph node metastases was 20.8%, 17.4% for intermediate thickness (n=1270) and 37.6% for thick (n=290) melanomas. The sentinel node identification rate for these groups of patients was 99.4% and 100%, respectively, and the percentages of sentinel node involvement 16.0% and 32.9%, respectively. During this long term follow-up, lymph node recurrence was observed in 4.8% and 10.3% of the patients with intermediate thickness and thick melanoma and a melanoma free sentinel node (false negative sentinel node biopsy). The authors conclude that as a result of these data the sentinel node biopsy procedure is a reliable diagnostic procedure for the staging of occult lymph node metastases.

The primary endpoint of the study was melanoma-specific survival (calculated time lapse for death due to melanoma to occur), while secondary end-points were disease-free survival, difference in survival between patients with positive (histological involved) and negative (histological non-involved) sentinel node, and distant disease-free survival.

The 10-year melanoma-specific survival was similar in both arms for the entire group of patients. However, for patients with intermediate-thickness melanoma and occult lymph node metastases the 10-year melanoma-specific survival was significantly higher in the sentinel node biopsy group (85.1±1.5% vs. 62.1±4.8%, hazard ratio of death due to melanoma 0.56 (95% confidence interval 0.37-0.84), p=0.006). The difference also remained significant when patients with a false negative sentinel node biopsy procedure were included. In patients with thick melanoma, a significant difference was not observed.

As expected, the survival of patients with a positive sentinel node was worse that of patients with a negative sentinel node. In a multivariate analysis, the status of the sentinel node was the most important prognostic factor for death from melanoma. It was also not surprising to see that patients in the sentinel node biopsy-arm had a better disease-free survival, since a significant portion of patients in the observation-arm had occult nodal metastases which were anticipated to become clinically detectable during follow-up.

Distant disease-free survival was also significantly better when patients with lymph node metastases of intermediate thickness melanoma underwent early (in case of positive sentinel node biopsy) instead of delayed (when nodal metastases became clinically evident) lymph node dissection (hazard ratio for development of distant metastases 0.62 (95% confidence interval 0.42-0.91), p=0.02). This effect was not observed in patients with thick melanoma.

DISCUSSION

In the above mentioned study of great importance,[6] the positive effect of the early treatment of lymph node metastases based on sentinel node biopsy, on distant disease-free and melanoma-specific survival in patients with intermediate thickness melanoma has been demonstrated. Although the diagnostic procedure and treatment were undertaken relatively way back (1994-2002), in the subsequent period (as the authors themselves also disclose) during which experience with this sentinel node biopsy has increased and techniques have improved, the reported results remain extremely important.

Frequently, the false negative rate of sentinel node biopsy has been erroneously calculated by dividing the number of false negative procedures by the total of patients who underwent a sentinel node biopsy.[6] With this method of calculation, the rate displayed is too favourable. Because of the low incidence of nodal metastases, the false negative rate is even low with a high number of nodal recurrences after negative sentinel lymph node biopsy. However, when the false negative rate is calculated by dividing the number of patients with a false negative sentinel lymph node biopsy by the total number of patients with positive regional lymph nodes (i.e. patients with false negative sentinel node biopsy plus patients with a positive sentinel node biopsy), as suggested in the literature,[7] this percentage is considerably higher: for all melanomas 19.4% vs. 4.8%, for intermediate thickness melanoma 20.3% vs. 4%, and for thick melanoma 17.4% vs. 6.9%. Hence, it seems that the sentinel node biopsy procedure as used in this study is a relatively reliable diagnostic technique for the detection of occult lymph node metastases, but there is definitely room for improvement of this method. With increased experience, improved collaboration among the disciplines involved and novel technical developments, it is warranted to believe that the technique has become now more reliable.

The criticism on the interval analyses of this trial has been answered in the final report. While in the interval analyses only patients with intermediate thickness melanoma were included, in the final report the data of patients with thick melanoma were also reported. Because of the small number of patients with thin melanoma included in this trial and the very low risk of nodal metastases, this patient group was excluded from analysis.

Earlier reports had been criticized because the lymph node status was initially only known for the patients who had undergone sentinel lymph node biopsy. In the observation-group of patients, lymph node metastases would remain undetected for a long period of time. At the beginning of the follow-up period the incidence of nodal metastases was indeed higher in the sentinel lymph node biopsy-group than in the observation-group. In this way, subanalysis of patients known with lymph node metastases in both groups may not have been reliable ('stage migration effect' or 'Will Rogers phenomenon'). This potential bias seems to decrease with the longer follow-up (period of 10 years opposed to 5). However, a higher incidence of lymph node metastases remains in the group of patients who had undergone sentinel lymph node biopsy. For patients with intermediate thickness melanoma regional lymph node metastases were found in 17.4% in the observation group and in 20% (16% sentinel lymph node positive + 4% during follow up) in the sentinel node biopsy group. The authors noted estimated 10-year cumulative lymph node positivity of 19.5% and 21.9%, respectively. For patients with thick melanoma, the differences are smaller: the observed rates of lymph node positivity were 37.6% and 39.9% (32.9%+6.9%), respectively, while the estimated 10-year rates of lymph node positivity were 41.4% and 42%, respectively. To amend for the fact that nodal status was initially known only in the sentinel node biopsy group, the authors performed an accelerated-failure-time latent-subgroup analysis, which showed an obviously smaller effect of sentinel lymph node biopsy on distant disease-free and melanoma-specific survival (hazard ratios of 0.73 with p=0.04 and 0.68 with p=0.05, respectively). Possibly, the latency period is not the only important parameter. Some critics stress that it is not entirely certain whether each occult lymph node metastasis found at sentinel lymph node biopsy will ultimately become a clinically evident lymph node metastasis or whether in some patients the immune system will destroy these melanoma cells that are disseminated to the sentinel lymph node. The latter might also explain the persistent difference in lymph node positivity between both groups of patients after long follow-up and renders the effect of the sentinel lymph node biopsy difficult to assess.

Distant disease-free survival is in such a study a better outcome end point than disease-free

survival, because the most significant recurrence site (the regional lymph nodes) has already been treated with the surgical intervention. Therefore, it is important that this outcome parameter has been mentioned in the final report. Statistically significant differences in distant disease-free and melanoma-specific survival for patients with lymph node metastases were noted for intermediate thickness melanomas and not for thick melanomas. On one hand, this might be due to the already high risk of occult distant metastases at diagnosis and, on the other hand, this might also be caused by the small number of patients with thick melanoma included in this study.

CONCLUSIONS

In the MSLT-1 study,[6] it appeared that sentinel node biopsy is a relatively reliable staging procedure. Sentinel node biopsy does not improve survival of all melanoma patients, but identifies patients which exhibit a survival benefit by early removal of lymph node metastases. In patients with intermediate thickness melanoma and occult lymph node metastases, distant disease-free and melanoma-specific survival were significantly higher for those who had undergone positive sentinel lymph node biopsy and early lymph node dissection than for those who underwent delayed lymph node dissection when lymph node metastases became clinically evident during observation. This was not the case for patients with thick melanoma and occult lymph node metastases. Besides the fact that sentinel lymph node biopsy offers detailed staging, the status of the sentinel lymph node is the strongest prognostic factor and the sentinel lymph node biopsy procedure is of importance in selecting patients for eventual adjuvant systemic treatment. Earlier publications of the same study have already demonstrated that sentinel lymph node biopsy is a safe procedure with very limited morbidity,[8] while lymph node dissection for clinically evident lymph node metastases is associated with increased risk of lymph oedema, longer hospital stay and consequently higher costs when compared to selective lymph node dissection after a positive sentinel lymph node biopsy.[9]

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REVIEW

Sentinel node biopsy in patients with early oral cancer
New developments

R. de Bree[1], D.A. Heuveling[1], G.A.M.S. van Dongen[1,2], O.S. Hoekstra[2]

[1]Departments of Otolaryngology-Head and Neck Surgery and [2]Radiology & Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands

ABSTRACT

Sentinel node biopsy (SNB) using the combination of ^{99m}Tc-labeled colloid and blue dye reliably stages the clinically negative neck (cN0) in early stage (T1/2) oral squamous cell carcinoma (OSCC): sensitivity of 93% and negative predictive value of 80-100%. However, the procedure has some clear limitations for preoperative detection as well as for intraoperative SN detection and removal. SNs close to the primary are often missed, second echelon lymph nodes are erroneously considered to be SNs, and biopsy of the SN can be technically challenging. To make SNB a high precision and minimally invasive procedure, preoperative information to identify the SN among the 150 lymph nodes per neck side must be as detailed as possible, and intraoperative techniques to localize the SN with high precision should be developed. This paper describes the different ways in which such improvements of the SNB procedure could be achieved. Technical improvements for intraoperative real-time imaging like the use of a portable gamma camera or freehand declipse SPECT visualize additional SNs. New tracers for PET and fluorescence imaging, ^{89}Zr-, ICG- and IRDye800CW-nanocolloidal albumin, have been developed and are currently tested in early oral cancer patients as single or hybrid tracers. These improvements may increase the sensitivity of SNB further and limit the exploration needed to harvest SNs, reducing the risk of complications and operating time.

KEY WORDS: Sentinel node; oral squamous cell carcinoma; lymphoscintigraphy; fluorescence

SENTINEL NODE BIOPSY IN ORAL CANCER

Head and neck squamous cell carcinoma (HNSCC) has a high propensity to metastasize through lymphatics to regional lymph nodes rather than to spread haematogeneously. Moreover, regional metastasis at time of diagnosis is one of the most important prognostic factors. Patients with multiple, contralateral or bilateral metastases in the neck have a markedly reduced survival. It is universally

Correspondence address:
Remco de Bree, MD, PhD, Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands, Tel.: +31-20-4443689, Fax: +31-20-4443688, E-mail: r.bree@vumc.nl

accepted that the neck has to be treated by either surgery with or without adjuvant (chemo)radiation or by primary (chemo)radiation in case of overt lymph node metastases. However, the management of the clinically negative (cN0) neck is still a controversial issue. There is general agreement that elective treatment of the neck is indicated when there is a high likelihood of occult, i.e. clinically and radiologically undetectable, lymph node metastases, when the neck needs to be entered to resect the primary tumour or to reconstruct the surgical defect, or when the feasibility of regular follow-up is questionable.[1]

The rationale for elective (prophylactic) treatment is based on the following assumptions. First, occult metastases will inevitably develop into clinically manifest disease. Secondly, even with watchful waiting some patients will develop extensive or even inoperable disease in the neck with a wait and see policy. Finally, if left untreated, disease in the neck may be associated with a higher incidence of distant metastases, developing while the undetected lymph node metastasis is growing to a clinically detectable size. The arguments against elective treatment of the neck are as follows. Firstly, a large proportion of patients are subjected to the morbidity (e.g. shoulder dysfunction) and costs of unnecessary treatment. Secondly, such treatment could alter a route of cancer spread in case of local recurrence or second primary tumour. Unfortunately, there is no single (non-)invasiveimaging techniquewhich could reliable detect occult lymph node metastasis and replace elective treatment of the neck by a watchful waiting follow-up policy.[1]

Sentinel node biopsy (SNB) is a diagnostic staging procedure, which is applied in a variety of tumour types, including melanoma, breast cancer and HNSCC. The procedure aims to identify the first draining lymph node(s), the sentinel node(s) (SN(s)), which is most likely to harbour metastasis. Conceptually, the histopathologic status of the SN reflects the histopathological status of the rest of the nodal basin. Additional treatment of the nodal basin (e.g. surgery) should be performed in case of metastatic involvement of the SN. A negative SN, i.e. without metastasis, would justify to refrain from treatment of the nodal basins.

In short, the routine SNB-procedure consists of preoperative peritumoural injections of technetium-99m (^{99m}Tc)-labeled nanocolloidal albumin followed by lymphoscintigraphy using planar or single photon emission tomography/computed tomography (SPECT/CT) imaging. Based on the preoperative lymphoscintigraphy results the position of the SN is marked on the skin. SNB is performed under general anaesthesia and intraoperative detection of the SN is possible by a combination of peritumourally injected blue dye (coloration) and a portable (free hand) gamma probe (radionuclide detection). Ideally, one or more blue and radioactive ('hot') SNs are identified and excised. However, lymph nodes that are either blue or 'hot' alone are also considered to be SNs. After surgical removal, the SN is investigated by meticulous histopathological examination using stepped serial sectioning and immunohistochemistry.[2]

If the SN contains metastatic disease, treatment of the neck is recommended, usually in a second procedure.[2] The SNB-procedure is more accurate than anatomical imaging procedures and less invasive than elective neck dissection. Moreover, the procedure is associated with significantly less postoperative morbidity and better shoulder function as compared to elective neck dissection.[3] Furthermore, SN biopsy with eventual subsequent neck dissection is cost-effective as compared to elective neck dissection in early oral carcinoma patients.[4] Current best practice guidelines for the provision of SNB in early oral squamous cell carcinoma (OSCC) patients have been outlined, which provide a framework for the currently evolving recommendations for its use.[2]

To safely assign patients to surgery or watchful waiting high demands are put on feasibility and sensitivity of the SN procedure. The American College of Surgeons Oncology Group (ACOSOG) Z0360 validation study with 140 patients in 25

institutions showed a sensitivity of 90% and a negative predictive value of 96%, and these figures were even better for experienced surgeons.[5] However, standard histopathological procedures were used as the gold standard. Routine histopathological examination can miss micrometastases in up to 15.2% compared to serial sectioning and immunohistochemistry.[6] Therefore, the Z0360 results likely overestimated the sensitivity of the SN technique. Since the neck contains up to about 150 lymph nodes per side it is practically impossible to examine all lymph nodes from a neck dissection specimen by step serial sectioning and immunohistochemistry. Because isolated tumour cells and micrometastases can be missed by routine histopathologicaltechniques, long term observation of the neck should be a better reference standard. After initial studies to validate the SN concept in early OSCC patients, several prospective observational studies have been reported. In these studies a neck dissection was performed only when the SN contained a metastasis, while a watchful waiting strategy was followed when the SN did not contain metastasis. In a European multicenter study[7] of 134 cT1/2N0 OSCC patients, 79 patients underwent SN biopsy as the sole staging tool, while 55 patients underwent SN biopsy followed by elective neck dissection (END). In 125 (93%) patients the SN was successfully harvested. For the two groups together, using a reference standard of 5 years follow-up after SN biopsy staging, a sensitivity of 91% and a negative predictive value of 95% were found. The better performance of the SN biopsy-assisted END group (sensitivity 96%, NPV 97%) compared to the SN biopsy-alone group (sensitivity 87%, NPV 94%) can again be explained by the use of standard histopathological examination of the neck dissection specimen versus 5 years follow-up as a gold standard for metastasis. In a large single centre study no false-negative ipsilateral findings were found in a study of 103 oral and oropharyngeal patients. Lymphoscintigraphy revealed a hot spot in 98%, the detection rate was 96% and a mean of 2.65 SNs were harvested per patient.[8] In another single centre study[9] of 79 cT1/2N0 patients lymphoscintigraphy showed a hot spot in 95%, the preoperative detection rate was 99%, and a mean of 2.7 SNs were harvested for a sensitivity of 91% and a negative predictive value of 90%. In a recent retrospective study[10] of 90 previously untreated early OSCC patients with a clinically N0 neck who underwent SNB (only neck dissection after positive SNB) a lymphoscintigraphic identification rate of 98%, surgical detection rate of 99% and upstaging rate of 30% were found. Using a median follow-up of 10 months the sensitivity was 93% and the negative predictive value was 97%. The observational multicentre European Sentinel Node Trial (SENT)[11] with more than 400 patients, has completed accrual and is waiting for long-term follow-up. A recent meta-analysis including 847 patients from 21 studies showed a pooled sensitivity of 93% (95% confidence interval (CI) 86-95%) in oral cancer patients. When neck dissection was used as reference standard sensitivity was 94% (CI 90-97%), versus 91% (CI 84-95%) when follow up was the reference standard. The vast majority of the studies included were performed in patients with early OSCC. The negative predictive values ranged from 80 to 100%.

LIMITATIONS OF CURRENT SENTINEL NODE BIOPSY PRACTICE

From aforementioned studies it can be concluded that successful SNB using the combination of ^{99m}Tc-labeled colloid and blue dye reliably stages the cN0 neck in early stage OSCC. However, the procedure has some clear limitations for preoperative detection as well as for intraoperative SN detection and removal.

Using the conventional SNB procedure, biopsy of the SN can be technically challenging because of a lack of detailed anatomical information of the localisation and intraoperative visualisation of the SN. As a result, an extensive intraoperative search and exploration is sometimes needed to

find the SN. Less exploration will also result in less fibrosis during an eventual subsequent neck dissection and may at the end result in a reduction of complications and not-intended sacrificed structures in the neck. In addition, improved topographical orientation and delineation of SNs against surrounding structures may also reduce surgical time.

In floor of mouth (FOM) tumours, the SN procedure appeared to be more difficult than in other primary head and neck sites: SNs were successfully harvested in 88% vs. 96% and at a significantly lower sensitivity (80% vs. 97%, respectively).[7] This is probably due to the close spatial relation between the primary tumour and the first draining lymph nodes (SNs). The injection site (around the primary tumour) produces a large hotspot on lymphoscintigraphy possibly hiding SNs in the close proximity of the primary tumour ("shine through").

Although SPECT/CT has the potential to detect more SNs as compared to planar lymphoscintigraphy, it still has some difficulties in visualization of SNs in close spatial relation to the injection site.[12] Because SPECT lacks dynamic information, differentiation between real SNs and second-echelon nodes may be difficult due to the typically fast kinetics of lymph drainage in the head and neck area. As a result, second echelon (non-sentinel) lymph nodes may erroneously be considered also as SNs and are removed, making sentinel node biopsy unnecessary extensive. Moreover, the resolution of the gamma- or SPECT-camera is not always sufficient to visualize and localize these SNs.

Blue dye is injected in the same way as the radiocolloid, just before surgery, allowing for real-time lymphatic mapping. Blue dye follows lymphatic vessels and accumulates in the draining lymph nodes giving them a blue staining.[13] However, real-time detection of this blue staining is only possible if there is no overlying tissue. Moreover, blue dye is a relatively low molecular weight compound with a very poor retention in the SN and is therefore restraint to a short period of time. As a consequence, the use of blue dye appears to be of limited added value in the head and neck area.[10,14]

Current SN detection has limitations, especially in case of FOM tumours. SNs close to the primary are often missed, second echelon lymph nodes are erroneously considered to be SNs, and biopsy of the SN can be technically challenging. To make SN biopsy a high precision procedure, preoperative information must be as detailed as possible, and intraoperative techniques to improve the detection should be developed.

NEW DEVELOPMENTS TO IMPROVE SENTINEL NODE BIOPSY

For improvement of the preoperative SN detection, positron emission tomography (PET)/CT can be considered as it provides dynamic 3-dimensional information at a higher spatial resolution than achievable with a gamma camera and it provides detailed anatomical information. Recently, a PET-tracer, zirconium-89 (^{89}Zr)-nanocolloidal albumin, dedicated to lymphatic mapping and SN detection using high resolution PET/CT has been developed. In a lymphogenic metastatic tumour model using rabbits bearing auricular VX2 carcinomahigh-resolution PET imaging showed distinguished uptake of ^{89}Zr-nanocolloidal albumin in the SNs, with visualization of afferent and efferent lymphatic vessels, and a biodistribution pattern comparable to conventional planar lymphoscintigraphy. No statistical differences were found between both tracers with respect to nodal and non-lymphatic tissue uptake.[15] These findings justified further clinical evaluation of ^{89}Zr-nanocolloidal albumin as a tracer for SN detection by PET. The clinical feasibility of PET/CT lymphoscintigraphy using ^{89}Zr-nanocolloidal albumin was evaluated in 5 OSCC patients. PET/CT imaging was able to visualize 5 additional foci (in 2 patients) considered to be SNs, all located in proximity of the primary FOM tumour. On

SPECT/CT, these foci were hidden by the hotspot at the injection site. In 4 patients, lymphatic vessels could be visualized in the early phase of the dynamic PET/CT scan, and in one patient this led to a better differentiation between a "true SN" and a second echelon lymph node, compared to SPECT/CT imaging.[16] Thus, compared to gamma-based techniques, improved detection and more precise localization of SNs could be achieved on PET/CT.

Intraoperative real-time imaging with a portable gamma camera provides an overview of all radioactive spots and can show SNs near the injection site by adjusting its position and can be used to determine the distribution of the remaining radioactivity after excision of SNs. This portable gamma camera was able to visualize SNs at difficult sites more efficiently and identifies 9 additional SNs in 6 of the 25 head and neck melanoma or OSCC patients.[17]

To improve SNB, recently the technique of freehand SPECT has been introduced. Freehand declipse SPECT is a 3D tomographic imaging modality based on the imaging concepts of SPECT, but with the major difference of being based on data acquisition by a freehand scan using handheld detectors instead of gantry-based gamma cameras. The technology was designed to use conventional gamma probes for detection of radiation and positioning systems to determine the position of the detector relative to the patient. Based on the integration of the acquired set of probe read-outs and their position and orientation, the system is capable of generating 3-dimensionalnuclear images similar to a SPECT image. Of particular interest are the availability of information on the direction and the distance of the SN in relation to the tip of the gamma probe provided on screen by the freehand SPECT system. Freehand SPECT may aid the process of surgical excision of the SN in several ways. Due to its freehand nature and the flexible, mobile hardware required, it can be integrated into the operating room without considerable changes of the standardized workflow. In practical terms, the standard instrumentation is extended by a positioning system and processing means in order to generate images. The system enables the generation of 3-dimensional images with the patient lying on the operating table making in situ planning of the biopsy possible. The possibility of generating images in the operating room could be used again after the procedure, but before closing the wounds, in order to confirm harvesting of all hotspots. More precise information on the localization of the SN may reduce the risk of damaging vulnerable structures such as nerves and vessels in the neck improving the safety during surgery. Promising results in OSCC patients have been reported, but also this technique has some difficulties in visualization of SNs in close spatial relation to the injection site.[18]

Near-infrared (NIR) fluorescence imaging might be a very attractive option to facilitate intraoperative detection. NIR fluorophores have the advantage to exhibit reasonable tissue penetration of excited and emitted light with negligible autofluorescence, resulting in higher target-to-background contrast. NIR fluorescence imaging provides high resolution images which can be obtained in real-time during the surgical procedure, even if the structure of interest is covered by some tissue (in contrast to blue dye). Another advantage of NIR fluorescence imaging is that it is much better suited for detection of SNs close to the primary, because there is negligible influence of fluorescence signal coming from the injection site (in contrast to the radioactive nanocolloidal albumin). Nowadays, the only FDA approved NIR-fluorescent compound that has been extensively evaluated for SN detection is indocyanin green (ICG). Because ICG alone has a poor retention in SN it is combined with nanocolloidal albumin. The feasibility of near NIR fluorescence-guided SN detection has been demonstrated in HNSCC where fluorescence imaging of ICG was used as fluorescent tracer. Using ICG-^{99m}Tc-nanocolloidal albumin, in 4 of the 14 OSCC patients where the SN was located close to the primary injection site the SN could only be localized using fluorescence imaging.[19]

Ideally, NIR-fluorescence imaging alone could also replace the use of the preoperative lymphoscintigraphy. If so, the whole SNB procedure can be performed without using radioactivity, which would be a great advantage with respect to logistics, safety, and legislation. A promising next generation NIR fluorophore is IRDye800CW (LI-COR biosciences, Lincoln, NE). This NIR fluorophore shows a much better quantum yield and can be covalently conjugated to a broad spectrum of biomolecules. The latter property allows for conjugation of IRDye800CW to nanocolloidal albumin, which should be considered as the most attractive carrier compound for SN detection, since this colloid is widely used for many years in the clinical SN procedure in Europe. Recently the NIR fluorescent tracer nanocolloidal albumin-IRDye800CW was developed and preclinically evaluated. This tracer showed optimal retention in the SN in the aforementioned animal model, therefore having the advantage that it can be used in the two-days protocol SNB procedure with tracer injection the day before surgery (as performed in most centres), resulting in minimal visualization of non-sentinel lymph nodes. Non-invasive detection of the SN appeared possible within 5 minutes after injection of nanocolloidal albumin-IRDye800CW, which appeared comparable for the reference tracer ICG/HSA. No decrease in fluorescent SN signal and no increase of background fluorescence were observed with nanocolloidal albumin-IRDye800CW after 24 h, while in contrast a strong decrease or disappearance of the fluorescent signal was seen at that moment for ICG/HSA. Fluorescence-guided detection and excision of fluorescent lymph nodes was very easy in this model.[20]

The hybrid tracerICG-^{99m}Tc–nanocolloidal albumin has been used for SNB in oral squamous cell carcinoma allowing for a single session of peritumoural injections.[19] In the near future probably also other combination for concomitant radio- and fluorescence-guided SNB will be developed. It can be anticipated that the combination of PET-CT lymphoscintigraphy and NIR fluorescence imaging provides optimal information about the localisation of the SN, through which sensitivity of the SN biopsy procedure can be improved in complex situations like close spatial relation between injection site and SN like with FOM tumours with minimal risks of complications and prolonged operating time.

CONCLUSIONS

SNB is a reliable diagnostic staging technique of the clinically negative neck in early oral carcinoma. However, improvements are needed for tumour sites with close spatial relation of the potential SNs as in FOM tumours. New tracers for PET and fluorescence imaging, ^{89}Zr-, ICG- and IRDye800CW-nanocolloidal albumin, have been developed and are currently tested in early oral cancer patients as single or hybrid tracers. These improvements may increase the sensitivity of SNB further and limit the exploration needed to harvest SNs, reducing the risk of complications and operating time.

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REVIEW

Evaluation of mediastinum in non small cell lung cancer and the role of PET CT

P. Alexidis, S.P. Stylianidou

Radiotherapy Department, Papageorgiou General Hospital of Thessaloniki, Greece

ABSTRACT

Non small cell lung cancer (NSCLC) is being treated in a multimodality way (surgery, chemotherapy, radiation therapy) according to the stage of the disease and the histological findings after surgery. Mediastinal lymph node disease is an important prognostic factor which also determines the treatment that will be selected for the patient, while it is decisive for the treatment planning and for the volumes to be irradiated during radiation therapy (RT). PET CT helps determine the mediastinal nodal extension of cancer and has become a gold standardin the treatment of NSCLC and at the same time it has give radiation oncologists the opportunity to differentiate the fields that were used previously achieving in this way better therapeutic results.

KEY WORDS: Lung cancer, lymph nodes, PET CT, elective nodal irradiation, involved filed irradiation

INTRODUCTION

In the case of non-small cell lung cancer, surgical operation is possible depending on the stage of the disease and the performance status of the patient and it can be followed by post-operative radiotherapy according to specific indications. Stages I-IIIA are considered operable while stage IIIB patients are treated with radical radiotherapy as are earlier stage patients who are unfit for surgery due to a lower performance status. Post surgically the indications for adjuvant RT include N2 disease, positive surgical margins and extranodal extension of positive lymph nodes. Before treating a patient, the radiation oncologist must first determine the primary site of the disease and the pathological lymph nodes and ensure that, by irradiating the appropriate tissues, he will achieve a local control and also decrease the probability of distant metastases. The previous years there was a trend to use larger fields in order to irradiate not only the pathological lymph nodes but also deliver a prophylactic dose to the rest of the mediastinum (elective nodal irradiation, ENI), while today with the use of PET CT and the better location of the lymph nodes harboring disease, smaller fields are used (involved filed irradiation IFRT) with a view to deliver the desired dose with less toxicity.

Corrresponding author:
Petros Alexidis, Resident in Radiotherapy, Radiotherapy Department, Papageorgiou General Hospital of Thessaloniki, 9 Maria Kallas Street, 54645 Thessaloniki, Greece. Tel.: 6945803354, e-mail: alpet70@gmail.com

ENI vs. IFRT

Many studies have compared elective nodal and involved field irradiation and tested wether the former contributes to the local control of the disease. In the past (1970-1980) the dominant tendency was to use larger fields when treating NSCLC in order to deliver prophylactic radiation to the mediastinal lymph nodes, to the hila of the opposite lung and even to the supraclavicular areas. The currently prevailing trend is to omit ENI and instead use smaller fields in order to achieve greater dosages in both the primary site and the lymph nodes in which the disease has been confirmed by clinical and laboratory examinations.[1] The reasoning behind this practice is based on the high rate of recurrences observed in areas within the radiation fields and on the strong possibility of distant metastases, as compared to the low frequency at sites outside the fields. Therefore, if the primary site can not be adequately controlled, what is the use of enlarging the treatment fields thus causing greater toxicity (figure 1)?[2] The transition from larger to smaller fields has been achieved due to three factors: the concomitant use of chemotherapy, 3DCRT radiotherapy and the involvement of PET-CT in the planning. Data from more recent studies indicate that ENI omission doesn't actually decrease local control, with 8% of the recurrences occurring in areas that had not been treated. At the same time, the smaller fields resulting from ENI omission decrease toxicity, thus permitting increased dosage in the primary site.[3] Moreover, according to G. Fletcher's findings, it is generally accepted that most of the epithelial tumors require a dose of 50 Gy for the microscopic disease to be eradicated, with the corresponding dose ranging between 65 and 75 Gy for tumors from 1 to 3 cm.[4] It is therefore obvious that a T2 stage lung cancer is already bigger than 3 cm, a fact that underlines the necessity of increasing the dose in the primary site. Dosoretz et al.[1] observed that there is no correlation between the size of the site and the result of the therapy, while Rozenweig et al., in a study of 171 subjects who received IFRT without ENI, observed that only 6.4% of the patients developed a disease in previously non-pathological lymph nodes, which indicates that the major concern is controlling the primary site.[1] The low percentage of recurrence in the lymph nodes was partly attributed to the incidental radiation of non pathological lymph nodes due to their proximity to the primary site, something which was more strongly observed in central tumors close to the mediastinum; therefore, it seems that ENI actually occurred even where it was theoretically not expected to occur.[7] Remarkable findings concerning the same fact derive from the study of Martel et al.[4] in which 10 IIIA-B stage patients were submitted to radiation therapy to doses more than 69 Gy. The percentage of lymph node stations receiving dosages of more than 50 Gy were: ipsilateralhilar 100%, contralateralhilar 40%, subcarinal 96%, lower paratracheal 68%, upper paratracheal 0%, aortopulmonary window lymph nodes 57%. Finally, reference should also be made to CHART (Continuous Hyperfactionated Radiation Therapy) and its results in lung cancer. CHART is a treatment technigue in which the

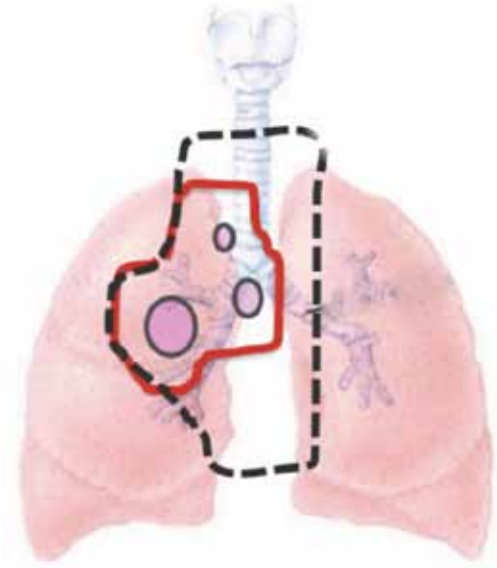


Figure 1. Dashed line represents the ENI field while red line the IFRT one. The reduction of field size (resulting in less toxicity) is obvious.

dosage is highly fragmented, continually applied (even during weekends) and in which more than one sessions take place in a day. The reasoning behind this regimen is to compensate for the accelerated regeneration of neoplastic cells so as to better control the disease.[6] According to a randomized study, the 2- and 3-year survival rate increased from 21% and 13% for the 60 Gy conventional therapy to 30% and 20% for CHART, respectively. Local control in year 3 increased from 12% to 17% resulting in a lower metastasis percentage (the metastasis-free percentage at 3 years was 40% for CHART as compared to 33% for the 60 Gy conventional therapy). The therapeutic benefit of CHART was mainly observed for squamous cell carcinoma.[4]

LYMPH NODE DISEASE IN NSCLC

The correct and precise detection of lymph node disease in lung cancer is of crucial importance for the appropriate treatment and better prognosis for the patient. This is further strengthened by a study comparing clinical to pathologic staging. The pathologic evaluation of the surgical specimens showed metastasis in 26% of stage I patients. The pathologic overstaging of the disease is a constant and recurrent finding in 25% of T1N0 stage and in 35% of T2N0 stage patients, which indicates the existence of undetected micrometastases in patients who have not undergone surgery.[4] It is also important that the attending physician predicts to some degree the possibility as well as the location of a possible spread of the disease in the lymph nodes. This possibility is related to the size and the location of the tumor. Nohl-Oser[4] carried out a study involving 749 subjects which led to the findings described below. In the case of tumors in the right upper lobe, the disease mainly spreads in the upper and lower paratracheal as well as the ipsilateralhilar lymph nodes, while the incidence of disease metastasis in the subcarinal and contralateral lymph nodes was rare. Tumors in the right lower lobe spread to the right tracheobronchial, the ipsilateralhilar and subcarinal lymph nodes. The left upper lobe tumors spread to the ipsilateralhilar and tracheobronchial lymph nodes, while tumors in the left lower lobe can spread to the opposite side of the mediastinum. Another important issue is skip metastases,[4] in other words the occurrence of the disease in lymph nodes with the previous lymph node station being negative. According to a study by Bonner et al.,[4] 52 (15%) out of more than 336 surgically treated patients had disease only in N2 lymph nodes. Among patients free of hilar lymph node disease, mediastinoscopy revealed unexpected mediastinal disease (N2) in 6% while 34% of N2 patients do not show hilar lymph node disease. The possibility of metastasis in the lymph nodes increases depending on the tumor size (0% lymph node metastases for tumors <1cm, 17% for tumors 1.1-2cm and 34% for tumors >2cm), while the subclinical disease in them was an independent prognostic survival factor more frequently observed in poorly differentiated tumors.[7] Additionally, adverse features for lymph node disease are the histological type of the lesion (adenocarcinoma) and pleural participation. Stage IA patients showing at least two of the previously mentioned factors are more than 40% likely to have positive lymph nodes.

TREATMENT PLANNING AND PET CT CONTRIBUTION

The treatment is planned on a CT scan with 3-5 mm slices obtained from the cricoid cartilage to the superior aspect of L2 vertebra. The tissues to be irradiated along with the organs at risk are delineated. The organs at risk include the spinal cord, esophagus, heart, the rest of healthy lung and the brachial plexus and the doses that they will receive should be kept under specific limitations in order to avoid acute toxicity or damage of them (table 1). Different CT windows are used in order to better determine the primary tumor and mediastinal disease along with comparison to PET CT images. PET CT permits the oncologist to

Table 1. Dose limitations for organs at risk. VxGy: the volume of the organ that receives more than x Gy, mean dose: the median calculated dose that an organ receives.

Organ	Dose Limitation
Spina cord	RT alone: maximum dose <50 Gy Chemo-RT: maximum dose <46 Gy
Esophagus	Maximum dose <75 Gy Without chemo V60 Gy <50% With chemo V55 Gy <50%
Heart	V40 Gy <50%
Lungs	Combined volume of both normal lungs receiving >20 Gy: RT <40%, chemo-RT <35% Mean lung dose: RT <20 Gy, chemo RT <16.5-20 Gy
Brachial plexus	Maximum dose <60 Gy

determine the extension of disease to the lymph nodes with greater accuracy and at the same time helps to avoid ENI and focus in dose increase in the primary site and the pathological lymph nodes. Lymph nodes with a diameter >1 cm (short axis) are considered to be pathological in CT, but still 20% of the lymph nodes with a normal size in CT are actually pathological and 80% of them can be detected with PET CT.[8] Also, PET CT has a mean sensitivity rate of 85% and 90% specificity in mediastinal evaluation, the respective values for CT being 57% and 82%.[9] As for the primary tumor the patients that benefit more from PET CT are those having a tumor near the hilum or mediastinum. Therefore, physicians who use CT in planning may irradiate non pathological lymph nodes and omit pathological ones or may irradiate an atelectasis mistaking it with a tumor, conditions that can definitely be differentiated by PET CT. The timing of the scan is of great importance and it should be obtained close to the date that the radiotherapy has been planned. Everitt et al. conducted a study on 82 patients (18% stage II, 61% stage III) which revealed 32% upstaging of the disease in 24 days, while the treatment intent changed from curative to palliative in 29%

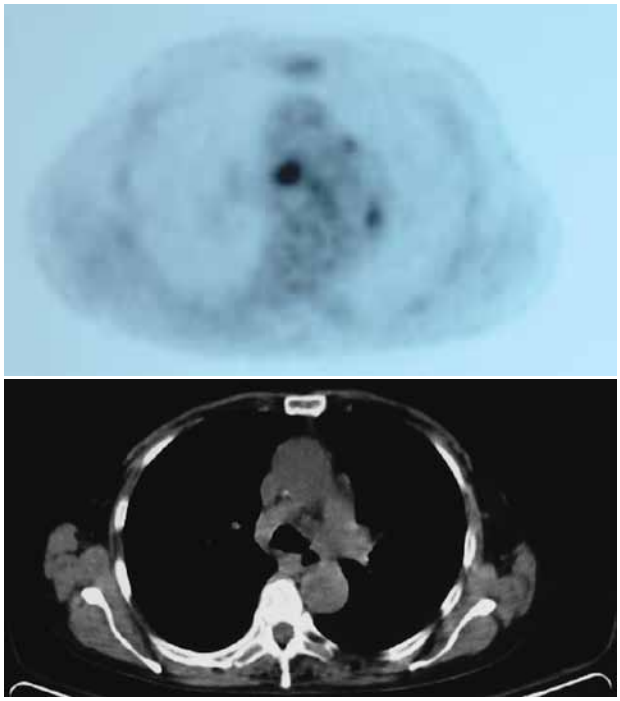
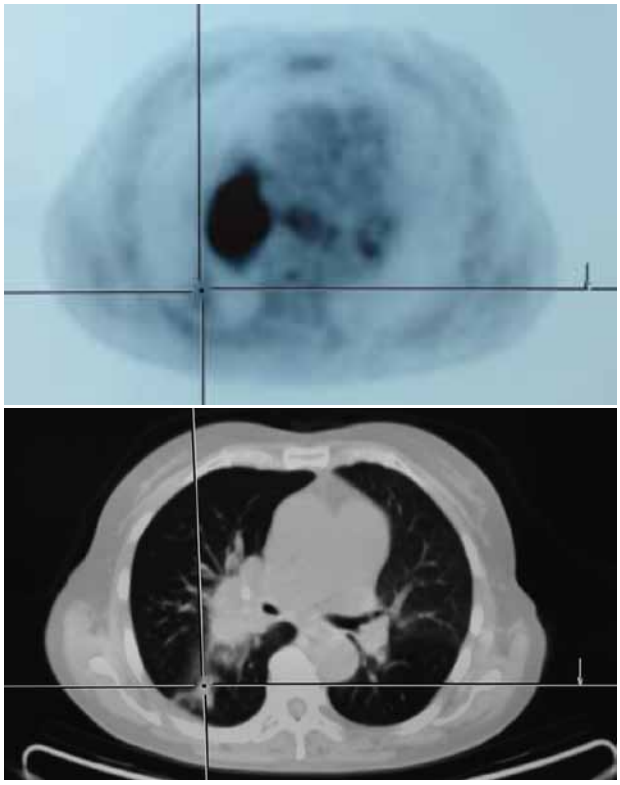


Figure 2. A positive mediastinal LN as seen on CT and PET CT images. When using CT for diagnosis, positive LN could be missed.



Figures 3. A positive pulmonary nodule found on PET CT.

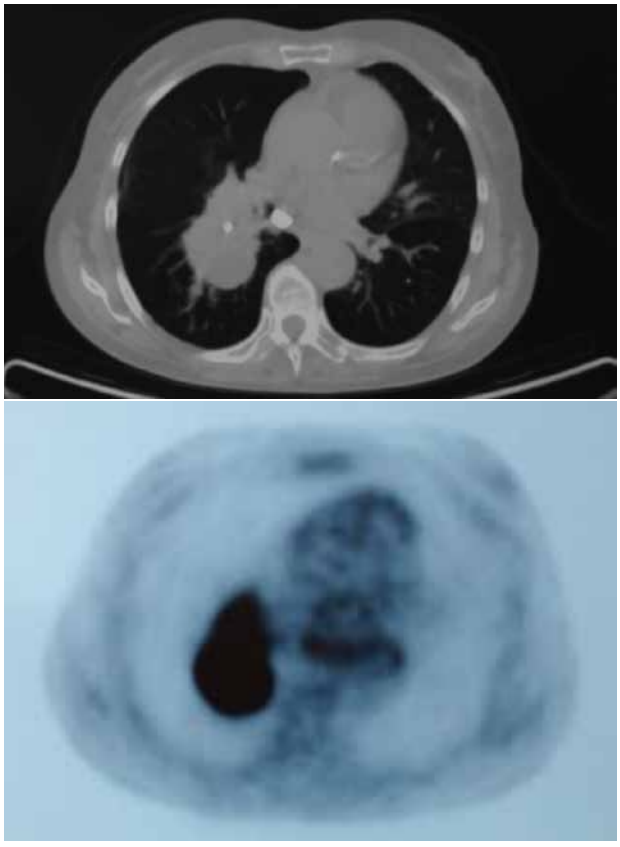


Figure 4. It is not always possible to differentiate between atelectasis and tumor by using either pulmonary or mediastinal window. PET CT helps to identify a pulmonary tumour as shown in figure 4b.

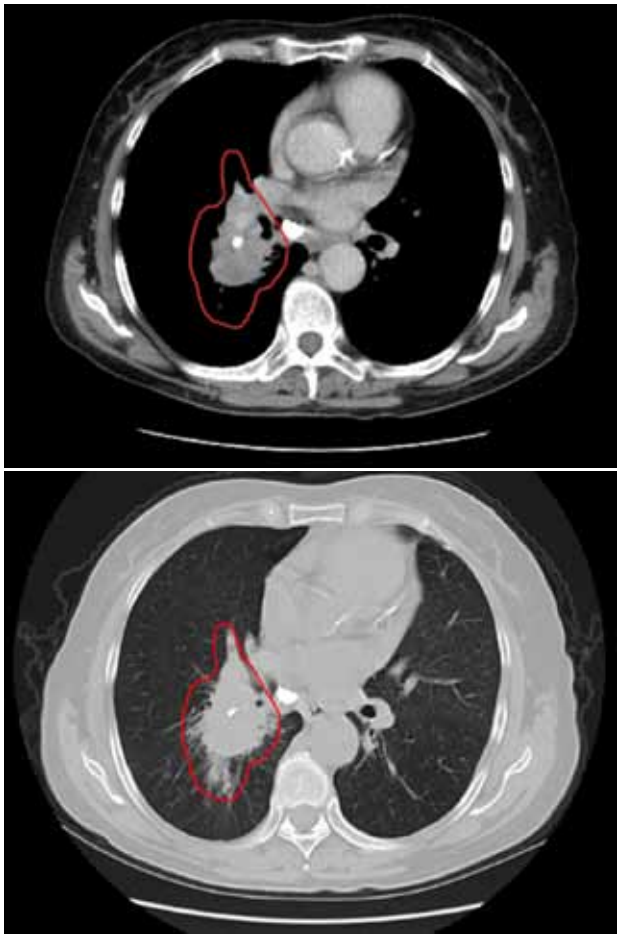


Figure 5. Primary tumor is best defined on lung window and pathological lymph nodes on mediastinal. A delineated tumor as seen on both windows.

of patients.[10] However, it is worth mentioning that despite the great contribution of PET CT in diagnosis and staging, there are cases of false positive or false negative results.[4] False positive results may arise for instance due to an infection (tuberculosis, sarcoidosis) and false negative in a small size tumor (such as a pulmonary nodule <1 cm) in the case of metastases to lymph nodes from low grade tumors (bronchioloalveolar Ca, carcinoid) or shortly after chemotherapy. Reaching to the treatment delivery, it is determined by the location of the primary tumor and the stage of the disease. In the case of stage I-IIIA disease, a three field conformal plan is used. Many tumors are closer to the chest wall than to the mediastinum and ipsilateral beams will minimize the dose to the contralateral normal lung tissue. For larger tumors, in particular those crossing the midline in the mediastinum, or those close to the spinal cord are better treated in two phases. In phase I opposing antero-posterior fields are used in order to achieve better dose distribution to the mediastinum, with esophagus and spinal cord within the treated volume. Then in phase II a three or four field plan is used in order to give higher lung dose. The dose delivered should be 60-66 Gy, while in the post operative setting 50.4 Gy with a boost of 10-16 Gy at sites of extranodal extension is recommended for N2 disease and 60-66 Gy to areas of positive surgical margins.

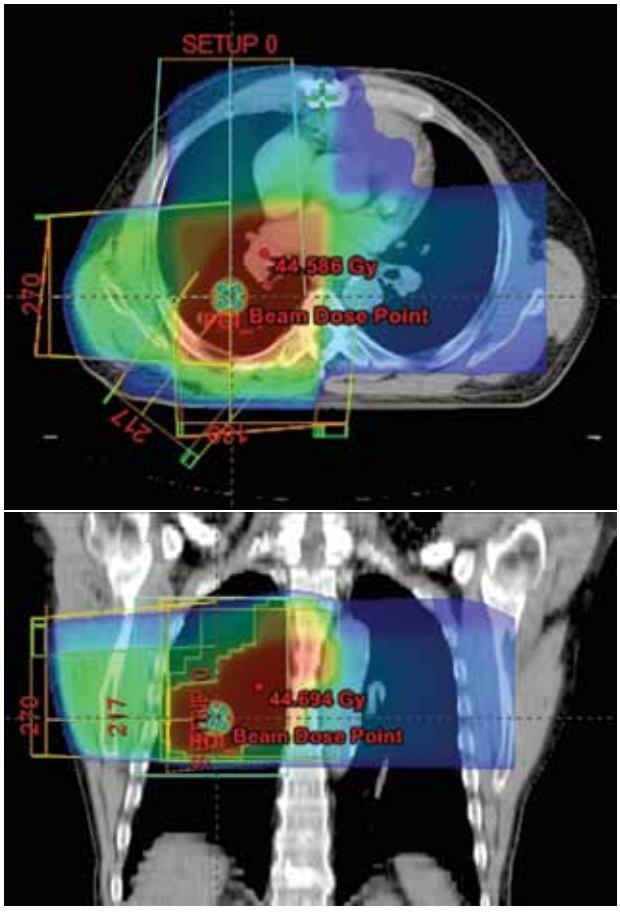


Figure 6. A conformal radiation therapy plan for cancer of the right lung.

CONCLUSIONS

Lymph node disease in lung cancer is a decisive prognostic factor and the treatment of the pathological tissues (primary site and positive lymph nodes) should be the main priority of the radiation oncologist. This is not the case in negative lymph nodes as existing studies have shown that their preventive radiation does not increase total survival. Thus, now that the focus has shifted more to dose increase in the affected areas, PET CT along with the existing knowledge on the spread of the disease to the lymph nodes depending on the characteristics of the primary site (location, size) have a major contribution to the detection of these areas and the best therapeutic result possible.

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REVIEW

The role of radiation therapy as an adjuvant or salvage therapy after radical prostatectomy

P. Alexidis, S.P. Stylianidou

Radiotherapy Department, Papageorgiou General Hospital of Thessaloniki, Greece

ABSTRACT

Radiation Therapy (RT) have a decisive role in the treatment of prostate cancer and can be used either as a definitve therapy or as an adjuvant one. Choosing RT postoperatively is very usual and contributes significantly to the local and distant metastases control, as well as to the overall survival. Choosing to irradiate the surgical bed after radical prostatectomy can be due to adverse features predicting a higher rate of recurrence or to biochemical failure and in both cases it is an important step in the treatment of the disease.

KEY WORDS: Biochemical failure, postoperative radiotherapy, radical prostatectomy, adjuvant, salvage

INTRODUCTION

Prostate cancer is a disease which can be treated in various different ways according to the stage of the disease and specific indications. The treatment options include radical prostatectomy, radiation therapy and hormone therapy with other chemotherapy regimens reserved for second line treatment in metastatic disease. A combination of the first three is also possible depending on the features of the disease (stage, histological findings). Patients with prostate cancer stage T1-T2b (no involvement of seminal vesicles) can be submitted to both radical prostatectomy (RP) or radical RT (RT) with comparable results concerning the overall survival. If there is involvement of the seminal vesicles then RT is the treatment of choice. When treating prostate cancer it is common to combine RP and RT if there are indications to do so. RT follows RP either as an adjuvant therapy or as salvage when there is residual or recurrent disease present. Finally hormone therapy is given as a monotherapy only to patients with metastatic disease, while it can be combined with radiation therapy (either radical RT or postoperatively) under specific indications that will be discussed. This review focuses on the RT at the post operative setting.

DEFINITION OF ADJUVANT AND SALVAGE RT

Both adjuvant and salvage RT (SRT) are given postoperatively but there are specific differences

Corrresponding author:
Petros Alexidis, Resident in Radiotherapy, Radiotherapy Department, Papageorgiou General Hospital of Thessaloniki, 9 Maria Kallas Street, 54645 Thessaloniki, Greece. Tel.: 6945803354, e-mail: alpet70@gmail.com

between them concerning mainly the indications. In the case of adjuvant RT the surgical excision of the porstate is thought to be complete without residual disease, but there are strong factors predicting recurrence at the future so RT must follow the radical prostatectomy. The indications for adjuvant RT are: involvement of seminal vesicles, extension of the disease to prostate capsule, positive surgical margins. In the case of salvage RT, the patient experiences biochemical failure. This condition is common in patients with prostate cancer following radical prostatectomy or radical radiotherapy and suggests persistent or recurrent disease. It is defined as the existence of detectable PSA levels following surgery or non-detectable PSA levels that consequently rise in two successive measurements with PSA value >0.2 ng/ml. After radical radiotherapy, biochemical failure is defined as a PSA rise by at least 2 ng/ml above nadir (defined as the lowest PSA value recorded) with the time of failure located at the time of rise. This recurrence may be due either to a localized or a distant disease (metastasis) and this particular differentiation is important, as it is decisive for the treatment to be given. The patient is submitted to full clinical and laboratory control in order to determine whether the disease is local or metastatic and thus choose the most appropriate treatment. However, it has frequently been observed that a patient may suffer from a metastatic disease despite negative control results and for this reason, it is important to know the factors that imply the presence of a metastasis.

LOCALIZED RECURRENCE OR METASTATIC DISEASE?

Patients diagnosed with biochemical failure have to be staged before proceeding with the treatment. They are thus submitted to clinical and laboratory control that can include abdominal and pelvis CT/MRI, bone scan and a biopsy when deemed required (according to ESMO 2012, a biopsy is not recommended following radical prostatectomy and is indicated only in the case of recurrence following radical radiotherapy and when the attending physician is oriented towards localized treatment).[1] Still, as already mentioned, this control is not adequate and it is therefore important to be aware of the factors that may imply the existence of metastasis. A study by Stephenson AJ et al[2] on 501 patients who suffered from biochemical failure following radical prostatectomy and were treated with salvage radiotherapy focused on this issue. The following were negative prognostic factors: GS 8-10, PSA levels above 2 ng/ml before SRT, invasion of seminal vesicles, negative surgical margins and PSA doubling time (PSADT) of 10 months or less. Stressing the diagnostic difficulties in those patients, the study underlines the fact that patient separation between those suffering from a localized disease and those suffering from a metastatic disease is not always possible based on laboratory control. For this reason, sometimes SRT can also have a diagnostic role (a decrease in PSA value implies local recurrence).[1] Similar were the conclusions deriving from the study by Andrew J. Stephenson et al[3] involving 1540 patients with biochemical failure following radical prostatectomy all of whom were given SRT. Again, indications such as high PSA and GS levels, low PSADT and lymph node invasion were negative prognostic factors regarding the disease-free survival. The time salvage radiotherapy is initiated is also of great importance and more specifically the initiation of SRT within 2 years after the biochemical recurrence has a positive impact on the PCSS (prostate cancer specific survival).[4] As for the recurrence free survival (RFS) it has been shown that it is directly related to the PSA value at the time of initiation of SRT (the lower the value the longer the RFS). This conclusion derives from a published paper based on 41 studies (5597 patients) who underwent salvage radiotherapy.[5] More specifically for every PSA increase of 0.1 ng/ml there was a 2.6% decrease in RFS (PSA >2 ng/ml was a particularly negative prognostic factor where RFS fell below 35%). It can therefore be concluded that

the prognostic factors of a metastatic disease are: *negative surgical margins, invaded seminal vesicles or lymph nodes, GS >8, initiation of SRT >2 years after the time of recurrence, PSADT <10 months and PSA >2 ng/ml.* It should also be mentioned that when PSADT is too short, less than 3 months in particular, then theprognosis is quite poor, while according to ESMO 2012, with such a PSADT value the patient is considered to be metastatic and should be given hormone therapy, which is the treatment of choice for the metastatic disease. In a study by Anthony V. D'Amico[6] based on 8669 patients treated with radical prostatectomy (5918) and radical radiotherapy (2751), PCSS decreased substantially for PSADT <3 months regardless of the preceding therapy (Table 1).

Table 1. Prostate cancer spesific survival (PCSS) by reference to PSA doubling time (PSADT) after surgery (radical prostatectomy) or radical radiotherapy.[6]

	PSADT <3 months	PSADT ≥3 months
3 years		
Surgery	84.1%	99.8%
Radiotherapy	79.1%	99.6%
5 years		
Surgery	68.8%	99.4%
Radiotherapy	61.6%	96.1%
8 years		
Surgery	51.5%	98.9%
Radiotherapy	41.6%	87.6%

CHOICE OF TREATMENT FOR PATIENTS SUFFERING FROM BIOCHEMICAL FAILURE

The therapeutic choices a doctor disposes of in the treatment of biochemical failure (localized or metastatic) following radical prostatectomy are radiotherapy and hormone-treatment. In the absence or in the low suspicion of metastasis (localized recurrence) the treatment of choice is SRT with or without hormone treatment. In the case of symptomatic localized disease, metastatic disease or strong suspicion of metastasis, the indicated therapy is hormone treatment.[1] Radiation oncologists should therefore take into account the factors analyzed previously in combination with the examination results in order to choose the appropriate treatment. A further problem arises in the case of patients suffering from localized recurrence: the option of hormone treatment.

SALVAGE RADIOTHERAPY IN COMBINATION WITH HORMONE THERAPY IN PATIENTS WITH LOCALIZED RECURRENCE

The addition of hormone therapy to SRT for the treatment of localized recurrence has not been fully clarified at present and it is not recommended as standard of care therapy (ESMO 2012). A study aspiring to shed light on this issue is a retrospective study of 101 patients who received salvage radiotherapy, 59 of whom additionally received hormone therapy.[7] All patients have been benefited with the exception of those showing positive surgical margins and PSA <0.5 ng/ml, factors which were considered to be favorable. Spiotto et al[8] carried out a study of 160 patients who were given adjuvant radiotherapy and salvage radiotherapy following radical prostatectomy. 114 of them were considered to be high risk patients (GS >8, PSA >20 ng/ml, extra capsular extention, invasion of seminal vesicles and lymph nodes), and 72 of them received whole pelvis radiotherapy (WPRT) while the rest of the patients were given radiotherapy to the tumor bed alone. In addition, a short course of androgen deprivation therapy was randomly given to 87 patients. Benefit from WPRT was observed in high-risk patients alone and only when combined with hormone therapy, despite the poorer prognosis for these patients. The conclusion that seems to derive from these two studies is that patients with poor prognostic factors are more benefited by hormone treatment. Safer conclusions are expected to derive from study RTOG 9601, the only randomized study on con-

currently given androgen deprivation therapy and radiotherapy. RTOG 9601 is a double blind phase III study of T2-T3N0 stage patients with positive surgical margins divided in two arms. Patients in one arm received radiotherapy whereas patients in the other arm received both radiotherapy and hormone therapy (bicalutamide 150 mg/day for a period of 24 months and after conclusion of RT). So far, the arm "hormone therapy + radiotherapy" seems to show slightly more positive results concerning total survival (91% versus 86%) while more results are still expected as there aren't enough end points available for the time being. Finally, the possible side-effects of hormone therapy should be taken into account, such as vasomotor disturbances, hot flushes, osteoporosis, obesity as well as the higher risk of diabetes or cardiovascular diseases.

TREATMENT PREPARATION FOR POSTOPERATIVE RADIOTHERAPY

The first step in order to deliver the treatment is to take a CT scan with 3-5 mm slices and then delineate (contour) the structures that the physician wants to irradiate along with the ones that he wants to protect (organs at risk). The target at the post operative setting is mainly the surgical bed, meaning the anatomical site of the prostate and seminal vesicles and the nearby structures that are at high risk of recurrence or residual disease. The sites with the highest probability for recurrence are the following: 40% of the recurrences occur at the area posteriorly to the bladder, 29% at the vesico-urethral junction, 22% at the seminal vesicles. So while contouring it is important to keep these facts in mind. To better describe the area that will be irradiated (CTV: clinical target volume) one should focus on the borders of the CTV as it is contoured on the planning CT. So the inferior border is found either 8 mm below the vesico-urethral anastomosis or immediately above the penile bulb (whichever is superior). The anastomosis is located at the CT slice just below the last one where urine is visible. The anterior margin is at the posterior edge of symphysis pubis up to the top of it. Then 1.5 cm anteriorly to posterior bladder wall. The lateral border is at the medial border of levatorani and obturatorinternus. The superior border is at the level of the seminal vesicles (if they have not been excised completely during surgery) or approximately 2 cm above symphysis pubis. Finally, the posterior border is at anterior border of the rectum (Figures 1-5).[9] The treatment is delivered with a box technique where four fields (anterior, posterior, and two lateral) are used to ensure a uniform distribution of the dose to the prostate and at the same time protect the surrounding organs at risk (urinary bladder, rectum, femoral heads, penile bulb). This is known as a conformal technique. A complex technique can also be performed (IMRT) where multiple fields with intensity modulated beams are used in order to achieve an even better dose delivery. The preffered dose is 66 Gy.

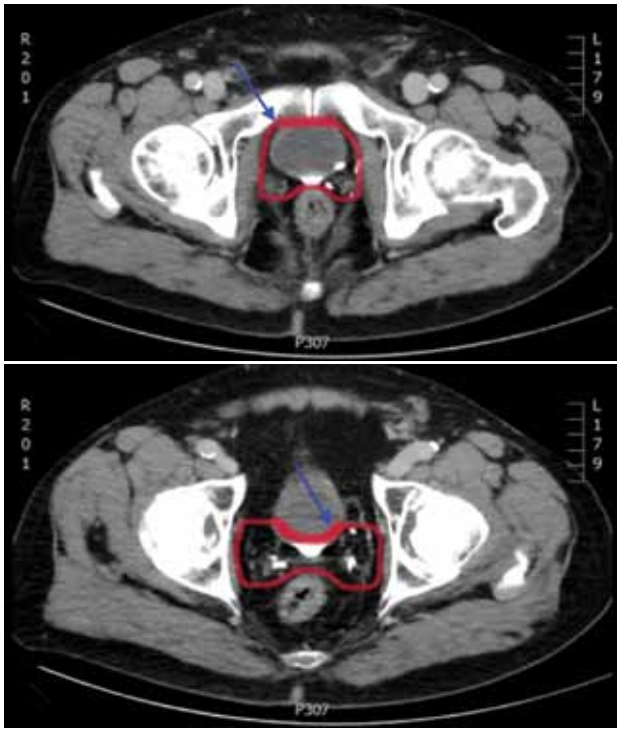

Figure 1. Anterior border of CTV: behind pubic symphysis and 1,5 cm inside bladder when above pubic symphysis.

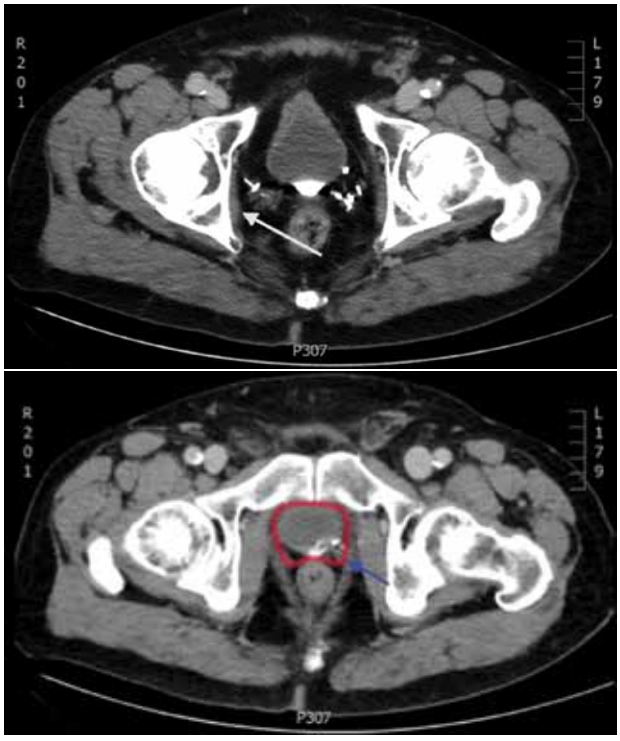

Figure 2. Lateral borders of CTV: at the medial edge of obturatorinternus and levatorani.

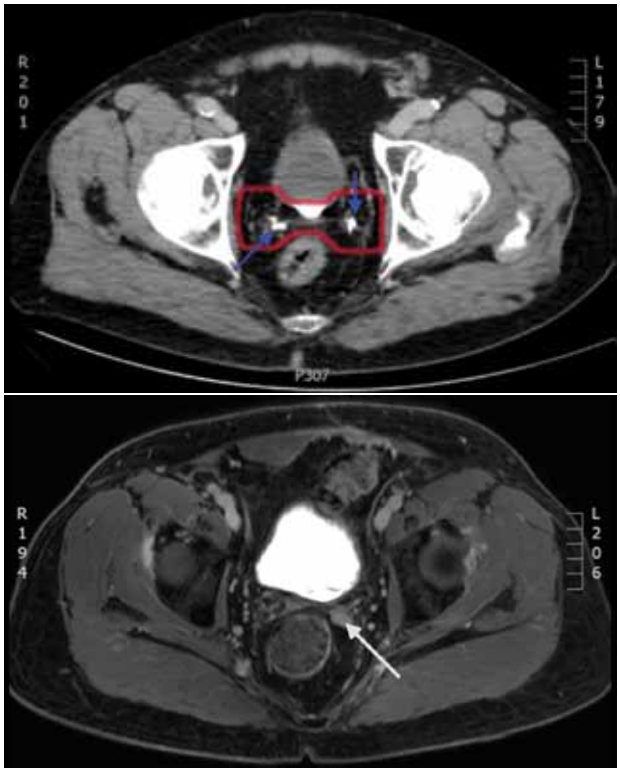

Figure 3. Superior border of CTV: at the level of the remaining seminal vesicles or at the surgical clips of vas deferens.

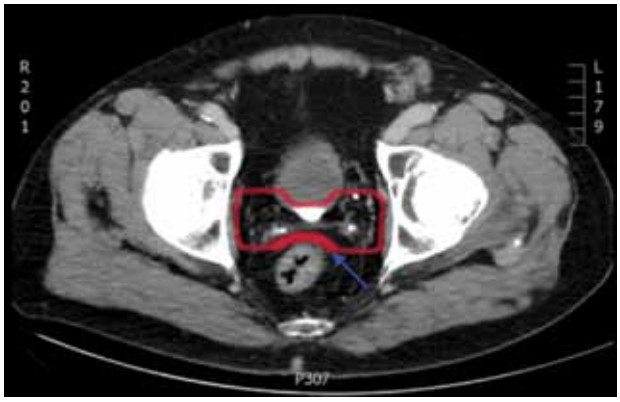

Figure 4. Posterior border of CTV: anterior surface of rectum.

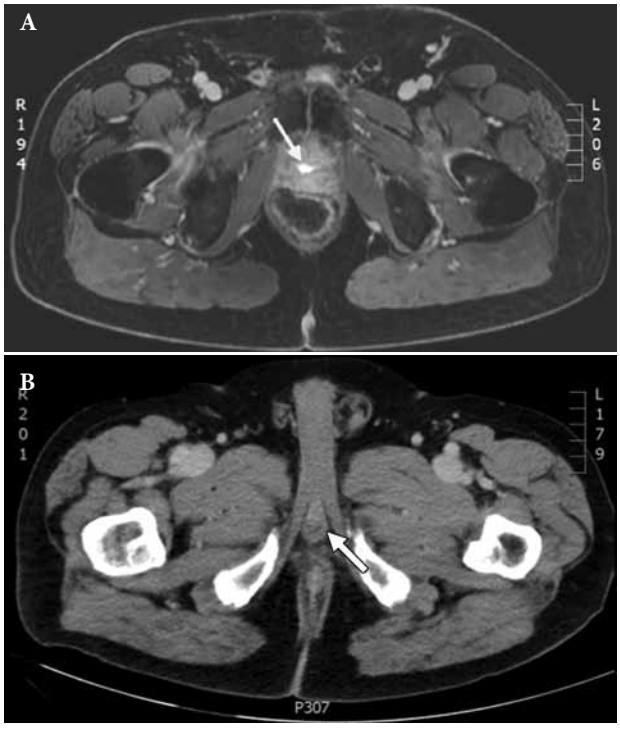

Figure 5. Inferior border of CTV: A. Vesico-urethral junction just below the last CT slice where urine is visible. B. Inferior border immediately above penile bulb.

CONCLUSIONS

Postoperative RT, either adjuvant or salvage, is a very important step in the treatment of prostate cancer affecting both the local recurrence and the overall survival. And while for adjuvant RT things are quite clear, regarding the indications and the

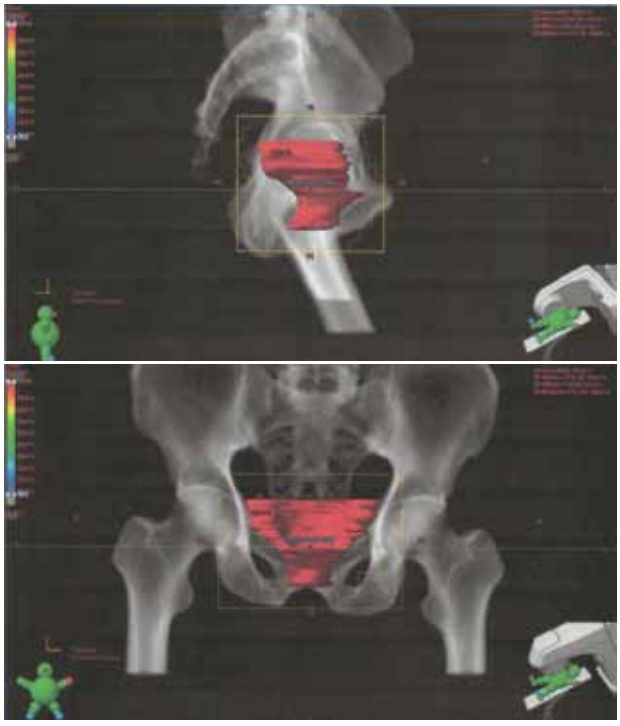

Figure 6 & 7. The final representation of the CTV as it is seen on antero-posterior and lateral view.

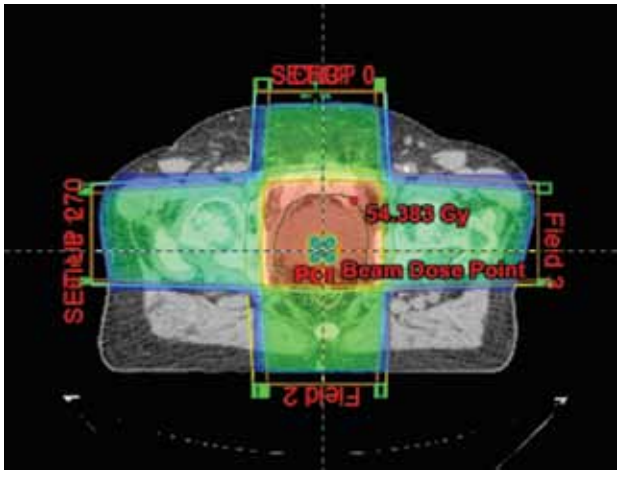

Figure 8. Box technique. Four fields are used with the dose distribution centered on the CTV while the surrounding organs at risk are protected due to segmentation of the dose (green color represents lower doses while red the higher ones).

treatment options, for salvage RT things seem to be more confusing. It is obvious that the most suitable treatment for patients suffering from biochemical recurrence following radical prostatectomy has not been fully defined yet and the attending physician is required to correctly evaluate all the information he disposes of. Given the importance of the correct initial patient evaluation, laboratory control is not adequate and factors helping to foresee the possibility of metastatic disease should equally be taken into account. Regarding the use of hormone treatment administered concurrently with salvage radiotherapy in localized recurrence it seems, based on the existing retrospective studies, that high-risk patients are benefited by the addition of hormone treatment, while the results of the RTOG 9601 study are expected to shed more light on the issue.

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ORIGINAL PAPER

Radical radiotherapy and patient -reported quality of life in prostate cancer patients treated with 3DC- EBRT

Acute and chronic toxicity

S.P. Stylianidou[1], I. Tzitzikas[1], P. Bousbouras[2]

[1]*Department of Radiotherapy Oncology, Aristotle University of Thessaloniki, AHEPA University Hospital,*
[2]*Department of Medical Physics, Aristotle University of Thessaloniki, AHEPA University Hospital*

ABSTRACT

Aim-Background: 3 Dimension Conformal External Beam Radiotherapy is widely-used technique for delivering high-dose radiation, in radical radiotherapy, for patients with localized or locally advanced prostate cancer. There are some short term side effects such as bladder inflammation, diarrhea, sore skin in the genital area, worsening of hemorrhoids, or rectal irritation, and fatigue during and after radiotherapy. Also there are some possible long term side effects such as, proctitis, increased frequency of bowel movements, problems passing urine, impotence. We evaluated patient-reported outcomes for quality of life from 3 Dimension Conformal Radiotherapy in prostate cancer patients. **Material and Methods:** In the period between October 2010 and July 2012, 36 patients with localized prostate adenocarcinoma were submitted to 3 Dimension Conformal Radiotherapy in the Department of Radiation Oncology in AHEPA University Hospital in Thessaloniki. The radiotherapy was divided into phases. Finally the treatment field covered only the prostate to total dose 72-76Gy. During radiotherapy, after treatment completion and every 6 months all patients were monitored for toxicity. **Results:** Radiotherapy to a total dose of 72-76Gy to the prostate was in general well tolerated by most of the patients. 3 Dimension Conformal Radiotherapy has made possible to keep the incidence of toxicity to organs at risk low, reducing morbidity compared to two-dimensional radiotherapy. **Conclusions:** Our experience suggests that a dose of 72-76Gy by 3 Dimension Conformal Radiotherapy can be safely delivered to the prostate and gastrointestinal tolerance during treatment and follow-up period was excellent. This technique allowed localized therapy with excellent results, decreasing side effects and improving the quality of life in these patients.

KEY WORDS: External beam radiotherapy, Prostate cancer, Quality of life, Toxicity

INTRODUCTION

External beam radiotherapy is a well established curative treatment for localized prostate cancer.[1]

Corresponding author:
Styliani P. Stylianidou, Aristotle University of Thessaloniki, Department of Radiotherapy Oncology, AHEPA University Hospital, 1 St. Kyriakidi str., 54636, Thessaloniki, Greece, Tel. + 302310993421, +306941677422, e-mail: stell_star@yahoo.gr

Acute and late toxicity rates after radiotherapy can be considerable and have been subject of many studies. Dose- volume effect relationships have been described extensively.[2-6] Dose escalation studies support the benefit of a dose escalation to total doses approaching 80Gy concerning the biochemical tumor control or disease- specific survival.[7-9] Dose escalation was also associated with a significant increase in late gastrointestinal toxicity.[9,10]

Three dimensional conformal radiation therapy (3DCRT), a technique of external beam radiotherapy, allowing a more accurate localization of the radiotherapy target and organs at risk, with the delivery of high doses to the target volume and better control over the radiation dose in healthy structures. The high radiation dose for prostate cancer has allowed a better biochemical control in prospective randomized studies although without resulting in increased overall survival[11,12] and with an increase in toxicity.[13] However, the high doses released with 3DCRT generate lower toxicity as compared with conventional radiotherapy with conventional radiation doses.[14]

During the course of radiation treatment, the doses delivered to critical surrounding structures, primarily to the rectum, are the main limiting factors in the dose-escalation process. Since conformal technique, i.e. 3D-CRT and IMRT (intensity modulated radiotherapy), were implemented into clinical practice, many authors from different institutions have studied the principal predictors of toxicity from radiation treatment of prostate cancer.[15-20]

In the present observational study, we report the results on early and late toxicity in relation to dose-volume parameters in a series of 36 patients with localized prostate cancer who underwent 3D-CRT to a total dose 72-76Gy by using conventional fractionation.

MATERIAL AND METHODS

In the period between October 2010 and July 2012, 36 patients with localized prostate adenocarcinoma diagnosed by means of transrectal biopsy were submitted to 3DCRT for curative purposes in the Department of Radiation Oncology in AHEPA University Hospital in Thessaloniki. The medians (range)/mean age was 66 (50-80) yr. Karnofski performance status ranged from 70 to 100 (median, 90). Clinical stage was T1b-T3bNoMo of the UICC classification.[21] Low-, intermediate- and high-risk categories were defined as reported by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, version 2010. Twelve patients were previously treated by transurethral resection because of obstructive symptoms of benign hyperplasia.

Twenty-nine patients received neoadjuvant and concomitant hormone therapy. Seven of them continued on hormone therapy after radiotherapy.

All patients were treated in a supine position with a partially filled bladder and empty rectum using a knee-ankle fixation device for immobilization and three skin tattoos for position verification. Simulation was performed by a conventional simulator and spiral CT scan, obtaining 5-mm slice images spaced from L4 to 2cm below the ischeal tuberosities. The images were transferred to the treatment-planning system, by a local network.

The clinical target volume (CTV) was drawn on computerized tomography (CT) images by a radiation oncologist. The therapy targets were delineated on the tomographic slices as follows: a) prostate- whole volume delineation (gross tumor volume-GTV); b) seminal vesicles-whole extent delineation (GTV, when affected; clinical target volume-CTV in subclinical disease); c) drainage-lymph nodes of internal and external iliac vessels from the candal region of the sacroiliac joint, and lymph nodes of the obturator vessels, excluding the lateral perirectal lymph nodes (CTV in high-risk patients). Margins for target displacement and positioning errors measured 10mm for all the dimensions and 3mm posteriorly (PTV). Organs at risk were delineated as follows; a) bladder-whole volume by the outer muscular

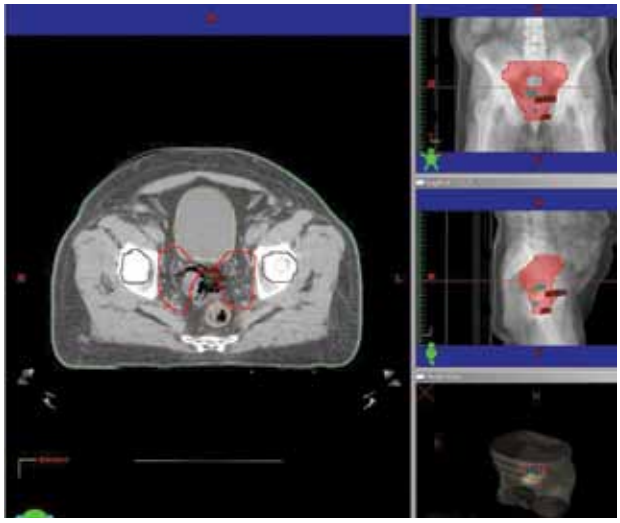

Figure 1. Organs at risk: Femoral heads, bladder, rectum. Red: CTV.

layer; b) rectum-whole volume by the outer layer, from the rectoanal transition to the rectosigmoid transition; c) femoral heads. Energies of 16M and four radiation fields were utilized (Figure 1, 2).

The radiotherapy treatment was divided into phases, of follows: in the first phase, pelvis, seminal vesicles and prostate were irradiated (PTV1) with total dose 45Gy; following the treatment volume was restricted to the seminal vesicles and prostate (PTV2) to total dose 56 Gy; and, finally, the treatment field covered only the prostate with respective margins (PTV3) to total dose 72-76Gy (only the prostate) (Figure 3, 4, 5).

In the absence of pelvic irradiation, the treatment was comprised of two phases, irradiation of seminal vesicles and prostate (PTV1), and following, only the prostate (PTV2).

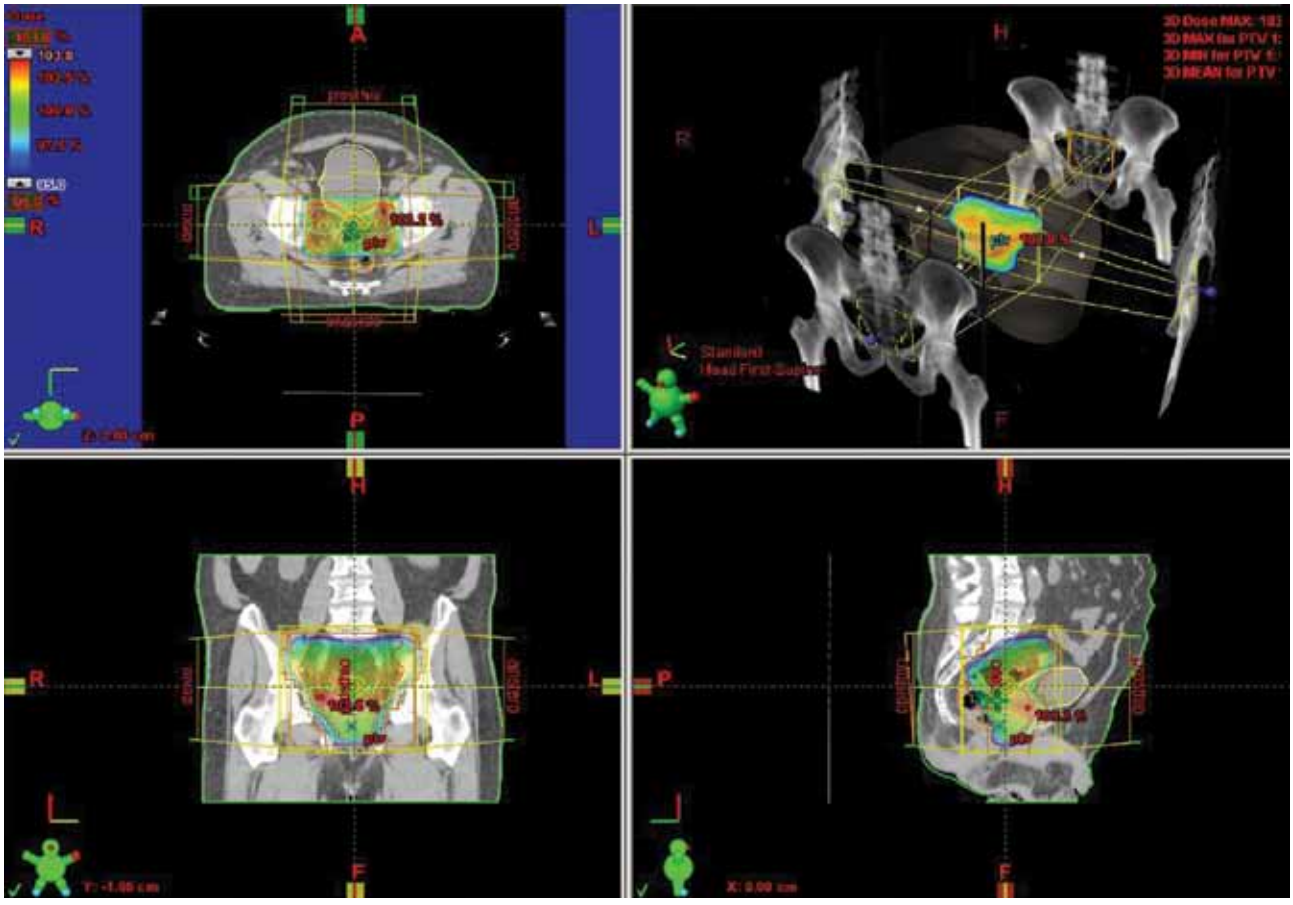

Figure 2. Four radiation fields, box technique.

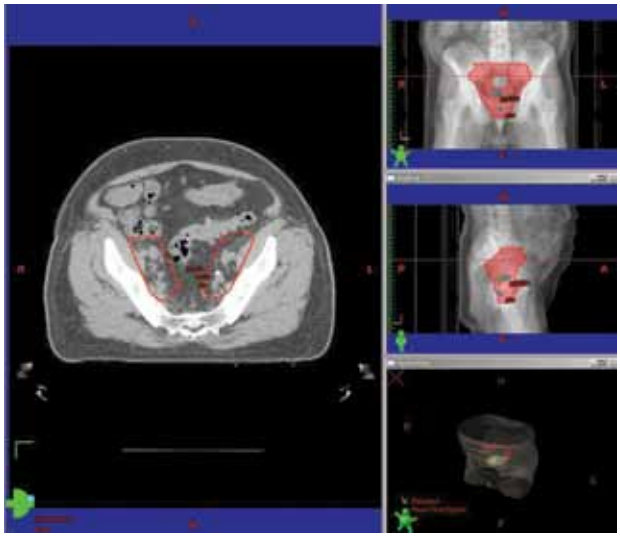

Figure 3. PTV1: (first phase): pelvis, seminal vesicles and prostate. Total dose 45Gy.

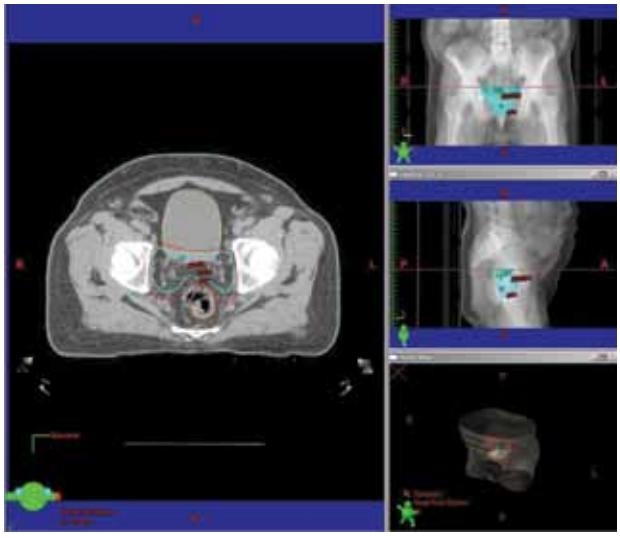

Figure 4. PTV2: (second phase): seminal vesicles and prostate. Total dose 56Gy.

Restriction of doses in healthy tissues corresponded to: a) rectum: 50% <50 Gy, 25% <70 Gy; b) bladder: 50% <50 Gy, 30% <70 Gy; c) femoral heads: <55 Gy; the prescription dose corresponded to 95%. Isodose curves and dose-volume histograms (DVH) were calculated by the algorithm of the treatment planning system and displayed for all the target and non-target structures: PTV1, PTV2, PTV3, rectum, bladder and femoral heads. (Figure 6). Radiotherapy was delivered by 16MV photons from a linear accelerator equipped with a multileaf collimator (MLC). The patient set up was systematically verified by portal vision at the first treatment session and subsequently every week.

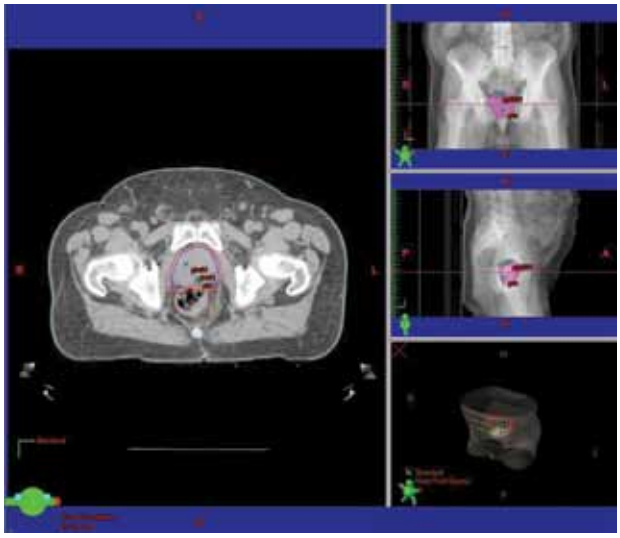

Figure 5. PTV3: (Third phase): treatment field covered only the prostate with respective margins. Total dose 72-76Gy.

During radiotherapy, all patients were monitored on a weekly basis for early toxicity following the RTOG scale[22] and were given supportive care as needed. After treatment completion, all patients were followed by clinical examination and PSA serum dosage every 6 months. Any toxicity 6 months after radiotherapy was considered as a late side effect and was scored by the RTOG scale.[22]

RESULTS

Radiotherapy to a total dose of 72-76Gy to the prostate was in general well tolerated by most of the patients. Acute toxicity was observed in 6 patients (76Gy), at the level of the rectum, - grade I in 4 patients and grade II in 2 patients. At the level of the bladder, acute toxicity was observed in 8 patients- grade I in 5 patients and grade II in 2 patients. Acute-short term side effects- were accessed during 3rd – 4th week of treatment: diar-

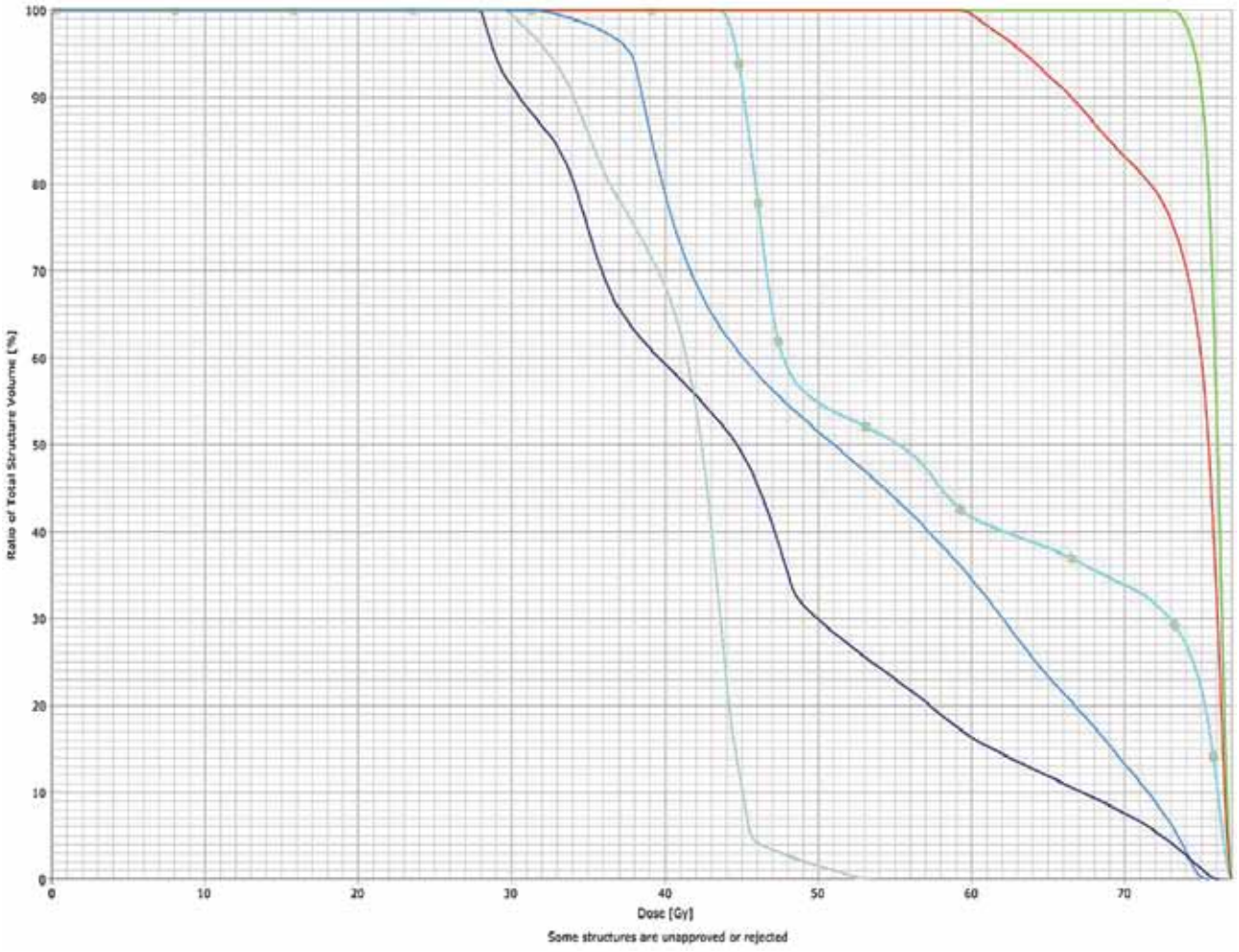

Figure 6. DVH: dose-volume histograms and isodose curves for all the target and non-target structures: PTV1, PTV2, PTV3, rectum, bladder and femoral heads.

rhea, softer and smaller volume bowel movements, increase of the frequency of urination, urinary urgency, difficulty starting urination. No patient interrupted radiotherapy for rectal or urinary toxicity. Late toxicity was assessed in 20/36 patients, all with at least 7 months of follow up. Grade I rectal toxicity was detected in 3 patients and grade II in 2 patients, mainly consisting of rectal bleeding. Grade I urinary toxicity occurred in 4 patients and grade II in 2 patients. No toxicity higher than grade II was observed in the whole series. Long term side effects such as proctitis, cystitis, urinary retention, hematuria, urinary incontinence, rectal bleeding, rectal pain, intestinal obstruction, impotence, can be defined as clinically not significant.

Patients responded to a QoL validated questionnaire before, at the last day, two months (median time) after and more than 5 even months after treatment. The questionnaire, expanded prostate cancer Index Composite (EPIC)[23,24] comprises 50 items concerning the urinary, bowel, sexual and hormonal domains for function and bothersomeness. In accordance with data in the literature, mean QoL changes of below 5 points can be defined as clinically not significant, 5-10 as "little" changes, 10-20 as "moderate" changes and >20 as "very much" changes.[25,26] The questionnaire was handed over to the patients personally by

one of the physicians. Patients presented in the department six to ten weeks after the end of treatment. Missed questionnaires in the acute phase (two months after radiotherapy), were sent to the patients with a return envelope. If a questionnaire was not returned within four weeks, patients were contacted by telephone and urged to complete it. Those of patients who reported the greatest adverse changes of urinary or bowel bother scores, 6 months after treatment were in a particular focus of this study. Then were defined as patients with adverse long-term urinary or bowel QoL. Considering pretreatment urinary/bowel QoL scores and QoL score changes relative to baseline scores at the last day, (time B) two months after RT (time C) and six-seven months after RT (time D), the highest correlation coefficients were found between changes at times C and D. Focusing on great/moderate bother from particular problems (specific items of the questionnaire), we found a missing dependence from pretreatment symptoms, and the strongest dependence from symptoms several weeks after radiotherapy. 18 patients reporting great/moderate bother with urinary/bowel problems at time C reported to have great/moderate at time D. Only 2 of the patients without great/moderate bother with urinary/bowel problems at time C reported to have great/moderate bother at time D. Bowel QoL changes at time B were independently predictive for adverse long-term bowel QoL.

DISCUSSION

3DCRT in patients affected by localized prostate cancer, has made possible to keep the incidence of toxicity to organs at risk (such as the bladder and rectum) low, reducing morbidity compared to two-dimensional radiotherapy conventional techniques.[27] Our observational study on 36 patients with a median Follow-up of 8-12 months tends to support such clinical evidences.

The incidence of acute and late rectal toxicity in our study was relatively low. A number of studies in the literature have analyzed dose-volume parameters in order to find and possible correlation with early and late toxicity during and after conformal radiotherapy for prostate cancer.[27,31,32] A review of studies from the last 10-15 years by Morris et al.[27] showed that rectal V70 and V75 are the main predictive factors for acute toxicity, and a multicenter trial conducted on over 1100 patients highlighted the impact of the mean rectal dose and rectal volume on the risk of acute bleeding.[31]

The incidence of acute and late urinary toxicity observed in our study was relatively low. The finding may be related to the recommendation to the patients of maintaining the bladder full at each treatment session in order to limit the irradiation of the urinary mucosa and maintain low V60 and V70. The low incidence even of grade 1 toxicity of our series may suggest the presence of a bias represented by an underestimation of clinical symptoms and signs during radiotherapy and follow-up in the absence of a specific questionnaire that could facilitate the recording of any alteration of urinary function.

The impact on urinary toxicity of 3D-CRT compared to two-dimensional radiotherapy was reported by Morris et al.,[27] who showed a significant advantage on late grade 3 toxicity for the 3D technique. The main predictive factor for acute toxicity seems to have a significant predictive value for grade 2 and 3 complications.[28] Other factors to take into account are the early onset of urinary symptoms like dysuria, frequency and nicturia during radiotherapy[29] and a trans-urethral prostate resection done before radiotherapy.[28]

In the present study, we did not observe any correlation between dose-volume parameters, in particular V50 and V60, and the incidence of acute urinary toxicity, similarly to that reported by other authors.[30] However the limited number of observations does not allow us to draw any definitive conclusion in this regard.

In contrast to studies in the past, based on grading system,[33,34] a quality of life analysis was used to elaborate the impact of consequential

late effects on long-term quality of life. EPIC questionnaire measurements have the advantage of being more sensitive to changes in acute bowel toxicity in comparison to RTOG acute morbidity scoring criteria or proctoscopic toxicity scores.[35] Prostate cancer radiotherapy with doses >70Gy can lead to a relevant severity and duration of acute radiation effects.

Urinary and bowel QoL after radiotherapy was found to be strongly dependent on urinary and bowel QoL before radiotherapy. Acute bowel problems were gradually improving over time. In contrast to bowel bother scores, no further improvement was noticed for urinary bother scores between time C and D. We have focused on the patients with the greatest long-term QoL impairment relative to baseline scores. A particular aspect of this evaluation is a homogenous treatment of the total study group concering the technique, planning target volume definition and dose prescription. In most other study populations, patients with varius techniques and total doses are combined.[1,3,33,34,36] The significant impact of dose to critical structures on toxicity could be demonstrated in these studies with different dose levels. This correlation could not be shown in our homogenous study population (all patients treated with the same technique to a dose of 72-76Gy). We have to be aware that the dose-volume histogram is related to a single treatment planning CT scan. Taking into account changing organ volumes during the treatment,[37,38] it might not be sensitive enough to discriminate clearly between patients with higher or lower volumes within certain dose levels over the entire treatment. Considering QoL scores of patients with the greatest long-term impairment in comparison to other patients, differences of QoL scores became well evident with time. A considerable divergence of urinary scores resulted at time C: patients with adverse long-term QoL were not able to recover from their acute symptoms- in contrast to a complete recovery for other patients. Urinary and bowel score changes at time C have been shown to predict both adverse urinary and bowel long-term QoL in univariate analysis. Patients with reduced repair capacity of the bladder wall or urethra are more likely to have a reduced repair capacity of the rectal wall and vice versa.

The results of this study emphasize the need of close follow-up and early prophylactic actions for patients with greater and longer acute radiotherapy- associated toxicities to possibly prevent late toxicities, though these possibilities are currently limited. The time to filter candidates for these actions can be two months after radiotherapy (median time of time C questionnaire). Conformal radiotherapy to the dose of 72-76Gy was administered with good compliance by most of the patients. The incidence of acute and late rectal and urinary toxicity was relatively low, most likely in relation to our restrictive dose- constraints. The dose-volume and clinical data from this trial is being used to generate predictive toxicity models. Quantitative dose volume histogram information as well as the spatial distribution of doses to the rectum and bladder are being analyzed to provide clinicians and researchers with tools to minimize toxicity to patients treated for early stage prostate cancer with radical radiotherapy. These analyses will be the subject of future manuscripts.

CONCLUSION

Consequential late effects play a major role after radiotherapy for prostate cancer. Patients with greater and particularly longer non-healing acute toxicity are candidates for closer follow-up and possible prophylactic actions to reduce a high probability of long-term problems. Urinary symptoms without recovery within a few weeks after radiotherapy are likewise highly predictive for adverse long-term urinary quality of life.

Our experience suggests that a dose of 72-76Gy by 3D-CRT can be safely delivered to the prostate and gastrointestinal tolerance during treatment and follow-up period was excellent. The incidence of acute and late toxicity was relatively low in ac-

cord with our dose constraints. Rectal V70 proved to be a reliable prognosticator of late toxicity; as already observed by other studies.[15]

The appropriate application of 3DC-EBRT in patients undergoing radical radiotherapy for prostate cancer requires a standardization to target delineation as well as clinical quality assurance procedures. 3DC-EBRT technique allowed localized therapy with curative intent, (after high dose RT) decreasing side effects, giving excellent results and improving the quality of life in these patients. Longer follow-up is needed to assess late toxicity and clinical outcome in these series.

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ORIGINAL PAPER

Treatment of dermatofibrosarcoma protuberans

E. de Bree[1], D. Michelakis[1], M. Papadakis[2], A. Manios[1], E.-S. Krüger-Krasagaki[3], S. Kachris[4], O. Zoras[1]

[1]Melanoma and Sarcoma Unit, Department of Surgical Oncology, [2]Department of Pathology, [3]Department of Dermatology and [4]Department of Radiotherapy and Oncology, Medical School of Crete University Hospital, Heraklion, Greece

ABSTRACT

Aim: Dermatofibrosarcoma protuberans (DFSP) is a rare tumour characterized by locally aggressive behaviour and very low metastatic potential. Since its local recurrence rate is high after surgical excision with limited margins, wide local excision, followed in selected cases by adjuvant radiotherapy, has been generally recommended. The aim of the present study is to analyse the treatment of DFSP in our unit, with special focus on the width of the surgical excision and the use of adjuvant radiotherapy. Material and Methods: The archives of our unit were studied to identify patients treated for DFSP during the last 15 years. The patients' characteristics, clinical presentation, treatment and outcome were recorded. Results: Twenty-two patients, 9 men and 13 women, were identified. Their median age was 45 years (range 30-63). Seventeen patients had a primary DFSP and 5 patients local recurrence after limited excision elsewhere. All patients underwent a wide local excision of the tumour with a 2 to 4 cm margin (median 3.0). Two patients who presented to us with recurrent disease underwent adjuvant radiotherapy. After a median follow-up period of 50 months (range 7-129) all patients were free of disease. Conclusions: DFSP is a rare tumour. Surgical excision with limited margins will most probably lead to local recurrence. Wide local excision with peripheral margins of 2 to 3 cm seemed to be associated with excellent local tumour control, as in the present series. Adjuvant radiotherapy may probably be helpful in selected cases which include recurrent tumours, to reduce the local recurrence rate.

KEY WORDS: dermatofibrosarcoma protuberans, treatment, surgery, radiotherapy

INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumour, comprising approximately 0.1% of all malignancies.[1] Its overall incidence has been estimated to be 4-5 per million citizens per year.[1,2] DFSP is characterised by locally aggressive behaviour, with very low metastatic potential.[3,4] Metastatic disease occurs in approximately 1% of the cases.[3,4] DFSP is a slow-growing, insidious

Correspondence address:
Eelco de Bree, MD, Department of Surgical Oncology, University Hospital, P.O. Box 1352, GR-71110 Heraklion, Greece, Tel.: +30-2810-392056 / 392382, Fax: +30-2810-392382, e-mail: debree@med.uoc.gr

tumour which is often misdiagnosed clinically for years after initial presentation, thus resulting in delayed treatment. The mainstay treatment consists of surgical excision which, however, has been associated with a high local recurrence rate, especially when the extent of the excision is limited. Therefore, surgical excision with sufficiently wide margins, followed in selected cases by adjuvant radiotherapy, has been advocated traditionally in order to reduce the local recurrence rate.[3,4]

In the present study, the treatment of DFSP in our unit was analysed, placing special focus on the width of the surgical excision and the use of adjuvant radiotherapy, and their impact on local recurrence risk.

PATIENTS AND METHODS

The archives of the Melanoma and Sarcoma Unit of the Department of Surgical Oncology of the Medical School of Crete University Hospital were studied to identify patients treated for DFSP during the last 15 years. The patients' characteristics, clinical presentation, treatment and outcome were recorded. Special attention was paid to the width of the surgical margins used and the application of adjuvant radiotherapy and their correlation to the occurrence of local recurrence.

RESULTS

Twenty-two patients, 9 men and 13 women, were identified to have been treated for DFSP in our unit during the last 15 years. Their median age was 45 years (range 30-63, mean 45). Seventy-eight percent of the patients was between 30 and 50 years old. Seventeen patients were diagnosed with a primary DFSP (figure 1), while 5 patients presented with local recurrence after limited excision, mainly excisional biopsy, elsewhere (figures 2a and 3). Recurrence had occurred after a median period of 29 months after initial excision (range 2

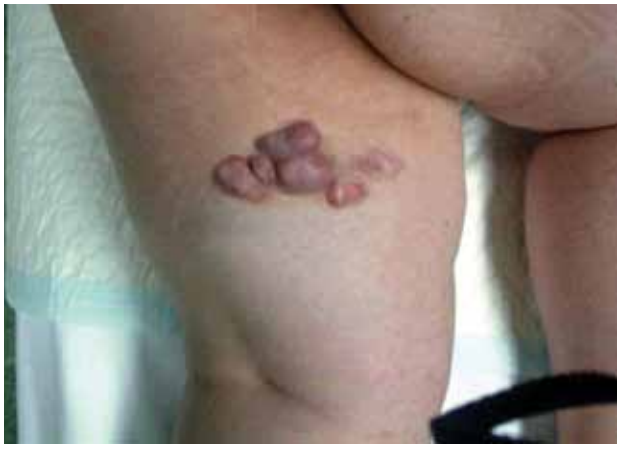

Figure 1. Primary dermatofibrosarcoma protuberans on the left thigh of a 58-year old female.

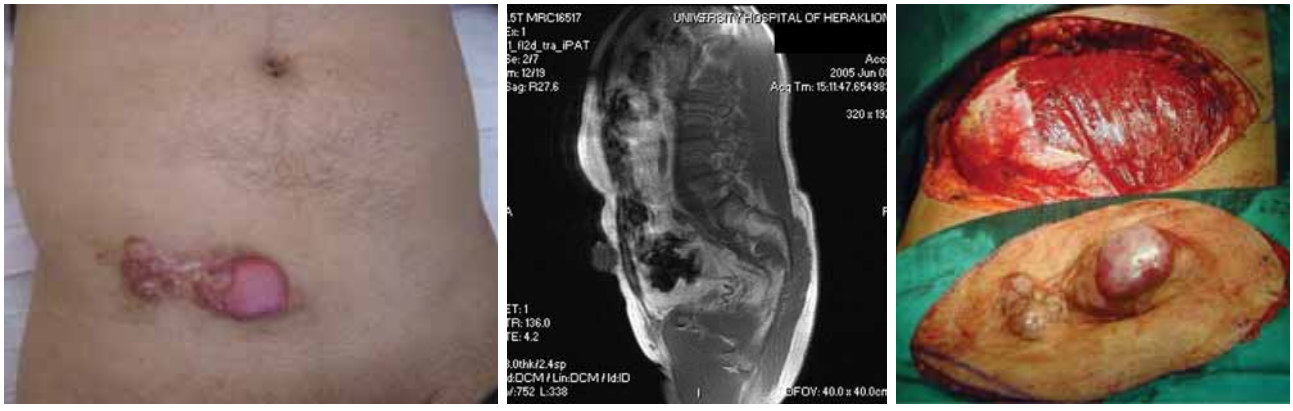

Figure 2. Local recurrence of dermatofibrosarcoma protuberans on the abdominal wall of a 49-year old male 29 months after initial limited excision elsewhere (a). Magnetic resonance imaging demonstrates invasive tumour growth only into the subcutaneous fat (b). The tumour was excised with a 3 cm margin with en block removal of the underlying fascia (c). More than 8 years after wide local excision of his local recurrence, he is free of disease.

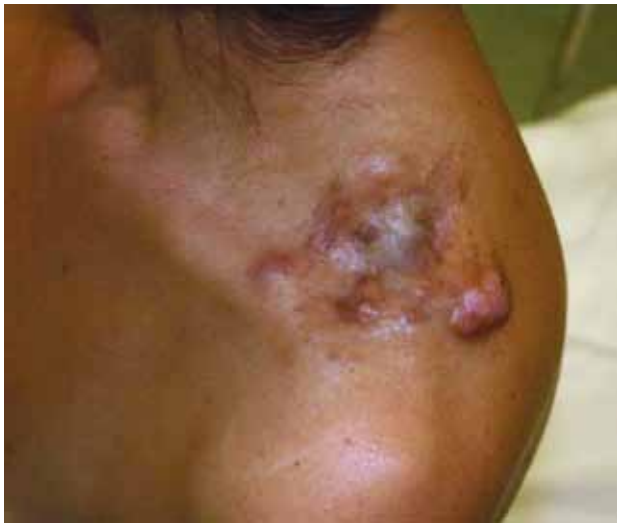

Figure 3. Local recurrence of dermatofibrosarcoma protuberans on the left shoulder of a 46-year old female more than 17 years after initial limited excision elsewhere.

months to 17 years, mean 66 months). The largest diameter of the tumour varied from 0.6 cm to 8.0 cm (median 2.8 cm, mean 3.1 cm). The primary DFSPs were significantly smaller than the recurrent lesions (2.4 cm vs. 5 cm, p=0.049 with the Fisher exact test and the median value of primary lesions as cut-off point). The lesions were located in the shoulder area in 5 patients, on the upper limb in 2 patients, on the trunk in 6 patients, in the inguinal area in 2 patients and on the lower limb in 7 patients. Magnetic resonance imaging of the area of interest was performed in patients with large or recurrent tumours in order to assess the deep extent of the tumour growth (figure 2b). In all patients chest computed tomography had been negative for metastatic disease.

All patients underwent a wide local excision of the tumour with a peripheral margin of 2 to 4 cm (median 3.0, mean 2.8) including the underlying muscular fascia (figure 2c). In 7 patients, the peripheral margin was 2 cm, in 13 patients, 3 cm and in 2 patients, 4 cm. In 8 patients, the wound was primarily closed. A skin graft was used for closure of the defect in 12 cases, a split skin graft 11 times and once, a full thickness skin graft. A cutaneous flap was applied for closure of the skin defect in 2 patients. In a 38-year old male patient, who was operated for local recurrence on his left shoulder after initial primary excision elsewhere, the deep margin was focally involved. He underwent a re-excision with removal of a superficial layer of the underlying muscle. This patient, as well as a 46-year old female patient, who was also operated for a local recurrence on her left shoulder after having been operated initially elsewhere (figure 3), both underwent adjuvant radiotherapy (50 cGy). Postoperative morbidity was minimal, with wound infection in one patient and limited skin graft necrosis in another case.

The patients were regularly seen at the outpatient clinic, usually every 3 months during the first 3 to 5 years and afterwards bi-annually or annually. Magnetic resonance imaging of the area of interest and computed tomography of the chest were added to the patient's history and physical examination depending on the initial size, depth, location and kind of tumour (primary or recurrent). After a median follow-up period of 50 months (range 7-129, mean 60) all patients were free of disease. The median follow-up duration after excision with 2 cm, 3 cm and 4 cm margins was 28, 63 and 85, respectively.

DISCUSSION

DFSP is an uncommon, locally aggressive, spindle cell tumour of the skin with infiltration of the subcutaneous fat. DFSP may at times be difficult to differentiate from other fibrous tumours, including dermatofibroma, fibrosarcoma, atypical fibroxanthoma, and the less common, nodular fasciitis.[3] Dermatofibroma in particular may be difficult to differentiate from DFSP on routine haematoxylin-eosin stained tissue. Immunohistochemical stains with CD34 and factor XIIIa have been used to differentiate between those two entities.[5] While CD34 is strongly expressed in almost all DFSPs but rarely in dermatofibroma, the coagulation factor XIIIa is generally not expressed in DFSP but strongly

expressed in dermatofibroma. In difficult cases, stromolysin-3, a member of the metalloproteinase family, has been shown to be helpful in differentiating dermatofibroma from DFSP.[6]

DFSP is most frequently diagnosed between the ages of 30 and 50, although it has been described in all age groups.[3] The age distribution in our series is consistent with those in the literature, with 78% of our patients being between 30 and 50 at presentation. Generally, the tumour is found in similar frequencies in men and women.[3] In our series a slight female predominance (59%) was observed. DFSP seems to be more common in people from African origin than in caucasians.[1] DFSP should be suspected in a patient with a history of a firm, asymmetric, slow-growing cutaneous nodule. The definite diagnosis is made by histology after incisional or excisional biopsy, often with the assistance of immunohistochemical stains, as outlined above.[3] Determining tumour size and extent of penetration into underlying tissue is essential, and special attention should be given to palpation around the tumour and to regional lymph nodes. Since nodal metastases are found in less than 1% of cases, additional imaging and sentinel node biopsy are not indicated.[3,47] Although not necessary in every case, magnetic resonance imaging has been found to be most effective in determining the extent of local tumour penetration. The lungs are the most commonly reported site of metastasis, with pulmonary metastases occurring in not more than 1-4% of all DFSP cases.[3,4,7] In rare instances, DFSP can transform into a fibrosarcomatous type of DFSP, which is a more aggressive form characterized by repeated local recurrences and significantly higher metastatic potential.[4] Therefore, chest computed tomography should be considered to evaluate for pulmonary metastases, especially for the fibrosarcomatous type of DFSP, longstanding tumours, extensive locally invasive disease and repeated recurrences.[3]

Treatment of DFSP consists of surgical excision, but a mean local recurrence rate of approximately 50% has been reported after simple excision.[7,8] This high recurrence rate is probably due to the unique asymmetric growth pattern with microscopic fingerlike seemingly random projections emanating from the centre of the tumour and sometimes extending for long distances.[3,4] These tentaclelike projections can extend through normal collagen, adipose tissue, fascia, and muscle and may mimic normal tissue histologically. The latter may be at least in part responsible for the high local recurrence rate, especially when present at the resection margins unrecognized by the pathologist. The presence of granulation tissue and early scar formation can add to these difficulties. Because of this growth pattern, the width of the surgical excision beyond the macroscopic tumour is of utmost importance.[3,4] Regarding the depth, the first underlying macroscopically normal tissue layer, usually the fascia, should be included in the excision. Moreover, the width of the peripheral margin around the macroscopic disease is crucial. For example, in the series of Monnier et al.[9] the local recurrence rate was 46% when the peripheral surgical margins were smaller than 3 cm and 7% when they were larger. In general, surgical margins of 2 to 5 cm have been advocated. Nevertheless, if the margins are histologically positive, re-excision is necessary because otherwise local recurrence will definitely occur. After wide excision of the tumour, the local recurrence rate varied from 0% to 46% (mean 7.3%) in series with at least 3 years of follow-up.[3] This minimal duration of follow-up in many of these series may not be optimal, since median and mean duration from surgical excision to local recurrence have been reported from 32 to 68 months, with up to more than 30% occurring after more than 5 years.[10-13] Tumours located on the head and neck have higher local recurrence rates, primarily because it can be difficult, if not impossible, to achieve wide margins in these anatomical areas.[3] Additionally, recurrent tumours have a higher risk of a new local relapse after wide local excision. Because of the width of excision, reconstructive surgery with skin grafts or tissue flaps are often needed, as also observed

in our series. We prefer to close the defects with skin grafts, despite the inferior cosmetic result when compared with tissue flaps, to allow for better detection of eventual local recurrence. The need for reconstructive surgery is associated with increased morbidity and costs. Therefore, it is important to avoid unnecessarily wide excision while maintaining a low local recurrence rate. Whilst French centres initially advocated margins of 5 cm, [14-16] the width of excision around the macroscopic tumour or the scar of previous excisional biopsy has generally been reduced to 3 and even 2 cm, without an obvious negative impact on local tumour control.[3,4,17] In the absence of randomized trials and large non-randomized comparative trials, there is no hard evidence in favour of any specific width of excision. In a systematic review,[17] studies with peripheral margins of 3 cm and more reported in general lower local recurrence rates than those with peripheral margins of less than 3 cm (0-35% vs. 22-47%). However, it has to be noted that in the latter studies excisions with narrow margins (<1-2 cm), which were most probably responsible for increased local recurrence rate, were also included. In a relatively small non-randomized comparative study,[18] no local recurrence was observed after excision with margins of 2 cm or more, while excision with smaller margins resulted in a 19% local recurrence rate (p=0.059).

Mohs micrographic surgery (MMS), during which limited excisions are repeated until the surgical margins are free of tumour at frozen section or paraffin-embedded microscopic examination, may provide a low local recurrence rate and simultaneously normal tissue conservation with optimal cosmetic and functional result. Local recurrence rates of 0% to 8% have been reported in mainly small series often with limited follow-up duration.[3,8,13,19-23] However, in the absence of randomized trials, it remains unclear whether MMS is indeed more effective than wide local excision. Only small retrospective comparative case series are available and these are highly prone to biases.[13,24] In systematic reviews,[13,17] the local recurrence rate was lower after MMS, but the difference was not statistically significant. Disadvantages of MMS are the highly demanding technique, the extra resources, the long duration of the procedure and the much higher costs.[24] In a retrospective comparative study,[22] the median operative time was considerably higher for MMS (257 minutes versus 77 minutes for wide local excision, p<0.001). With MMS, it has been calculated that a surgical margin of 1 cm leaves microscopic disease behind in 50-70% of the cases, while for macroscopic margins of 2 cm, 3 cm and 5 cm the risk is 10-40%, 0-15% and 0-5%, respectively.[8,19,20] These results and those of the study reported below support the practice of obtaining peripheral surgical margins of 2 cm or, preferably, 3 cm during wide excision of the tumour in order to achieve satisfactory local tumour control as well as low surgical, cosmetic and functional morbidity.

Recently, an interesting approach was reported, in which a wide excision with 1-2 cm margins and primary or delayed closure was followed by additional, generally 1 cm, re-excisions each time the pathologist revealed positive margins after a few days of meticulous pathological evaluation.[25] The median number of excisions of excisions to achieve negative margins was 1 (1-4) with a median excision width of 2 cm (0.5-3). A total margin of excision of ≤1cm was adequate in 36% of the cases, of >1 to 2 cm in 56% of the cases and >2 to 3 cm in the remaining 8% of the 203 cases. Translating this into standard wide excisions means that with a 1 cm margin, microscopic disease is left behind in 64% of the cases, with a 2 cm margin in 8% of the cases and with a 3 cm margin in none of the cases. The local recurrence rate was 1% after a median follow-up of 64 months (1-201). It has to be noted that the follow-up of many of these patients was considerably short. A disadvantage of this approach is the fact that 20% of the cases needed more than one operation because of positive margins and another is that patients underwent delayed reconstructive surgery after the pathologist reported negative margins when primary

closure had not been feasible. An advantage of the method, besides the low local recurrence rate, is the conservation of tissue pre-empting optimal cosmetic result.

At present, there is no consensus regarding which patients are best treated with MMS, which by wide excision, and for those undergoing wide excision, which excision width should be used.[24] In a questionnaire survey of the British Society for Dermatological Surgery members, 62% of respondents used wide local excision in the treatment of DFSP and 38% MMS.[26] In cosmetically sensitive areas such as the head and neck where achieving narrow margins is preferable, MMS may be optimal, whereas in other regions, traditional wide local excision with a 2 to 3 cm margin may be recommended.[24,27] In the present series, peripheral surgical margins of 2 cm, of 3 cm and of 4 cm were all associated with absence of local recurrence after a median follow-up of 28, 63 and 85 months, respectively. It has to be noted that for the patients with a surgical margin of 2 cm, the follow-up duration has been shorter. Therefore, the conclusion from our series that 2 cm margins are as effective as margins of 3 cm or more might be premature yet.

In our series, all patients presenting with recurrent disease had undergone elsewhere a limited excision, mainly an excisional biopsy, without subsequent wide surgical excision. Physicians should definitely know that when excisional biopsy of a skin tumour reveals DFSP, wide local excision should be performed in any case, and similarly when the pathologist reports negative surgical margins. Inadequate treatment results in significantly larger and deeper recurrent lesions, as also observed in our series, which are more difficult to manage and prone to new local recurrence after surgical excision.[28] In general, the surgical treatment of locally recurrent DFSP is similar to that of primary tumours.

Adjuvant radiotherapy has been successfully used to decrease the rate of local recurrences after surgery for large or recurrent tumours, and when surgical margins are histologically positive after maximal surgery.[2-4,10,11,17,25,27-29] In two patients operated for recurrent DFSP, adjuvant radiotherapy was used. New local recurrence has not been observed as yet, but the follow-up duration has been relatively short for this type of tumour. Primary radiotherapy has only been used in the case of inoperable tumours. In the case of locally (inoperable) advanced disease or systematic metastases, promising results have been reported in case reports and small case series with the use of Imatinib mesylate, which targets the tyrosine kinase PDGFB that is usually overexpressed in DFSP.[2-4]

In conclusion, DFSP is a rare tumour. Surgical excision with limited margins will most probably lead to local recurrence. Wide local excision with peripheral margins of 2 to 3 cm seems to be the treatment of choice for DFSP and is associated with excellent local tumour control, as indicated in our series too. The role of MMS has still to be defined. Adjuvant radiotherapy may probably be helpful in selected cases which include recurrent tumours, in order to reduce the local recurrence rate.

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CASE REPORT

Waldenström's macroglobulinemia and synchronous carcinoid and adenocarcinoma of the lung

A very rare case report

N. Baltayiannis, M. Chandrinos, I. Kasselaki, D. Anagnostopoulos, A. Kempapis, K. Konstantinidis, E. Nikolaidis, N. Bolanos, I. Lekka, A. Hatzimichalis

"Metaxa" Cancer Hospital, Piraeus, Greece

ABSTRACT

The Waldenstrom's macroglobulinemia belongs in B-cell origin lymphomas of low malignancy. This disease due to proliferation of B-lymphocytes expressing CD19, CD20, and IgM. Highly IgM levels may lead to hyperviscosity syndrome. The etiology of the disease is unknown. Waldenström's macroglobulinemia usually involves the lymph nodes, bone marrow, and spleen. Respiratory tract involvement is very rare (3% - 5%) with symptoms of dyspnea, nonproductive cough and chest pain while 15% of patients are asymptomatic. Carcinoid of the lung constitute 25% of all tumors and amount to 1-2% of all lung neoplasms Twenty five percent of patients with carcinoid of the lung are asymptomatic. In this paper we presented a case of a male patient aged 64 years with simultaneous coexistence macroglobulinemia Waldenstrom, typical carcinoid lung and adenocarcinoma of the lung.

KEY WORDS: Waldenstrom's macroglobulinemia, Adenocarcinoma of the lung, Carcinoid of the lung, Synchronous tumors of the lung

INTRODUCTION

Jan Costa Waldenström, a Swedish physician, first, in 1944, described two patients with anemia, hepatospenomegaly, oronasal bledding and a peculiar protein in the serum. This description is known as the description of Waldenstrom before the development of electrophoresis. Today ,is known, that monoclonal proteins are found in population-based screening studies in 1% of patients over the age of 50 years and in 3% to 4% of patients over the age of 70 years. The distribution of monoclonal proteins found in samples are IgG 59%, IgM 21%, IgA 11%, light chain 4%, biclonal 3,5% and IgD 0,5%. Diseases associated with IgM monoclonal proteins are MGUS (IgM

Corresponding author:
Nikolaos Baltayiannis, Thoracic Surgery Department, Metaxa Cancer Hospital, 51 Botasi str., 18537 Piraeus, Greece, Tel.: +302132079323, +302132079571, Mob.: +306974599288, e-mail: baltayiannisn@yahoo.gr

monoclonal gammopathy of undetermined significance) –is the most common 59%, Waldenstrom's macroglobulinemia-the next common 17%. IgM monoclonal protein may also be detected in patients with lymphoproliferative disorders 14%, malignant lymphoma 7%, chronic lymphocytic leukemia 5%, primary systemic amyloidosis 1%, cryoglobulinemia, and demyelinated neuropathies. Historically Waldenstrom's macroglobulinemia has been defined as an M protein >3 g/dl. Waldenstrom's macroglobulinemia also known as lymphoplasmacytic lymphoma, is one of the rare subtypes of non-Hodgkin's Lymphoma, accounting for only 1–2% of all non-Hodgkin's lymphoma cases.[1] In recent years it has been observed that the patients with Waldenstrom's macroglobulinemia are at higher risk of second cancers as compared with the general population.[2] In this paper we present a case of a patient with Waldenstrom's macroglobulinemia and simultaneous presence a typical carcinoid and adenocarcinoma in the same lobe of the lung.

CASE PRESENTATION

A 64-year-old man with a history with Waldenstrom's macroglobulinemia was admitted in our department. From quarter to chest computed tomography depicted dimensions 4×2 cm mass which does not go away with treatment of the basic disease i.e. Waldenstrom's macroglobulinemia (figure 1). The family described a medium weight loss of 4 kg and night sweating.

Our observations revealed he had a, blood pressure of 125/81 mmHg, a pulse rate of 80 bpm, and SpO2 of 97 percent on room air. Our initial investigations demonstrated a normochromic-normo-cytic anemia with a hemoglobin of 10.3 g/L without leukocytosis, lymphocytosis or thrombocytopenia. The erythrocyte sedimentation rate was 11 mm. Her biochemic picture was normal, but his lactate dehydrogenase was elevated at 328 units/L. The patient underwent complete preoperative clinical and laboratory

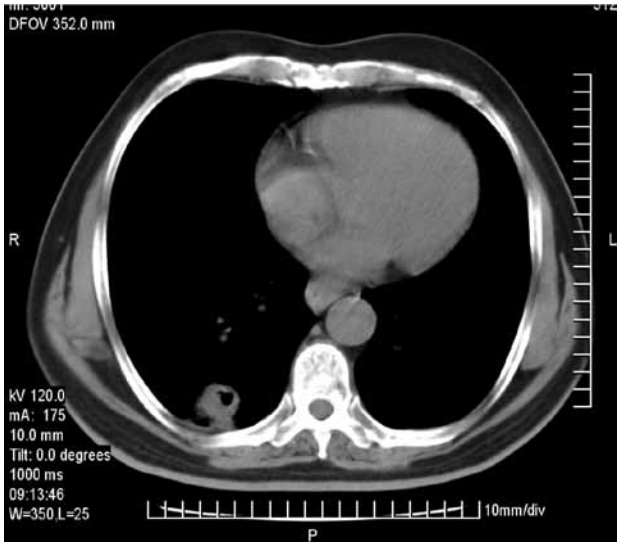

Figure 1. Chest CT: Right lung mass.

tests which revealed no metastatic disease (MRI of the Brain, CT and US of the abdomen, as well as skeletal scintigraphy showed no metastasis). Respiratory tests of the patient were also within normal limits. Fiberoptic bronchoscopy was not informative. Then the patient was taken to the operating room where he underwent right thoracotomy which revealed the mass of the right lower lobe of the lung. Rapid tumor biopsy showed lung adenocarcinoma and based on this diagnosis, the patient underwent lobectomy of right lower lobe and complete lymph node dissection. No intraoperative complications occurred. The postoperative course was uneventful and the patient was discharged at day 8 after surgery. The final histological examination found that the tumor (size 4.5×2×2.1 cm-stage T2aN0M0-Stage IB) has histological characters poorly differentiated adenocarcinoma (figure 2). The histochemical test (PAS, Alcian blue) confirms the glandular origin of carcinoma.Within the pulmonary parenchyma remaining recognized small region of size 2×1, 1 mm with morphological characters indicative of well-differentiated endocrine tumor (typical carcinoid of the lung) (figure 3). Immunohistochemical test showed strongly positive synaptophysin and chromogranin negative. The patient

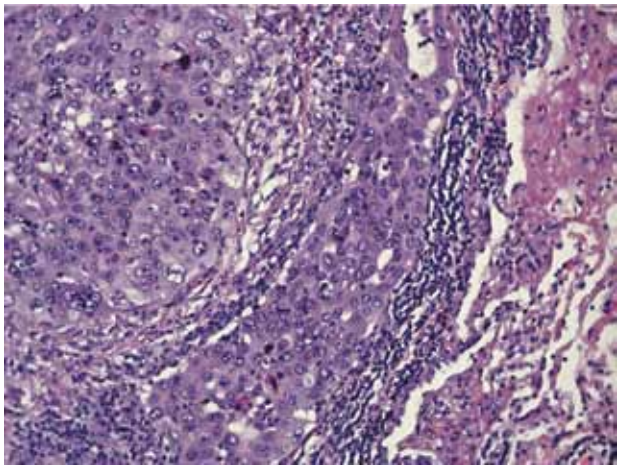

Figure 2. Histology of adenocarcinoma of the lung. H-E ×200.

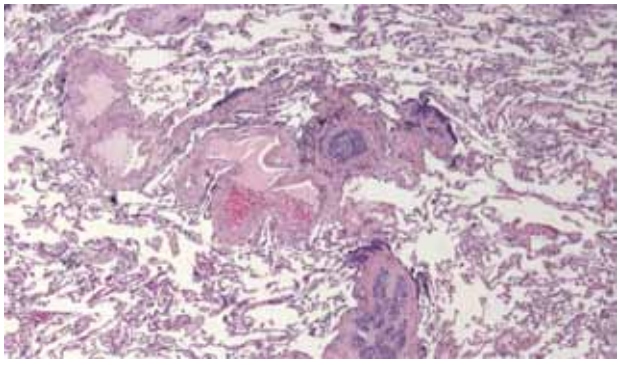

Figure 3. Histology of carcinoid of the lung. H-E ×140.

after surgery underwent adjuvant chemotherapy with satisfactory results.

DISCUSSION

Waldenstrom macroglobulinemia is a distinct B-cell lymphoproliferative disorder primarily characterized by lymphoplasmacytic cells infiltrating the bone marrow, along with demonstration of an IgM monoclonal gammopathy in the serum.

According to the Revised European American Lymphoma and World Health Organization (WHO) classifications, Waldenstrom macroglobulinemia is classified as a lymphoplasmacytic lymphoma (LPL).[3-6] In the United States each year, there are 1500 new cases diagnosed. The overall incidence of Waldenstrom macroglobulinemia is approximately 3 per million persons per year.[7,8]

Diagnostic criteria for Waldenstrom macroglobulinemia are defined by the presence of a serum IgM component accompanied by bone marrow infiltration of small lymphocytes (with plasmacytoid or plasma cell differentiation).

Patients with can present with an extensive range of signs and symptoms. The majority present with signs and symptoms related to the monoclonal serum protein and/or to the tumor infiltration.

Frequent clinical presentations are related to cytopenias, specifically anemia associated with the replacement of tumor cells in the bone marrow.

Patients may also present with symptoms related to hyperviscosity.

Approximately 20% of patients will experience hepatosplenomegaly and lymphadenopathy, and some patients may present with B symptoms including night sweats, fever, and weight loss.

Other common manifestations include neuropathy, cryoglobulinemia, skin rash (Schnitzler syndrome), cold-agglutinin hemolytic anemia, and amyloidosis.[9-11]

The involvement of the lung as the initial manifestation of Waldenstrom macroglobulinemia is very rare and only few cases, about ten, have been reported so far.

Pulmonary involvement in Waldenstrom macroglobulinemia occurs in 3%-5% of cases.[12-14] Symptoms at the onset include dyspnoea, nonproductive cough and chest pain, although 15% of the patients are asymptomatic. X-ray findings may include masses, diffuse or reticulonodular infiltrates, pulmonary nodules, mediastinal lymph node enlargement, and pleural effusions.[15-17] The histological confirmation of the disease is very important.

Chest symptoms in Waldenstrom macroglobulinemia are very rare, but autopsy series have shown that the lung and pleurae are affected often even in the absence of clinical findings.[18]

Hanzis et al, examined the incidence of other malignancies in 924 Waldenström's Macroglobu-

linemia patients .The most common malignancies were prostate (9.4%), breast (8.0%), non-melanoma skin (7.1%), hematologic (2.8%), melanoma (2.2%), lung (1.4%) and thyroid 1.1%). About 25 percent of patients had ≥ additional malignancy.[19]

Approximately 25%, of all carcinoid tumors, are located in the respiratory tract. Pulmonary carcinoids are rare, malignant neuroendocrine tumors that comprise approximately 2% of primary lung tumors.[20,21]

Pulmonary carcinoids produce symptoms as a result of their location within the tracheobronchial tree. Recurrent pneumonia, cough, hemoptysis, are common symptoms.

In recent series, about 20% to 40% of patients are asymptomatic and discovered as incidental findings on plain chest radiography.[22]

Carcinoid syndrome is relatively uncommon in pulmonary carcinoids. Symptoms such as flushing, sweating, or diarrhea occur only in 5 to 10% of patients and are reported mainly in those with bronchial tumors larger than 5 cm or in those with tumors metastasized to the liver.[23]

The patients with carcinoid tumors are more likely to have a negative positron emission tomographic scan because these tumors demonstrate a low level of uptake of fluorodeoxyglucose.[24-27] Immunoscintigraphy by In-111 octreotide is a diagnostic test of choice, of the carcinoid tumors although negative results cannot exclude. Checking for serotonin (5-hydroxy-indole acetic acid (HIAA)) levels whenever a carcinoid tumor is suspected in the absence of carcinoid syndrome is not recommended. Definite diagnosis of carcinoid tumors is made by bronchoscopy, thoracotomy, and fineneedle aspiration.

Histologic differentiation between typical and atypical carcinoids is important because of their different biologic behavior and prognosis. With regard to localized disease, surgery including lymphadenectomy when necessary is the treatment of choice and the only possibility for cure.[28]

Yano et al, reported a case of synchronous bronchial carcinoid and adenocarcinoma of the lung in a 58-year-old female. The authors argue that the coincidence of a bronchial carcinoid and an adenocarcinoma of the same side of the lung is a rare occurrence.[29]

Beshay et al, in 2003, described a case of a patient with bilateral presence carcinoid tumors in both lungs. Additionally Spaggiari et al, reported a case with bilateral, atypical and typical, carcinoid tumor in both lungs also.[30,31]

Nagamatsu et al, reported a case of the surgical resection of synchronous multiple primary lung cancer, comprising adenocarcinoma and carcinoid components. The patient was a 67-year-old Japanese and the histological examination of the resected specimen revealed cancer-in-cancer, consisting of adenocarcinoma and a carcinoid tumor.[32]

Waldenström's macroglobulinemia usually involves the lymph nodes, bone marrow, and spleen. Respiratory tract involvement is very rare.[33]

Waldenström's macroglobulinemia also rarely associated with other malignancies such as prostate, breast, colorectal, lung, and ovarian cancers.[34]

Pulmonary carcinoids are rare neuroendocrine malignancies that comprise 2% of primary lung tumors.

However, all in this case is rare. The disease, Waldenström's macroglobulinemia is rare. In Greece counted fewer than 50 cases a year. The appearance of the carcinoid in lung parenchyma is extremely rare. Finally, the multiple primary cancer incidence is between 0.73% and 11.7%, but the prevalence synchronous presentation of a solid tumor with a hematologic malignancy is also very rare.

In conclusion the presentation of this case imposed:

1. because of the rarity

2. in order to emphasize that in patients with Waldenström's macroglobulinemia when the mass of the lung is not reduced by the treatment we thinking second malignancy.

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