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Overview

Radiation therapy in older patients

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Abstract

As average population life span increases number of people of older age affected with malignant tumours also increases which became significant public health issue. Main modalities in treating cancer are surgery, chemotherapy and radiation therapy. They can be used either alone or in various combinations depending on tumour type, grade of a disease, patient's condition etc.

Current radiation therapy techniques give the possibility to deliver radiotherapy more precisely and with higher doses to the tumour meanwhile protecting surrounding tissue and preserving the physiological function of the regions in the body not involved with tumour. In this way it is possible to deliver curative doses of radiation therapy in older patients without compromising their general health and conserving the life quality in satisfactory manner. Subject of this work is clinical implementation of advanced radiation therapy techniques for the cancer treatment of older patients. Thus, different systems of assessment of overall patient performance were introduced and radiotherapy of most common cancer types in elderly population was reviewed and discussed.

INTRODUCTION

As some data indicate, the incidence of malignant tumours in population over 85 years of age rises over 3.5 % *(1,2,3)*. Consequently the percentage of people of older age affected with malignant tumours will also rise in time which is significant public health issue. Cancer treatment in older patients is often complicated and challenging but it could be as helpful as for younger patients. Bearing this in mind, each case must be analysed separately. Diagnostic medical data regarding the type and extent of disease, available treatment options, quality of life during and following the treatment, the risks and benefits of treatment, patients' choice of treatment as well as financial and social aspects of the treatment must be considered prior defining treatment of choice *(4,5,6)*. External beam radiation therapy (EBRT) is one of the efficient treatment modalities and as such it would be the subject of this paper.

CANCER TREATMENT MODALITIES AND OLDER POPULATION

Due to fear of acute side effects and impact on life quality the approach in treating older patients with cancer is often less aggressive and radical then it really might be. Nevertheless, in the majority of papers *(2,7)* discussing radiotherapy issues in older people there is no evidence of higher adverse event onset in the evaluated population if medically monitored and cared for properly.

Cancer treatment usually consists either of a single therapy modality or a combination of modalities. This can include surgery, chemotherapy and radiotherapy. The supportive care is also a valid option for patients who cannot or do not want to undergo an active treatment. The aim of such a treatment is to provide palliation of symptoms like pain and inappetence and to give a patient better life quality. Giving support to the family of patient plays also an important role in the integral oncological treatment.

Radiation therapy is modality of localized treatment and is applied alone or in various combinations with surgery and chemotherapy. Radiotherapy can be external (external beam radiation therapy-EBRT) meaning that is applied using high energy photon or charge particles beams or internal by placing radioactive sources in tumours or body cavities near the tumour volume. Patients mostly receive this kind of treatment as outpatients and most often there is no need for hospitalization. The treatment, given as a radical one, has duration of several weeks.

ASSESSMENT OF ELDERLY PATIENT PERFORMANCE STATUS

In the assessment of overall patient performance different systems are currently in use. Most widespread are ECOG (Eastern Cooperative Oncology Group) performance scale *(8)* and Karnofsky performance index. These systems may under-evaluate the scale of functional damage in older people because of their descriptive and general nature of enquiring everyday activities and health state. Therefore, other more detailed evaluation systems should be used, i.e. ADL (Activities of Daily Living scale) *(9)* which can allow us to precisely evaluate the psychophysical condition of the patient. This assessment tool is divided in three subcategories – BADL (Basic Activities of Daily Living), IADL (Intermediate Activities of Daily Living) and AADL (Advanced Activities of Daily Living).

BADL evaluates independence and ability of full scale basic self-care like feeding, fulfilling hygienic needs, dressing etc. IADL evaluates ability of doing everyday activities like preparing food, driving, going to shopping, using public transportation etc. AADL looks at complete familiar and social involvement of individual and involvement in different recreational or voluntary groups and actions *(10)*. The assessment of functional status of elderly people is just a part of the overall assessment which includes familiar state, social state, economical state, educational state, cognitive functions and other characteristics.

RADIATION THERAPY

Clinical implementation of radiation therapy for the cancer treatment is rather complex process which includes use of highly sophisticated equipment (e.g. linear accelerator, computed tomography simulator, treatment planning system, portal imaging device…) and different positioning and immobilization systems. Furthermore, from the prescription to the delivery of radiotherapy treatment a team of professionals from a number of disciplines is involved in a large number of steps, which makes a significant potential for errors *(11,12)*. Thus, clinical implementation of advanced radiation therapy techniques should be prepared seriously and with great care. For example, at University Hospital Rijeka the clinical implementation of advanced techniques has been started following participation of Radiotherapy department in Quality Audit in Radiation Therapy (QUATRO) *(13)* organized by International Atomic Energy Agency. The system has been developed according to the guidelines provided by the team of auditors and it has been upgraded permanently. Due to high level of complexity, functionality of each and every part of the system must be controlled and verified periodically. Therefore, comprehensive quality assurance/quality control (QA/QC) programme is required to assure treatment outcome and radiation safety of the patient *(14,15)*. In other words, after all assumptions for the successful delivery of radiotherapy have been satisfied and the process of delivering the treatment commenced, frequent quality control has to be implemented and conducted to minimize possible adverse events in all patients. Such procedures must take into account everything from daily recording and verifying the positioning of the patient on treatment couch, dose delivery and accuracy of the equipment for radiotherapy planning and delivery.

Clinical application of advanced radiation techniques (3 Dimensional Conformal Radiation Therapy and Intensity Modulated Radiation Therapy) brings significant improvement due to possibility of applying higher cumulative doses with sparing of healthy tissue and organs at risk. Nevertheless, at the same time the preparation of the treatment is quite complex and time consuming. It includes CT simulation with acquisition of patient anatomy data in the treatment position. Based on acquired anatomical data the process continues with contouring of target volumes and organs at risk *(16,17)* which is followed by the complex calculations of dose distributions and creation of the treatment plan according to, so called, dose volume constraints (DVC) *(18)*. Treatment plan evaluation requires knowledge of the effect of the radiation, not only on the intended target, but also the surrounding normal tissues. Literature brings estimations of tolerance doses and proposed dose-volume constraints for many of the organs at risk *(18)*. Technological advances have brought in wide use the 3 dimensional radiotherapy planning systems with advanced algorithms *(19)* and possibility of more accurate and precise calculation of dose distributions. Those calculations are used for the treatment plan optimization.

CLINICAL APLICATION OF RADIOTHERAPY IN OLDER POPULATION

A majority of elderly patients are usually not candidates for surgical treatment due to several reasons (age, comorbidities, patient wishes and preferences). There-

fore, external beam radiation therapy is the treatment of choice. According to our clinical experience it gives better overall survival then best supportive care in patients who cannot undergo a surgical procedure. One has to bear in mind that more than 80% of elderly people have two or more comorbidities thus the evaluation of comorbidities and seriousness of such conditions is extremely important in evaluating the possibility of radical radiation treatment. Patients, who are evaluated as those who could have serious adverse events of radiation therapy or those who have serious comorbidities and because of that short life expectance, should not get radical radiation treatment. The most commonly used tools for assessment of comorbidity risks are ACE-27 *(20)* scale and Charlson comorbidity index *(21)*.

Modern technological advances made possible to visualise the target areas, contour them in computer based radiotherapy planning systems and calculate accurate and precise dose distributions plans. Digital linear accelerators with multileaf collimators makes conforming of radiation fields to the shape of target volume possible allowing the radiation oncologist to raise the dose planned on target volume. Consequently, radiotherapy can be delivered more precisely and with higher doses to the tumour meanwhile protecting surrounding tissue and preserving the physiological function of the regions in the body not involved with a disease. In this way it is possible to deliver curative doses of radiation therapy in older patients without compromising their general health and conserving the life quality in satisfactory manner. Regarding the available data in literature there is no indication for a dose reduction in radiation therapy only because of age, especially in the curative setting *(2,7,22)*. Older adults usually withstand radiation therapy well and the side effects of radiation therapy are more dependent on the type of radiation treatment, dose delivered and location of the cancer being treated than on the age. It is also crucial for the treatment outcome that the positioning of the patient during 30–35 daily fractions of the treatment mimics the initial one. Thus the immobilization of the patient is very important and different kinds of positioning and immobilization devices are used for day to day treatment reproducibility.

Three most common types of carcinoma in elderly population *(23)* usually treated with radiotherapy are breast cancer, lung cancer and prostate cancer. The breast carcinoma is the most common type of cancer in feminine population *(23)*. Standard adjuvant therapy scheme usually includes radiotherapy. Radiation therapy in women treated with breast conserving surgery is typically delivered to the whole (entire) breast. The standard dose to the breast after lumpectomy is 50 Gy in 2 Gy daily fractions with the addition of a boost dose to tumour bed for the appropriate group of patients which ranges from 10–16 Gy in 2 Gy daily fractions. Therapy is applied via two angled (tangential) beams designed to minimize dose to the underlying normal lung tissue or using advanced planning (3DCRT or IMRT) with photon beams. Boost dose can be delivered in different ways, either with photon beams using 3DCRT, electron beams or using interstitial brachytherapy technique. Post mastectomy irradiation is applied to the chest wall as well as to the regions of possible lymphatic spread of the tumour depending on histological findings. The dose given in this case is 50 Gy in 2 Gy daily fractions. Radiation is usually delivered by tangential photon beams or direct appositional electron field. This kind of treatment is also applied in the older patient population with the same doses and techniques above mentioned.

It has been proven that adjuvant radiotherapy reduces the risk of breast cancer recurrence and death as a result of breast cancer. In the update of the Early Breast Cancer Trialists' Group metaanalysis, radiotherapy lowered the risk of breast cancer recurrence by about one half and lowered the risk of breast cancer death by one sixth *(24)*. It has been observed that the benefit of radiotherapy is correlated with the initial risk assessment for the recurrence of disease and has also been observed that the patients with low risk breast cancer did not have benefit from radiotherapy as those with high risk for recurrence.

The CALGB 9343 trial was designed to answer the above raised question analyzing the subset of older women with low-risk breast cancer. This study has been conducted on more than 600 women aged 70 or older with the disease assessed as having a low risk for recurrence. Study had two arms, one in which patients have been treated with tamoxifen and the other in which they have been treated with tamoxifen and adjuvant radiotherapy. The study results showed no significant difference in the rates of subsequent mastectomy, distant metastases, or overall survival between the two groups. The study has been initially published in 2004. with the median follow-up of five years and the rate of local or regional recurrence was 1 % in the radiation group and 4% in the group not treated with radiation. Study has been updated after 10.5 years follow up period and it has been shown that the local disease recurrence was inferior in the group receiving adjuvant radiotherapy (2 % vs. 9 %) *(25)*.

In the light of the described studies and principles it can be concluded that the radiotherapy of breast carcinoma has proven benefits in older patient population.

In the breast radiotherapy it should be taken into account that organs at risk are lungs, hearth and spinal cord, which if compromised by radiotherapy can significantly lower the life quality of older patient and raise the comorbidity and non cancer related death rate. Therefore, it is crucial to determine the risk for breast cancer recurrence based on clinical and hystological findings and possibly apply adjuvant radotherapy in patients whose disease is evaluated as having a high risk for recurrence.

Patients with newly diagnosed lung cancer in more than 50 % cases are of age 70 or higher *(26)*. The prevalence of comorbidity among lung cancer patients is significantly higher in patients aged higher than 70 years, together with a proportionate in cases in the number of

comorbidities per patient *(27)*. The rate of disease diagnosed in early stage is considerably lower in older population then in younger individuals and as such prognostically unfavourable. Despite the rising incidence of lung cancer with age, discrimination on the basis of age occurred occasionally. The elderly obtain lower histological confirmation rates *(28,29),* less accurate staging and lower rates of radical treatments despite more than 50 % of lung cancer patients aged 65 years or more have good or excellent performance status *(28)*. Concurrent chemoradiotherapy is now the standard of care for patients with stage III non-small cell and limited disease--small cell lung cancer. More than half of this patients were not eligible for concurrent chemoradiotherapy on the basis of criteria of age and important comorbidities *(30)*.

Current standard doses for the radical chemoradiotherapy are in range of 60–70 Gy in 2 Gy daily fractions. Also the results of recent phase III study shows that further dose increase has no influence on overall survival *(31)* of the patients with stage III non- small cell lung cancer treated with concurrent chemoradiotherapy. Therefore, for this group of patients the treatments of choice are either sequential chemoradiotherapy or radiotherapy alone with total doses up to 70 Gy. Thus the strict implementation of dose volume constraints in radiotherapy treatment and the consideration of the age of the patient and general physiological decrease of functionality of different organ systems are of extreme importance.

Further developments in technology introduced 4D CRT *(32)* techniques in clinical use which combines respiratory gating (delivering the radiation therapy in a certain moment of respiratory cycle and thus enabling the delivery of treatment to the same geometric area every time independent of the movement of thoracic wall) *(33)*. Stereotactic ablative radiotherapy (SART) is the novel technique recently implemented in clinical use. It is based on a concept of delivery of a large dose in a short time period to a very limited target volume in stage I lung cancer patient. This method may replace surgical procedures due to possibility of very high dose delivery. Some current clinical studies have demonstrated improvement in survival in patients treated with SART compared to 3D-CRT *(34)*. It has to be stressed that this kind of treatment requires a highly sophisticated technology and appliances with excellent logistics. Also the cost of this type of therapy is much higher compared with standard 3D CRT. Regarding this it is not widespread clinically implemented at the moment.

The other most common tumour type in elder male population is the prostate carcinoma, the second most common *(23)* type of cancer in male population in Croatia which correlates with epidemiological data from other countries worldwide.

Prostate carcinoma may be treated in several ways including surgery, hormonal therapy and radiotherapy. Every treatment modality has its own drawbacks and risks, especially in older population. Nevertheless, due to quite favourable side effect profile radiotherapy may be the most appropriate way of treating this entity. Furthermore, radiotherapy of prostate carcinoma shows significant advantages over surgical treatment because of avoiding complications like in- and post- surgery bleeding, risks related to blood transfusion, infections, urinary incontinence and anaesthesia related risks in cardiovascular and respiratory system (myocardial infarction, pulmonary embolism etc.).

In the past 20 years a major breakthrough has been made in radiotherapy of prostate carcinoma. In 1980s the standard routine was a 2D (two dimensional) treatment planning which allowed the administration of radiotherapy in the dose range of 66–70 Gy due to acute and chronic post radiotherapy toxicities. Therefore, Kuban et al. *(35)* conducted a dose escalation study in prostate carcinoma radiotherapy. It was performed randomizing 301 patients with different disease stage in two study groups. One group received total dose of 78 Gy on target volume while the dose to the target volume in other group was 70 Gy. It was reported *(35)* that the group receiving higher total dose had a significantly longer progression free period (biochemical and clinical, 78 % versus 59 %, $p=0.004$). These results lead the radiation oncologist community to conclusion that doses of up to 70 Gy are inadequate for the treatment of prostate carcinoma.

Considering the prostate carcinoma radiotherapy organs at risk which limit the total dose are bladder, colon and small intestine. These limitations can be dealt with by the implementation of advanced radiotherapy techniques and the corresponding toxicities and side effects of the treatment can be reduced *(36)*. The standard doses with these techniques are in the range of 74–78 Gy applied in 7–8 weeks of treatment. Further advances in technology have brought in clinical use intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT). This consequently allows further escalation of the total dose to 80 Gy. Also it has been demonstrated that despite the increase of the dose, using this methods the risk of gastrointestinal toxicities *(36)* decreased. Nevertheless, time per fraction in those techniques is significantly longer comparing with 3D conformal radiotherapy. This is usually the problem for older patients due to maintaining exact patient position during prolonged treatment time. Regarding this 3D conformal radiotherapy remains the treatment of choice for older patients in most cases.

CONCLUSION

Radiotherapy in older patient population represents a viable and reasonable treatment option in integral cancer treatment. Radical radiotherapy treatment can be definitive and curative therapy and it has to be applied in adequate dose levels and fractionation. It has its own drawbacks and possible risks. Regarding this, it is very important to evaluate every individual patient regarding patient's performance status, comorbidities, clinical find-

ings and tumour characteristics. Applying this personally "tailored" approach to therapy the possible risks for health deterioration and life quality disruptance can be diminished to acceptable levels. Fulfilment of all this presumptions allows applying high quality radiotherapy treatment for patients of older age.

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