In the last half-century, changes in population demography have been observed in western countries. There has been an increase in numbers of elderly people as a proportion of the total population. It has been estimated that in industrialized countries, 20% of the population is over 65 years of age, a substantial increase in recent decade (1).

With the aging of the general population, cancer in the elderly has become increasingly common. In the developed countries, about 60% of cancer patients are aged 65 years and over. Age-specific incidence rates for various cancers are several-fold higher in older than in young patients. It is estimated that individuals who are over 65 years of age have 11 times greater risk of cancer than people under the age of 65 years. In the elderly, the most common cancer sites are breast, large bowel and lung in women and prostate, lung and large bowel in men.

In our country, about 50% of cancer diseases occur in people aged over 64 years. Lung, large bowel, breast and prostate are the most frequent cancer sites (2). At the Institute for Oncology and Radiology of Serbia, there are about 1200 (25%) newly registered patients aged over 65 each year.

It is commonly believed that the diagnosis of cancer in the elderly is delayed for a variety of reasons. For example, symptoms are attributed to aging or other co-existing diseases there is a lack of awareness of bodily functions, fear of cancer, embarrassment, financial reasons etc. (3). Tests used for screening or early detection often perform differently in older patients.

Aging also has an impact on cancer's biology and behavior, with some cancers evolving more slowly and the others becoming more rapidly invasive in older patients (4).

According to the data from the hospital registry of the Institute, there are some differences in the epidemiological characteristics of most frequent cancers between patients over 65 years and younger ones.

About a third of lung cancer patients were over 65 years of age. Overall, those patients were presented more frequently with the localized disease at diagnosis and they had a different distribution of histological types in comparison with younger patients.

In breast cancer patients, the size of the tumor at diagnosis was on average smaller in younger groups than in older ones, both according to the clinical and pathological TNM. However, there was no significant difference either in the lymph node involvement or in the presence of distant metastases at diagnosis. The share of ductal carcinoma in all breast cancers was lower in older patients than in younger ones (46 vs. 51%) while the situation was the opposite for lobular carcinoma (34 vs. 25%). However, there were no differences in the tumor grades. Hormonal receptors were more frequently positive in older women. About 80% of patients in both groups underwent surgery; chemotherapy and radiotherapy were significantly less frequently administered in older women as opposed to hormonotherapy.

As for gynecological cancers, 21% of patients with cervical cancer and 49% of patients with endometrial cancer were aged over 65 years. Older patients with cervical cancer had a more advanced stage at diagnosis while no age-related differences were found for endometrial cancer.

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Cancer in the elderly: A challenge for 21st century

KEYWORDS: Neoplasms + therapy; Aged

For most of human history and probably to the origin of modern men, some 100,000 years ago, there was a stable pattern of birth and death, enough to produce slow population growth. Survival beyond 65 years was a rare event. During the 19th century improvements in public health and medicine began to influence forces of natural selection operating on the human species.

Since the beginning of the 20th century world population profile slowly started to change. In the West, population older than 65 years has been progressively expanding since 1950s (1). The classical pyramidal picture of population age profile has changed, and today looks more like a square because the young base has shrunk and older top has enlarged. In geriatric words, this shift is referred to as "squaring of pyramid". In some European countries such as Italy, the population older than 65 years has already exceeded the population younger than 20 years. In the USA this will happen around 2010 if the current trends in population growth persist (2).

The aging of the population has important social and medical implications. In dealing with a population of limited life expectancy, and affected by multiple conditions, the goal of treatment has shifted from cure to preservation of function and quality of life.

Cancer is an important problem in the geriatric population. The increase in cancer incidence has paralleled the aging of the population. In the aggregate, it is the second leading cause of death after heart diseases, and 50% of all documented cancers occur in 11% of the population over the age of 65 years. It is expected that as many as 60% of all neoplasms will affect older persons by the year 2010. Interestingly, incidence of many cancers levels off after age 80. In the USA this will happen around 2010 if the current trends in population growth persist (2).

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The aging of the population has important social and medical implications. In dealing with a population of limited life expectancy, and affected by multiple conditions, the goal of treatment has shifted from cure to preservation of function and quality of life.

The association of cancer and aging may be explained by two nonmutually exclusive hypotheses. First, carcinogenesis is a time-consuming process. It is the consequence of normal aging but is lacking in most cancer cells. This gene encodes the cyclin-dependent kinase 4 (cdk 4) that activates an inhibitor of cell proliferation (5).

Controversy continues over whether cancer is less aggressive in the elderly and some conflicting results have been reported. So, cancer is by large a geriatric disease but under no circumstances can be considered a consequence of normal aging.

Prevention of cancer must begin before people become old. Primary prevention is useful in older population owing to their increased susceptibility to late-stage carcinogens (6). The best evidence strongly recommends avoiding smoking, overuse of alcohol, exposure to toxic chemicals, and maintaining a low-fat, high fiber diet. Chemoprevention of cancer gains popularity today and older people seem to be ideal candidates for this technique. Indeed, many controlled studies confirmed efficacy of estrogen antagonists and SERM in breast cancer prevention. Randomized studies also showed that retinoids can prevent smoking-related neoplasms in head and neck, and nonsteroidal anti-inflammatory drugs (NSAIDs) may prevent colorectal cancer. Secondary prevention involves early detection of cancer by screening asymptomatic persons at risk. The value of these measures in older persons is not well established. However, reduced cancer related mortality can be achieved using serial mammography, annual fecal occult blood testing, serial cervical Pap smears, and possibly serial determinations of prostate-specific antigen (PSA) levels.

The management of cancer in older patients should always take into consideration probable benefits and potential risks. Proper selection of patients is the key to administering effective and safe therapy. Because aging is highly individualized, the best guide to cancer treatment may be provided by a comprehensive, multidimensional assessment of the older patients. This includes such areas of diversity as functional status, comorbidity, socioeconomic conditions, nutrition, polypharmacy and the presence of specific geriatric syndromes. All mentioned above could be estimated using appropriate scales such as: Activities of daily living (ADL); Instrumental activities of daily living (IADL); Mini mental status (MMS); Geriatric depression scale (GDS); Mini nutritional assessment (MNA); and so on. Together, they comprise so-called Comprehensive geriatric assessment (CGA) (7).

As mentioned before, age by itself is not a contraindication to cancer therapy. Two questions must be answered. First, is the patient able to tolerate life-prolonging treatment? Second, is the treatment going to improve the survival and symptoms?

Surgical treatment mortality does not appear to rise with the age (up to 80) for elective procedures. However, the incidence of postsurgical complications and hospital staying do increase with age. A number of surgical advances permit reduced extent of resection with particular benefits for the elderly. They include partial mastectomy, transanal resection for rectal cancer, intraluminal ablation in hollow organs, and stereotactic surgery in CNS.

Radiation therapy is particularly well tolerated by older patients. New forms of radiation therapy that promise to be beneficial in this group include brachytherapy for prostate cancer and radiosurgery for brain tumors. Hyperfractionated radiation appears to be more effective than standard treatment.

Chemotherapy should be strongly considered in clinical situations in which cure, prolonged survival or palliation can be achieved. Because aging is associated with important pharmacologic changes in body, antineoplastic therapy may be less well tolerated by elderly patients. The major pharmacokinetic changes include decreased renal excretion of drugs, decreased drug metabolism, and decreased volume of distribution of water - soluble drugs. Pharmacodynamic changes include decreased intracellular catabolism of...
drugs, incomplete repair of DNA damage, impaired apoptosis and increased expression of MDR-1 gene. Older patients also appear to be at special risk for severe and prolonged myelosuppression and mucositis, as well as cardiomyopathy and neuropathy. Of special interest is also chemotherapy and anemia-related fatigue in elderly.

To minimize these complications, certain measures must be taken, namely dose adjustment of drug to GFR, correction of anemia, use of antidots (G-CSF, dexrazoxane, amifostine, pyridoxine), prophylactic use antibiotics in neutropenia, fluid resuscitation in diarrhea and mucositis.

A number of new drugs allow the safe treatment in elderly because of favorable toxicity profile. These include gemcitabine, vinorelbine, and taxanes in low-weekly doses (8). A variety of older chemotherapeutic drugs remain useful. Anthracyclines should be administered by continued IV infusion on small daily doses. Mitoxantrone or liposomal form of drug may substitute doxorubicin.

Palliative therapy must be integrated into treatment plan of elderly patients, and one can always use some form of it.

So, we may conclude with the following:

1. Old age carries important risk for development of cancer (but not obligatory).
2. Advanced age alone is not reason enough for withholding effective treatment that could improve survival and/or quality of life.
3. Treatment of elderly with cancer must be individualized according to CGA.
4. To define best form of treatment, old people must participate in clinical trials.
5. Geriatric oncology will be an interesting area for future research.

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Do clinical trials help us to optimize chemotherapy in the elderly? The lymphoma experience

KEYWORDS: Lymphoma, Non-Hodgkin; Antineoplastic Agents; Aged

Malignant non-Hodgkin’s lymphomas in the elderly are a rather common condition in medical oncology, nevertheless these conditions probably require a specific therapeutic approach. The issue is relatively controversial. Specificities of this subpopulation have been brought to attention of hematologists and medical oncologists only a decade and a half ago, when European School of Oncology Organized the first and second intercity meeting on management of non-Hodgkin’s lymphoma in the elderly.

SPECIFICITIES OF PRESENTATION OF NON-HODGKIN’S LYMPHOMA IN THE ELDERLY POPULATION

The first fact that emerged by a revision of several series of non-Hodgkin’s lymphoma (NHL) patients in the late eighties of the last century provided the information that at least 34%-37% of all lymphoma patients is aged over 65.

The most frequently observed histological pattern was that of a diffuse large cell lymphoma belonging to the intermediate or high-grade group according to the working formulation. In some series the diffuse large cell pattern accounted for up to 84% of all lymphomas in the elderly. Some observations claimed that the frequency of intermediate and high-grade histology among elderly patients did not significantly differ from the one observed in younger patients. However large case series confirmed that low-grade histology and follicular growth patterns are less frequently represented in the elderly group.

Another characteristic of the non-Hodgkin’s lymphoma in the elderly was that initial extranodal presentation or extranodal diffusion found in 45-50% patients ate the onset. The extranodal presentation or involvement might provide an additional risk or bad prognostic factor.

Another risk factor might be provided by the fact that decrease of total T cells accompanied or not by inverted helper.suppressor ratio is more marked in the elderly than in the total population of non-Hodgkin’s lymphoma patients. Altered organ sensitivity to drugs, especially the age-dependent decrease in

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the number of stem cells in the bone marrow, seems to be the crucial factor, according to broad clinical experience, in determining the degree of tolerance of patients to cytostatic agents in general.

**GOOD NEWS**

Several studies have tended to demonstrate that elderly patients are able to tolerate standard dose doxorubicin based regimens and even more aggressive regimens such as full dose ProMACE-CytaBOM in a similar way as younger patients. The conclusions of a retrospective analysis of SWOG clinical studies, dealing with diffuse large cell lymphoma, suggests that patients over 65 years and younger adult patients with same clinical characteristics obtain a similar complete response rate when treated with a comparable dose of chemotherapy, and that there is no correlation between age and toxic side effects from CHOP. According to German Study Groups including the Kiel Lymphoma Study Group, in unfavorable lymphomas of elderly people as well as in those of the younger population, incidence of toxicity, grades of toxicity and results of treatment were equivalent to those observed in younger patients. According to results from several prospective clinical studies of efficacy of different lymphoma related chemotherapy regimens ranging from the standard dose CHOP to the aggressive ProMACE-CytaBOM there appeared to be absolutely no difference in tolerance to chemotherapy and treatment results between the elderly and non-elderly population of high-grade lymphoma patients.

**BAD NEWS**

In most studies of different chemotherapy regimens designed for high-grade non-Hodgkin's lymphomas the inclusion criteria were unfit for the elderly group. They included limited age distribution (mostly up to 65, exceptionally to 70 years, usually the population aged between 65 and 70 years being poorly represented), normal bone marrow, liver and renal function, normal cardiac function, performance status 0 or 1 and no significant comorbidity. In a study reported by Miller and Jones patients over 65 years had a relatively mild toxicity with CHOP at initial dose reduced to 50% of the calculated full dosage. However 70% of patients received only 2 to 4 courses because of prolonged myelosuppression and were shifted to other treatment modalities. Thus this experience points to the fact that patients who are likely to need more prolonged treatment (patients with aggressive lymphoma stage III or IV) might not be able to receive CHOP even at reduced doses without significant toxicity. An Italian study comparing full dose CHOP to a specifically designed regimen for the elderly reported 30% toxic deaths on full dose CHOP in a population of elderly patients who otherwise would not completely fill criteria to be included in a classical chemotherapy trial because either of performance status or comorbidity.

The EORTC lymphoma group in a retrospective study of elderly patients suggested that evaluation of toxic deaths in the elderly could be more difficult than in younger patients because the effects from tumor progression, comorbidity states deterioration and side effects of chemotherapy are often similar and hardly distinguishable. Therefore, regimens specifically designed for elderly patients have been developed and analyzed in single arm or randomized trials. The results remain highly controversial. There is still no consensus whether chemotherapy regimens for elderly patients with non-Hodgkin's lymphoma should be full dose doxorubicin containing or whether development of non-anthracycline containing regimens is warranted. On the other hand a number of these studies suffer from the pitfall in asking for a performance status 0 or 1 and absence of comorbidity, conditions which are not very common in the elderly and even less common in elderly patients with lymphoma.

The problem is further complicated by the poor compliance to treatment in up to 60% of the aged patients.

Age has been identified in some studies as the most important prognostic factor in aggressive NHL.

**MAJOR PITFALLS IN THE INTERPRETATION OF CLINICAL TRIALS FOR ELDERLY LYMPHOMA PATIENTS**

In a study reported 3 years ago we tried to analyze the impact of several potential prognostic factors affecting the results of elderly lymphoma patients treatment in clinical trials. We recruited 47 elderly patients (over 65 years,) with aggressive non-Hodgkin's lymphomas, chemotherapy naives, who were treated with two non-anthracycline containing combinations (BCNU-etopozide-procarbazine and mitoxantrone-etopozide-procarbazine). Both regimens achieved a response rate of 60% with a more modest percentage of complete responses; in several patients with partial response, complete response was achieved with additional involved field radiotherapy. The survival in both arms was identical. Since the response rate and survival were identical in both arms, we fused all patients together in order to analyze the impact of prognostic variables. The clinical stage (II, III or IV) had no impact on survival. The sex (male or female) had no impact on survival. Presence or absence of bulky disease had no impact on survival. Performance status (patients being divided in two groups, PS 0+1 and PS 2+3) had a survival impact; the difference in survival was on the significance level of $p=0.045$ (Figure 1).

![Figure 1. Impact of performance status on survival of elderly patients with diffuse large cell lymphoma](image1)

The impact of comorbidity was enormous. Difference of survival of patients with significant antecedent or concomitant disease and those who were negative for significant comorbidity was statistically significant on the level of $p=0.0004$ (Figure 2).

![Figure 2. Effect of comorbidity on survival of elderly patients with diffuse large cell lymphoma (SACD+= significant antecedent or actual comorbid states are present; SACD neg=no significant antecedent or actual comorbid states)](image2)
To complicate further the interpretation there was no correlation between comorbidity and performance status (Table 1).

Table 1. Correlation between comorbidity and performance status

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<th>Comorbidity</th>
<th>Performance status</th>
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<tr>
<td>Significant</td>
<td>0+1</td>
</tr>
<tr>
<td>Not significant or absent</td>
<td>11*</td>
</tr>
<tr>
<td>Significant</td>
<td>2+3</td>
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<tr>
<td>Not significant or absent</td>
<td>12*</td>
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Eleven patients had significant comorbidity but, due to successful symptomatic treatment, performance status was 0+1; 11 patients had both significant comorbidity and performance status 2 or 3; 12 patients had no significant comorbidity but performance status 2 or 3, which was therefore, lymphoma related. That leaves only 13/47 patients with both performance status 0 or 1 and no significant comorbidity.

That practically means that only 25% of elderly high-grade lymphoma patients can fulfill classical criteria to be included in a chemotherapy clinical trial. Comorbid situations, previously well compensated, tend to deteriorate irrespective of adequate treatment; deterioration might be due either to lymphoma or to chemotherapy or both. Therefore, clinical trials with elderly patients with aggressive non-Hodgkin's lymphoma with performance status 0 or 1 and no serious coexisting disease as inclusion criteria, target only to a minor prognostically better subpopulation among these patients and can not be extrapolated to elderly patients with non-Hodgkin's lymphoma in general.

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Age is a major risk factor for breast cancer. More than 50% of breast cancer occur in women 65 years of age and older. The increasing incidence of breast cancer with age has been seen predominantly in women older than 50 years (peak in 80 years, plateau between 80 and 85 years of age). According to cancer statistics, 1 in 15 women aged 60-79 years developed breast cancer compared to 1 in 25 women aged 40-59 years and 1 in 227 women younger than age 39 years (1).

With increasing age, the risk of co morbid conditions and cancer-related death also increase. As many as 50% of women 65 years of age and older who develop breast cancer die of the disease (2). Breast cancer in elderly population is presented with some specific characteristics with direct consequences on the therapeutic approach:

- They are frequently diagnosed at more advanced stage and most of them are metastatic at the time of diagnosis versus 5% in younger women.
- More indolent course of breast cancer with high prevalence of positive hormonal receptors, well-differentiated and slowly proliferating tumors.
- Higher comorbidity rate.
- Progressive declines of functional reserve of multiple organs with age.
- Poor financial and social background.
- Limited access to transport.

The multidisciplinary approach to this cancer includes prevention, early detection, treatment of localized tumors and management of advanced disease. Decisions related either to prevention or treatment need to be individualized, by weighing the probable benefits of treatment against the potential risk. Because aging is highly individualized, the best guide to breast cancer treatment in the elderly (3) may be provide by comprehensive geriatric assessment (CGA) which takes into account:

- Assessment of comorbidity
- Assessment of socioeconomic conditions
- Assessment of functional dependence
- Assessment of emotional and cognitive conditions
- Life expectancy

BREAST CANCER PREVENTION IN THE ELDERLY

Chemoprevention with estrogen antagonists is the most promising form of primary breast cancer prevention in older women. In the recent NSABP P-...
1 trial (tamoxifen versus placebo) which included all "high risk" women aged 60 years or older, there was nearly a 50% reduction in the incidence of invasive and noninvasive breast cancer after median follow up of 69 months (4). In this trial 30% of participants were older than 60 years, and 6% were older than 70 years. Balanced against this benefit was the risk of toxicities such as deep vein thrombosis, pulmonary embolism and endometrial cancer. New antiestdrogens (SERMs), such as raloxifen, could be attractive and may improve the risk to benefit ratio. NSABP P-2 (tamoxifen versus raloxifen) trial is underway.

Secondary prevention through the screening of asymptomatic women is the most established form of breast cancer prevention. Large randomized trials have shown that routine annual or biannual mammography in women aged 50-75 years is associated with reduction in breast cancer-related mortality of 25% to 30% within 5 to 6 years of initiation (5). Aging may affect screening results. The benefits of screening mammography are first seen three to seven years after initial mammography. Thus, screening mammography is not useful when life expectancy would be less than five years (6). At an older age, any specific screening strategies should become more individualized and based on life expectancy (i.e. the presence of comorbidity).

MANAGEMENT OF EARLY BREAST CANCER

Standard versus nonstandard treatment: Standard treatment of early breast cancer consider the integration of local and systemic treatment by use of curative surgery (radical mastectomy or quadrantectomy plus axillary lymph node dissection), radiotherapy and systemic therapy (hormonal or chemotherapy). Advanced aged is found to be a risk factor for under-treatment, even after control comorbidity, cognitive status, social support and functional status (7). Older women are less frequently treated by surgery (8) and also have less extensive surgical procedures and less adjuvant radiotherapy; as a result of under-treatment, a decrease of ten years disease-related survival was seen in older women compared with younger patients -32% versus 57% (10). Other authors have documented omission of adjuvant radiation after breast conservation and less breast-preserving procedures in older women (8,9).

The main factor affecting surgical morbidity in older women in not age but the presence of comorbidity (8,10). They tolerate breast surgery well, with only 1% to 2% of operative mortality. Even women aged 70 years and older prefer breast conserving surgery than mastectomy (11). Merchant and Solin find that standard treatment of breast cancer has similar outcomes in older and younger women (12,13), but the older women had more deaths from intercurrent disease (p<0.05).

The 1998 updated meta-analysis of adjuvant therapy (16) show the benefit of adjuvant tamoxifen therapy and adjuvant chemotherapy in improving relapse-free and overall survival in women with early breast cancer. Tamoxifen therapy offers marked benefit to women with estrogen receptor positive tumors, as did to women with unrecorded receptor status, as well as postmenopausal women including those older than age 70 years.

Compared with tamoxifen, less is known about the impact of adjuvant chemotherapy on disease-free and overall survival in elderly patients. In the Oxford overview, only approximately 600 women (3%) were aged 70 years and older (17), and this sample size was insufficient to determine the value of adjuvant chemotherapy in this age group. For patients aged 50-69 years, the mortality reduction translates into 2% and 3% net gains in 10-years survival. Anthracycline-containing regimens was associated with a small, but significant reduction in the risk of recurrence and with a marginal reduction in mortality compared with standard CMF chemotherapy. Non-anthracycline containing regimens might be preferable, because advanced age is associated with more pronounced doxorubicin-induced cardiomyopathy. Other possibility for older women might be the use of milder regimens as MF/L (metotrexat and 5-fluourouracil with leucovorin).

The availability of newer agents also poses a challenge for the adjuvant treatment of the elderly (capecitabin, docetaxel, paclitaxel, and trastuzumab). In elderly women two adjuvant trials with capecitabin are underway (capecitabin versus control and capecitabin versus FEC chemotherapy).

Nonstandard management. Tamoxifen as a first line treatment instead of surgery for operable breast cancer is therapy of choice in older patients who are unable to tolerate surgery or refused surgery. Despite high response rates of 30% to 60% most patients experienced relapse during tamoxifen therapy alone (more than 60%) requiring further local therapy-surgery or radiotherapy. Surgery results in better local control.

A recent meta-analysis of two large European trials (GREAT and CRC) evaluated the benefits of tamoxifen alone versus the combination of curative surgery with tamoxifen (14). These studies each randomized a total 466 and 447 patients, median age 76 years. After median five-year follow up, one study found that women 70 to 73 years of age had 33% reduction in risk of death following surgery plus tamoxifen compared with tamoxifen alone. But, women older than 73 years did not gain significantly in overall survival. These findings suggest that we can identify some frail patients who may not benefit from surgery.

Other non-standard combinations of tumor excisions, tamoxifen and radiation result in better local tumor control and may improve survival. Retrospective data of the use of tamoxifen alone after lumpectomy rise skepticism, because local recurrence rates may be higher without radiation (15).

The role of axillary lymph node dissection in older women is another field of controversy, because small retrospective reports suggested that this procedure might be avoided and replaced with sentinel node biopsy, which is associated with minimal morbidity and is helpful for assessing nodal status of patients.

MANAGEMENT OF METASTATIC BREAST CANCER

Metastatic breast cancer is incurable and requires systemic treatment. The treatment is palliative in nature and should be focused on maintaining the quality of life. Endocrine manipulation is the cornerstone of therapeutic strategy in metastatic breast cancer in elderly, because steroid receptors are positive in over 60% of cases. Response rate is directly correlated to hormone receptor status. If the status is unknown, a RR of 30-35% is observed, while ER+ has a response rate of 45-50% and ER+ and PR+ show rates of 55-60% (NIH Consensus 1980). In the event of unknown receptor status, it is adequate to start treatment with hormonal therapy if there are a long disease interval, non-visceral metastases in bone, lymph nodes or cutaneous metastases or response to prior endocrine therapy.

The specific activity of tamoxifen in elderly patients has been examined. An analysis of four prospective trials (n=396), suggest that among patients older the age 65 years tamoxifen was superior than in younger women in terms of time to progression and overall survival (18). In other study, tamoxifen yields higher RR (45% vs. 33%) and longer duration of response (10.4 vs. 7.9 months) when compared with CMF in patients older than then age of 65 years (19). In addition to tamoxifen, nonsteroidal or steroidal aromatase inhibitors, as well as megestrol acetate and medroxyprogesterone acetate (progestational agents) are available for therapeutic use.

In the absence of response to hormone therapy at any stage, chemotherapy is indicated, as well as in the presence of life-threatening metastases.

With few exceptions, chemotherapy use in the elderly should be little different from the use in younger patients. Conventional regimens appear to be active in the elderly as in younger patients. Case comparative studies (20) showed that women aged 70 years and older had response rates to multidrug chemotherapy similar to those for women aged 50-69 years and women younger than 50 years (RR: 29%, 31% and 40% respectively, p=0.53). Toxicity profiles of the standard chemotherapy regimens for metastatic breast cancer are similar in younger and older women who are in reasonable general health (20).

The recent introduction of trastuzumab (Herceptin) may be of interest for...
the elderly population, as this form of treatment appears fairly well tolerated.

Another anticancer agent - capecitabine (Xeloda) has been compared with CMF in women older than 55 years (median age 69 years). This study suggests that capecitabine is very effective (RR 25% versus 6%) and well tolerated (except hand and foot syndrome and diarrhea). Its oral formula facilitates administration (21).

The taxanes, both paclitaxel and docetaxel are also used in all groups without particular difficulties in the elderly.

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Chemotherapy of lung cancer in the elderly

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Lung cancer remains the leading cause of cancer-related death in Europe and North America. It causes 28% of all cancer death, more than breast, prostate, colorectal and ovarian cancers combined, upon to the American statistics (1). More than one half of patients with lung cancer are older than 60 years, and 30% are 70 years or older at diagnosis. Approximately 80% of all these patients belong to the non-small cell histologic subtypes. Large majority of these elderly patients, just like younger ones are diagnosed as advanced stage of disease, where curative therapeutic approach is not possible. These patients are candidates for palliative chemotherapy and/or radiotherapy.

The role of chemotherapy in the treatment of advanced non-small cell lung cancer (NSCLC) has been better defined in the meta-analysis from 1995 (2) and just published ESMO minimal clinical recommendation: cisplatin-based chemotherapy prolongs survival, improve quality of life and symptom control in metastatic NSCLC. Impact of chemotherapy (survival advantage of six weeks over best supportive care) in the different subgroups of patients is not clearly defined by the results of meta-analysis and other relevant papers. Are patients in advanced NSCLC and older than 65 years good candidates for chemotherapy?

Older patients have an increased prevalence of diseases and thus they often have multiple and, frequently, interacting diseases. Functional impairment and decreased performance status in elderly patients are the consequences of comorbidity rather than the cancer itself (3). The decreases in functional reserve and the increased comorbidity may make patient really old - in such situation, when general health status interfere with the management of cancer, patient older than 65 or 70 years are not candidates for chemotherapy. Having physiological rather than chronological age as an important criterion, two broad groups of patients 65 to 65 years old may be considered. The first group includes elderly patients requiring specialized care not dissimilar to that provided to younger patients and the second group includes the frail patients who are at high risk to develop life-threatening toxicity and require individualized treatment. As a result of above-mentioned considerations, in the clinical practice, elderly patients either do not receive chemotherapy or receive less aggressive treatments compared to younger ones.

For doctors who treat older NSCLC patients one of the great concerns is risk of early death (less than 30 days from the start of chemotherapy). In the

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Italian retrospective analysis carried out on a database of 1128 patients treated with cisplatin-containing regimens, the incidence of early deaths was found to be associated with age. It ranged from 0.5% in the patients with less than 55 years to 12.5% in older than 70 years, suggesting a possible relationship with chemotherapy toxicity, especially bone marrow suppression (4). On the other hand, prospective studies often include only very well performing patients (PS 0,1) without significant comorbidities. Results of such designed studies are usually encouraged, but at the expense of selection bias.

The recent development of several active antineoplastics for the treatment of NSCLC has created new possibilities for the management of this disease, free of cisplatin. Very few specific studies have been conducted to test the role of chemotherapy in elderly NSCLC patients. First, and most cited is ELVIS (The Elderly Lung cancer Vinorelbine Italian Study Group) study from 1999 (5), where patients were randomized to receive vinorelbine or best supportive care only, with primary end-point quality of life and survival as secondary end-point. It was planned 350 patients, but investigators stopped the recruitment after 160 patients because of the low enrollment rate. There was a statistically significant survival advantage for patients receiving vinorelbine (MST 28 vs. 21 week, 1-year survival 22% vs. 14%), and quality of life (QoL) scores (functional and cancer-related) were better, but not reaching statistical significance. Toxicity-related symptoms were reported to be worse in the vinorelbine group. To evaluate whether the addition of gemcitabine to vinorelbine improves survival and QoL in the same population Southern Italy Cooperative Oncology Group randomized patients older than 70 years to receive vinorelbine (V) or vinorelbine plus gemcitabine (V+G). On 120 evaluative patients difference in median survival was almost 3 months (29 vs. 18 weeks), and V+G therapy was also associated with a clear delay in symptoms and QoL deterioration (6). It was not easy for the authors to explain such survival gain. They found that the higher number of patients who did not progress in the first three months (50% vs. 30%) could be one of the explanations. They also stressed that the occurrence of toxic death in three patients with multiple unfavorable conditions at diagnosis suggests an exclusion of patients with high scores of comorbidity (Charlson score) irrespective of their performance status.

The role of taxanes in elderly population with advanced NSCLC is also under investigation in last few years: Hainsworth et al. reported (7) a phase II study with weekly docetaxel (36 mg/m²) on 39 patients older than 65 years. RR was 18%; median survival was 5 months and 1-year survival 27%. Fidias et al. presented (8) results of phase II study with weekly paclitaxel on 35 patients. RR was 18% and median survival 10.3 months. It seems that weekly administration of newer agents could increase dose intensity with acceptable toxicity, and it offers attractive options for the development of combination regimens.

In the retrospective analysis of prospectively conducted trials for advanced NSCLC from 1990 to 2000, at the Institute for oncology and radiology of Serbia 364 patients were treated with cisplatin-based chemotherapy (120mg/m²). Out of this number 54 patients were older than 65 years. RR was 18%; median survival was 5 months and 1-year survival 27%. Fidias et al. presented (8) results of phase II study with weekly paclitaxel on 35 patients. RR was 23% and median survival 10.3 months. It seems that weekly administration of newer agents could increase dose intensity with acceptable toxicity, and it offers attractive options for the development of combination regimens.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66-77</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 50, Female 44</td>
</tr>
<tr>
<td>Stage</td>
<td>IIIB 26, IV 58</td>
</tr>
<tr>
<td>Performance status</td>
<td>0-1 42</td>
</tr>
<tr>
<td>Total number of cycles</td>
<td>Median 103</td>
</tr>
</tbody>
</table>

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Grade</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>9</td>
<td>10</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>14</td>
<td>13</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood urea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. Toxicity

The enthusiasm for use of oral etoposide has been tempered after the results of two randomized British studies in the middle of 1990. MRC Lung Cancer Working Party (12) found on 339 patients in randomized study that combined chemotherapy (CAV or etoposide-vincristine) is superior over oral etoposide in terms of median survival (183 vs. 130 days) and toxicity. London Lung Cancer Group reported (13) similar results on 155 patients randomized to receive alternating CAV/PE or oral etoposide: RR (61 vs. 39%) and median survival (189 vs. 146 days) favored combined chemotherapy arm. WHO toxicity grade III and IV were uncommon in both arms. Evans et al (14) made a relatively successful compromise combining oral etoposide with carboplatin 150 mg/m² every three weeks: RR was 71%, median survival 59 weeks for limited disease and 46 weeks for extensive disease. They recorded 10 episodes of febrile neutropenia and 4 sepsis, all during the first course of chemotherapy, and grade 3/4 anemia in 75% of patients.

Considering particularly appropriate regimen for the initial treatment of elderly patients with SCLC, cisplatin-etoposide (PE) may be chosen, because it is less myelosuppressive than cyclophosphamide or doxorubicin-based regimen. Also, in the predictive models developed by Radford and Stephens (15,16), two drug regimens were associated with less severe toxicity and fewer septic deaths. Furthermore, the available data suggest that older patients tolerate cisplatin well although renal function decreases with advanced age. In circumstances in which preexisting renal dysfunction or neuropathy exists or aggressive hydration is problematic, carboplatin could be substituted for cisplatin without apparent loss of therapeutic efficacy.

In conclusion, all older advanced lung cancer patients with good performance status and without significant comorbidities and who desire treatment should be offered chemotherapy. No evidence so far exists to support the view that untreated patients live longer or have better quality of life.
REFERENCES


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Gastroenteroanastomosis (GEA): Method of choice in the advanced stomach cancer in older age

The incidence of locally advanced gastric cancer is increasing as the average life span is prolonging. Concomitant diseases in elderly patients often prevent radical surgery and/or treatment with chemotherapy. Thus, palliative surgery is a treatment of choice in this group of patients. The aim of the study was to investigate the outcome of these patients with high operative risk treated only with GEA at the Department of Abdominal Surgery. From 1994 to 1998 fifty-six patients were admitted at the Department because of gastric cancer. Seventeen patients were diagnosed with locally advanced stomach cancer and were treated with GEA. All of them were above the age of 65 and all of them had serious cardiovascular disease that was the contraindication for radical surgery. However, despite of this there were no postoperative complications in these patients. After median follow up of 3 years we noticed 14 out of 17 deaths. In none of them distant metastases were confirmed on the last examination. Furthermore, no one of them developed high gastrointestinal occlusion. The median survival of the whole group of 17 inoperable patients is 14 months (range 2.5 - 36 months). In conclusion, GEA is a safe and acceptable surgical procedure because it provides the chance for better quality of life of elder gastric cancer patients with no choice for cytoreductive surgery.

KEYWORDS: Stomach Neoplasms; Gastroenterostomy; Aged.
Adjuvant CMF and tamoxifen in the elderly breast cancer patients

During the period between 1997 and 2001, 18 elderly breast cancer patients were treated with adjuvant therapy (4 with CMF chemotherapy and 14 with tamoxifen) in the Oncology Dispensary in Loznica. Until 1998, modified four-day CMF regimen was used, and after that the regimen was changed to classical i.v. CMF. Median age of elderly patients, treated with chemotherapy, was 66.7. Chemotherapy was discontinued after 3rd cycle in a woman experiencing the moderate hematological toxicity. The remaining 3 patients tolerated well the adjuvant chemotherapy. In the same period, 14 elderly women were treated with adjuvant tamoxifen, 20 mg per day. Median age was 69.4 years. Disease relapse occurred in 4 women after 3.5 years on the average. After completion of adjuvant treatment, the in situ cancer of the uterine cervix developed in one of those patients. No other side effects were noted. In conclusion, both CMF chemotherapy and tamoxifen are safe and well-tolerated adjuvant therapies in operable elderly breast cancer patients.

Influence of age to the therapy and prognosis of the patients with breast cancer

Predictive and prognostic influence of age at the breast cancer patients is based on the fact that the most aggressive forms of disease are more common at the younger ones. On the other hand, aging is connected with accumulation of chronic diseases that can limit the application of some of the therapeutic procedures. We tried to explore age-dependent differences in the initial status, therapy and the further course of the disease at the 80 patients that were first-time treated at the Clinic of oncology in Kruševac during 1997. They were separated in three age categories of age (aged 50 years, aged 51 through 65 years, and older than 65 years). Most (36 patients - 45%) of them were in the middle-age group. In the oldest group (17 patients - 21%) metastatic and unresectable stadiums of disease were almost twice infrequent than in case (12:19-22%) of younger groups. All patients with limited disease were operated curatively, so the age should not be considered as a limited factor to surgery. From the medical, but also psychological and other reasons, breast-conserving proceedings were double frequently (26:13%) applied in the patients younger than 50 years than in the others. Treatment was terminated with operation (and possibly irradiation) in 7% of youngest, 14% of middle-aged and 24% of oldest patients. Adjuvant medical treatment of the youngest patients is the most aggressive, therefore it is based on the chemotherapy (71%) with anthracyclines (60%) and followed (41%) with hormonotherapy which is the most common mode (65%) of the treatment of patients older than 65 years. At the middle-age group chemo- and hormonotherapy are approximately equally (61%; 72%) represented, and the doxorubicin was implemented rarely (33%). Relapse was observed double more frequently (19%;9%) and 9 (14.8:23.7) months earlier in patients older than 50 years than in younger patients. This indicates possible induration of the disease in older women aged 51 to 65 years, respectively. For 36% patients from this group (and less then 20% from others) the overall duration of disease was less then 5 years.
Malignant diseases of the large bowel are among the most frequent cancers in both sexes. In addition to local, regional and distant extension of the disease, as more important ones, there are plenty of other indicators of the biological aggressiveness of the tumor and the patient's vitality that can influence to the further course and overall survival. Entire treatment, particularly surgical, is often strenuous, so it can be applied only to the persons with preserved health condition which can be compromised with concomitant diseases as an unavoidable companions of aging. We tried to explore age-depended differences in the initial status, therapy and the further course of the disease at the 60 patients with colorectal cancer who were first-time treated at the Clinic of oncology in Krusevac from 1994 to 1997. They were divided in three categories of age (aged 50 years, aged 51 through 65 years, and older then 65 years). The limited disease was most frequently (69.54-56%) found in the middle-aged persons; the majority (28%) of unresectable cancers was diagnosed in the oldest, and metastatic (46%) in the youngest patients. Primary tumor was completely eliminated in the half of the oldest and more than three fourths (77%-83%) of other patients. It means that resection was applied in case the every second younger patient with metastatic disease, but not on any patient older then 65 years in the same group. This conspicuous difference is probably consequence of the poor general condition and expected outcome in case of the majority of oldest patients. Adjuvant or systemic chemotherapy as a postoperative treatment was applied only to the (40%) patients younger then 65. In the group of curatively operated, relapse was most frequently (70%-55%) observed in the oldest (perhaps under-treated) patients. This fact has a repercussion to the differences in overall survival, that is 9 (22:31) months shorter for oldest group respectively to others. In disease-free period (23:25 months) and the duration of disease after relapse (14:12 months) there were no bigger differences.

**Age as prognostic factor in the patients with colorectal cancer**

**KEYWORDS:** Colorectal Neoplasms; Age factors; Prognosis; Treatment Outcome

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Although breast cancer incidence increase with age quantitative data are lacking on treatment practice and tumor characteristics in the elderly. Our aim was to determinate the local and systemic treatment for early breast cancer in women 70 years and older. From 1999 to 2001, the medical records of women aged 70 years and older diagnosed with non-metastatic breast cancer were retrospectively reviewed at the Clinical Center of Montenegro, Clinic for Oncology. A total of 625 medical records were reviewed, 104 patients older than 70 years and complete records were analyzed. Study population age ranged from 70 to 87 years, median age of 73.53 years. Of the 72 patient records with complete staging data 18% have T1N0, 41.6% T2N0, 29.1% T3 or T4 and 13.88 % N1 status. Histologic diagnosis included 75.4% ductal carcinoma, 13.7% lobular carcinoma, 5.45% tubular carcinoma and the remaining are combination of histological features. The majority of nuclear gradus is grade I (51.4%), histological gradus II is most frequent (65.2%) in this group of patients. The breast preservation procedures were performed in 52.85% patients, and the whole group received postoperative radiotherapy. Chemotherapy as adjuvant was given to 17.3% patients (5% in literature) endocrine treatment to 78%, and combination of these two therapeutic modalities was given to 13.4% of patients. A significant proportion of breast cancer patients, aged 70 years and older, did not receive standard local and systemic treatment. This is related to comorbidity, functional status and some problems in support.

**Breast cancer characteristics and treatment in women aged over 70 years**

**KEYWORDS:** Breast Neoplasms + therapy; Aged

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Lung cancer therapy treatments in the elderly

Lung cancer is one of the most frequent malignant diseases. Every third person that died of the malignant disease was treated of lung cancer too. It is predominantly a disease of the elderly. The main aim of this report is to estimate the percentage of the elderly in the whole number of patients with lung cancer, to determine the type of a treatment, and to predict the outcome according to the following: the age, socioeconomic background, tumor histopathology, and histological gradus. From 1995 through 1999, 69 lung cancer patients were treated at the Oncology and Pulmonary Departments, Medical Center in Gornji Milanovac. In the main group were the patients older than 60 years (34); in the control group were all the others (35). The average age of the patients in the main group was 66.8 and in the control group 51.3 years. Statistical difference was found after the analysis of the social status and educational level of the patients. Histopathology and histological gradus of tumor were similar. Both groups were treated by multimodal methods. Statistical difference was verified since in the main group chemotherapy was most frequent method of choice. Comparing the appearance of relapse to the appearance of metastasis, a statistical difference was found. The methods of choice and final results were similar. Lung cancer is the most common cause of cancer-related deaths among both men and women. It usually appears in the elderly from lower social class. At the time of diagnosis the cancer is frequently in advanced stage so the multimodal treatment with chemotherapy is used. Although lung cancer may be curable if detected early, most cases are fatal.

Transcutaneous radiotherapy as a single treatment modality in older patients with uterine cancers

Standard treatment of inoperable malignant uterine tumors connotes combined application of transcutaneous and intracavitary radiotherapy. Total irradiation dose and the percental involvement of these application modalities depend on the disease stage, tumor size, patient age, concurrent diseases etc. The aim of was to establish the frequency of use and role of transcutaneous radiotherapy as a single modality for inoperable uterine malignancies in older patients. At the Clinic of Oncology in Knez Selo from 1993 to 2001 transcutaneous radiotherapy of women over 65 years of age as a single modality for inoperable malignant uterine tumor treatment (FIGO, IIB, IIIA, IIIB, IVA and IVB) was used for 20 patients - in 14 patients for cervical and in 6 patients for corpus uteri tumors. Median age of the patients was 73 years for both groups (65-83 years), with the average pelvic dose of 48.6 Gy in 24 sessions. Transcutaneous radiotherapy for uterine cancers can be applied as a single modality with a palliative or curative intention. For intracervical tumors and when brachytherapy is not possible, after 40 - 45 Gy to the pelvis, a dose to the tumor site may be applied with small and oblique portals to the total dose of over 70 Gy (without technical possibilities in our institution). Based on the literature data and our own experience we believe that single transcutaneous radiotherapy for inoperable uterine tumors in older women should be individualized and selective. As a necessity, it should be applied for shorter life expectancy (due to disease seriousness or age) and as a must in case of technical impossibility to administer brachytherapy or in case of serious concurrent diseases.
Breast cancer morbidity in elderly patients treated at the outpatient department - Šabac

The aim of this report was to list characteristics of breast cancer morbidity among patients older than 65 years, treated at our department from 1996 to 2000. Searching medical records, we found that 63 out of 231 breast cancer patients were older than 65 years, with female: male ratio - 60:3. We searched next parameters: resectability, tumor size (T), histology, histological grade (HG), nodal status (N), treatment modality, disease free survival (DFS) and overall survival (OSS). The median age was 71 years (range, 65-89 years). Thirty-two patients had resectable disease, 23 non-resectable and 8 metastatic disease. We recorded 9 patients with T1, 16 with T2, 7 with T3, 18 with T4, and 13 patients without data about tumor size. Forty-six patients had carcinoma ductal invasivum, 2 had -carcinoma lobulare invasivum, 3 had carcinoma medullare, one patient had carcinoma mucinosum, 2 had carcinoma papillare, and 9 patients without definitive histology. Considering HG, 1 patient had HG1, 23 patients - HG2, 2 patients - HG3, and 12 patients had no data. Fourteen out 32 patients with resectable disease did not have nodal involvement, 12 patients had N1, and 6 patients had N2. Among patients with non-resectable disease, 3 did not have nodal involvement, 2 patients had N1, 7 patients - N2, and 7 patients were without data. The median DFI of 10 months was found in 8 patients (range, 6-63 months). Among patients with resectable disease, in 6 patients the median OSS was 36 months (range, 8-58 months), and 26 patients are still alive with OSS ranged between 39-100 months. Among patients with non-resectable disease, 3 did not have nodal involvement, 2 patients had N1, 7 patients - N2, and 7 patients were without data. The median DFI of 10 months was found in 8 patients (range, 6-63 months). Among patients with resectable disease, in 6 patients the median OSS was 36 months (range, 8-58 months), and 26 patients are still alive with OSS ranged between 39-100 months. Among patients with non-resectable disease, in 10 patients the median OSS was 12 months (range, 2-62 months) and 13 patients are still alive with median OSS of 43 months (range, 21-78 months). Forty-two patients were treated with hormonotherapy and 9 with combined treatment - hormonal plus chemotherapy (particularly CMF regimen). Treatment was well tolerated in majority of patients without significant toxicity, except in one patient when chemotherapy had to be interrupted due to severe diarrhea. Approximately one third of breast cancer patients treated at our department were older than 65 years. Based on provided tumor characteristics we may point out the indolent course disease in this study population. Treatment was tolerable with mild toxicity.

High dose rate intraluminal brachytherapy in the treatment of malignant airway obstructions in elderly patients: Preliminary results of single institution experience

Endobronchial brachytherapy has been increasingly used in an effort to improve local control and relieve symptoms of malignant airway obstructions. It has become an established treatment for major airway occlusion by inoperable carcinoma of the bronchus. Only limited objective data on its effect in elderly patients are available. Forty-four patients received HDR intraluminal brachytherapy, some of them in combination with teleradiotherapy. Three patients were lost of evidence and 14 did not finished treatment. The aim was to analyze preliminary results and acute complications in the group of 27 evaluable patients, 12 of them were 65 years old (group A) and 15 patients under 65 years of age (group B). Symptomatic improvement was achieved in 9 of 12 patients in group A, and 10 of 15 patients in group B. Objective bronchoscopic response (CR and PR) was seen in 10 of 12 patients in group A and 12 of 15 patients in group B. We observed 17 acute complications mostly in group B: 9 acute esophagitis grade 1-3, 7 acute bronchitis grade 1-3, and 2 hemorrhages from tumor, grade 1-2. Brachytherapy is an effective palliative treatment of malignant airway stenosis, but the effect on survival is not apparent, with satisfied tolerance in elderly patients with accepted rate of acute complications.
Oncology treatment of elderly breast cancer patients: Systemic CMF and tamoxifen treatment

Keywords: Breast Neoplasms; Tamoxifen; Antineoplastic Combined Chemotherapy

From 1997 to 2001, 31 elderly breast cancer patients (≥65) with advanced disease were treated in the Oncology Center in Loznica. Fourteen women were treated with systemic CMF chemotherapy in this five-year period. Their median age was 67.1. Therapeutic response (disease regression) was obtained in 2 women after 6 cycles, but chemotherapy was stopped in one of them due to very poor subjective tolerance. Disease progression was seen in 6 women after 2.3 cycle on the average. Short-term stabilization was achieved in 6 women after 5.5 cycles on the average. From 1-9 cycles were applied per patient. Hematological toxicity grade ≥1 was seen in 3 women (anemia grade II-III; leukopenia grade I). Systemic tamoxifen, 20 mg daily, was applied in 17 women in the same period. Disease progression was noticed in 11 women after 6.3 months on the average. Six women were without signs of progression, after 2.7 years on the average. In conclusion: Both systemic Tamoxifen and CMF chemotherapy are well-tolerated routine systemic treatment regimens in elderly advanced breast cancer patients.

Treatment of rectal cancer with combined external and endocavitary radiation in 80 years old female patient who refused surgical treatment: A case report

Keywords: Rectal Neoplasms; Radiotherapy; Aged

Seventy percent of patients with colorectal are 65 years or older. As elderly patients frequently exhibit adverse physical or socioeconomic conditions, an through geriatric assessment of the patient's suitability for therapy is essential before making a decision. Endocavitary radiation therapy constitutes an alternative to surgical therapy for some early rectal carcinomas. But the indications were extended to elderly patients who presented with a high surgical risk or who refused mutilating surgery. Case report: We treated 80 years old female patient who refused surgical treatment, with combined external and endocavitary radiation. She had low-grade adenocarcinoma of rectal cancer, at 3 cm from the anal verge. External radiation (30 Gy) was given during two and a half weeks followed by endocavitary radiation 500 Gy per fraction, per week. Six weeks after this palliative treatment she had partial regression of tumor, gained about 2 kg in weight, and had not any subjective symptom of disease or radiation toxicity. So, we decided to continue our treatment to radical dose. After palliative dose we achieved partial regression without severe radiation toxicity. Combined radiotherapy can be used to treat rectal cancer in elderly patients who refuse surgical treatment. Major advantage of this treatment is low risk of serious complications.
Radical radiotherapy for localized carcinoma of the prostate in elderly patients

KEYWORDS: Prostatic Neoplasms; Radiotherapy; Aged

Adenocarcinoma of the prostate is one of the most common tumors, which is predominantly found in elderly men and is becoming increasingly important as life expectancy rises. Careful examination of autopsy specimens demonstrates that approximately 40 to 50 percent of men over the age of 70 harbor a prostatic malignancy. However, only a third of diagnosed patients died due to the condition, and mortality is usually for other causes in the elderly patients.

Treatment modality for clinically localized carcinoma of the prostate is surgery, radiotherapy, hormonal therapy or a combination of these. Optimal management is especially important in the elderly to weight the potential benefits against the expected morbidity associated with any treatment. Radiotherapy as definitive treatment is commonly reserved for older patients and patients with high surgical risk, and is widely used as a treatment of choice. The aim of this study was to determine the role of radical radiotherapy for localized prostate carcinoma in elderly patients (>70 years) concerning local disease control, disease-free survival, and overall survival.

In the Institute for Oncology and Radiology of Serbia, from January 1991 to December 2001, a clinical prospective non-randomized study of 68 elderly patients with localized carcinoma of the prostate was performed. Patient's characteristics are presented in Table 1.

Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th>Total</th>
<th>68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years range)</td>
<td>73.93 (70-80)</td>
</tr>
<tr>
<td>Stage (by AJCC)</td>
<td>A (3.4%) B (46.7%) C (19.7%)</td>
</tr>
<tr>
<td>Pathology</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Grade</td>
<td>I (28.4%) II (24.5%) III (16.3%)</td>
</tr>
<tr>
<td>Initial PSA value (ng/ml)</td>
<td>Mean 18.8 ng/ml Range (139-100 ng/ml)</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>16 (26.5%)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>34 (50%)</td>
</tr>
</tbody>
</table>

Radiotherapy was administered continuously in all patients, due to the low-grade complications, which were treated with symptomatic therapy. Sixty patients (88.2%) achieved initial complete response, 7 (103%) developed partial response and 1 patient (1.5%) had stable disease. Mean follow-up time was 44.88 months (range, 12-117 months).

The disease outcome at the last follow-up show that 52 patients (76.5%) had no evidence of disease; 16 patients (23.5%) relapsed. The bones were the most frequent sites of relapse (11 patients) and biochemical relapse was detected only in 6 patients. Seven patients died due to cancer and 4 patients died from intercurrent disease.

Overall survival rates were 67.49% and 57.11% and disease-free survival rates were 65.75% and 59.77% at 5 and 10 years. Disease-specific survival at 5 and 10 years was 71.55% and 65.59%, respectively.

Late sequelae (gradus I and II) were noted in 17 patients (25%): skin fibrosis in 12 patients, urethral stricture in 2 patients, and proctitis in 3 patients.

Studies of many authors have shown that external beam irradiation is non invasive and very well tolerated, despite of age, with good local control (1-4). Our results relating disease outcome and treatment are in accordance with literature data. Reversible acute effects in Stanford study, proctitis registered in 8% of patients and cystitis in 14%, make no difference to the same acute complications in our study (1).

Arcangeli et al. found at 5 and 10 years overall survival of 70% and 50% in 199 patients and mean age of 69 years (2). The pattern of Care study and the series of the Fox Chase center in Philadelphia show that treatment results of patients aged 70+ years are similar to those registered in younger patients (3).

Late sequelae reported in TOG study, urethral stricture in 4.6% of patients and rectal complications in 1.7%, are very similar to our results (4).

In conclusion, external beam radiotherapy is generally well tolerated by the elderly patients. There was no any increased incidence of acute or long-term toxicity compared to younger patients. The treatment results were satisfactory.
REFERENCES


Aging is associated with an increasing prevalence of diseases and disabilities. In older cancer patients, comorbidity can have a major influence on survival and can enhance the risk of treatment complications. Moreover, the prognostic impact of the disease may be different according to its severity. A few validated scales exist for the assessment of comorbidity in the elderly cancer patients, such as the Charlson and the Cumulative Illness Rating Scale - Geriatric (CIRS-G). We chose to test prospectively the correlation between Charlson's scale and CIRS-G with quality of life (QoL) in an oncogeriatric inpatient setting. These scales represent two different approaches to comorbidity. The Charlson scale is restrictive and focused on a short list of selected 19 diseases weighted from 1-6 points. The CIRS-G is aimed at comprehensiveness and classifies comorbidity into 14 organ systems grading each condition from 0-4. The QoL was assessed using the Rotterdam Symptom Checklist that was scheduled at baseline (on the initiation of therapy) and subsequently at weeks 8, 16 and every 8 weeks thereafter until disease progression, intolerable toxicity or patient refusal to complete more questionnaires. According to study design, a next step will be to perform a Comprehensive Geriatric Assessment with particular regard to patients as it is proposed in provided algorithm. To date, a total of 21 patients' median age 69 (range, 65-74 years), all with ECOG performance status 0 and 1, 19 with solid tumors and 2 with hematological malignancies have been entered into the study. Among those 21 patients following comorbidities were observed: hypertension (14 patients), heart failure without congestion (7 patients), chronic pulmonary disease (4 patients), ulcer disease (3 patients), diabetes (3 patients), kidney disease (2 patients) and secondary non-metastatic cancer (2 patients). Comorbidities were mainly mild or moderate. In addition, 12 patients had multiple comorbidity condition. The number of included patients still insufficient to detect which of two scale for measuring of comorbidity better correlate with QoL and does severity of comorbidities may presume more changes in that end-point. Data evaluation is ongoing and the final results will be published when a number of included patients will content statistical consideration of the study.

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Correlation between comorbidity and quality of life in the elderly cancer patients treated with chemotherapy: An ongoing study

KEYWORDS: Neoplasms; Comorbidity; Aged; Quality of Life
Tamoxifen (TAM) is standard adjuvant therapy in steroid receptor-positive (SR+) breast cancer patients. It is well known that the effect of TAM is better in older women and in those with longer duration of menopause. The aim of this study was to analyze relapse rate in postmenopausal breast cancer patients treated with adjuvant TAM therapy in respect to age, menopausal duration and SR content. The analysis included 111 postmenopausal women with early breast cancer, with ER+ and/or PR+ status, who were mastectomized, treated with adjuvant TAM alone (2-5 years), with or without post-operative RT, in the Institute of Oncology and Radiology of Serbia. All of patients were postmenopausal, aged 47-78 years, and 10 patients were ≥70 years. Metastatic disease had been registered in 26 patients (23%). No difference was observed in relapse rates between younger (<60, n= 47) and older group of patients (≥60, n=64). In respect to menopausal duration (<5 vs. 5-9 vs. ≥10 years), patients with menopause ≥10 years had significantly lower relapse rate than the other two groups. There were no differences between rates of relapse according to SR content, either in the ER, or in the PR level. These results confirmed data that effectiveness of TAM is better in older patients with longer menopause.

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Adjuvant tamoxifen therapy in older patients with operable breast cancer

KEYWORDS: Breast Neoplasms; Tamoxifen; Aged


"Lost time" in the treatment of breast cancer

It is observed that older women come for the first clinical visit in the advanced stage of breast cancer. The purpose of this study was to estimate the influence of time between the onset of symptoms and the first clinical visit and the time between the first clinical visit and the beginning of treatment, on the clinical stage of the disease (CS) and on "disease-free" survival period (DFS). Sixty patients were included in the study, average age of 71.2 (range 65-84). They were treated in our department from 1994 to 2001. Median of the follow up period was 47 months. When the diagnosis was established 35% (21/60) of patients had CS-II while 65% (39/60) of patients had CS-III. The average "lost time" period between the onset of symptoms and first clinical visit for CS-II was 6.1 month and for CS-III was 32.1 month. Average time between first clinical visit and the beginning of treatment was 1.1 month. General survival for the whole group was 25% while "disease free" survival was 18.3%. Survival for patients with CS-II and CS-III was 43% and 18%, while DFS was 23.6% and 15.3%, respectively. Median for the first relapse for the whole group was 21.5 months, for CS-II group 35 months and 6 months for CS-III group. Patient survival difference between CS-II and CS-III group was highly significant (p<0.01) and showed that "lost time" had marked influence on CS and survival period. Older age may be associated with decreased motivation for treatment and may represent a bad prognostic indicator in the treatment of breast cancer.

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"Lost time" in the treatment of breast cancer

KEYWORDS: Breast Neoplasms; Time Factors; Aged
CHOP vs. BOCAD in elderly patients with diffuse large cell lymphoma (DLCL): Preliminary results

Keywords: Lymphoma, Large-Cell, Diffuse; Aged

Standard first line therapy for elderly patients (over 65 years) with DLCL is CHOP or CHOP alike, anthracycline-containing regimens. Due to cardiac comorbidity and absence of a confident tool for prediction of anthracycline-induced cardiac toxicity (early as well as late) there is a need for safer and more effective chemotherapy regimens. This interim phase II study is a single center experience with a non-anthracycline regimen compared with CHOP regimen. Over past 3 years 24 patients with DLCL in advanced stages, aged over 65 years, were randomized to receive either standard CHOP regimen or BOCAD (Bleomycin 15 mg day 1, Oncovin 2 mg day 1, Actinomycin D 1 days 2 and 4, Deticene 200 mg days 3 and 5, Pronison day 2-7, CCNU 40 mg) in four-week period. Eleven patients were included in the CHOP group with median age 69 years (range, 67-79 years) in stage II and higher, 4 patients with bulky disease and 3 in clinical stage IV; 2 with performance status 2, four of them with one comorbid disease. Thirteen patients were included in BOCAD group of median age 75 years (range, 67-81 years) in stage IIIA and higher, 4 with bulky disease and 6 in clinical stage IV, with 5 patients in performance status 2, nine of them with one or more comorbid disease. In CHOP group RR was 65% (4 CR + 2 PR) with time to progression (TTP) 16 months (4 still alive), in the BOCAD group RR was 33% (2 CR + 1 PR) with TTP 3 months (1 still alive). Proportion test didn't show statistically significant difference in RR, but significant difference between TTP in two group (P=0.02) by Kaplan-Meier test. Proportion test showed statistically significant difference (P=0.04) for RR in the BOCAD group between group of patients with comorbidity and without comorbidity. In the CHOP group there is no statistical differences between patients with comorbidity and without comorbidity. Differences in PS did not show any statistically significant difference in RR and TTP. Our preliminary results showed that comorbidity might influence therapeutic response. Regarding comparison of efficacy between two groups, further investigation is needed.

Influence of some breast cancer prognostic factors in older women

Keywords: Breast Neoplasms; Prognosis; Aged; Women

Breast cancer treatment selection and prognosis of breast cancer patients are influenced by various parameters. This study investigates the effects of some diagnostic and prognostic factors on breast cancer occurrence and treatment in older patients. A retrospective study of 741 women treated for breast cancer at the Clinic of Oncology from 1996 to 1997 was performed. Following prognostic factors were analyzed: disease stage, number of involved nodes, presence of bilateral disease, hormonal receptor values. Their influence on the frequency of local relapse, metastases and survival in 235 patients aged over 65 years was also evaluated. The results were compared to the findings obtained for the group of patients below 65 years. Comparisons of those aged over and below 65 years did not reveal any significant difference in histological analyses. Earlier disease stages were more frequent in those over 65 years (stage I, tumor <2cm, negative nodes), as well as lower tumor grades (I or II) and estrogen/progesteron positive receptor tumors. Synchronous or metachronous bilateral cancers were markedly more frequent in those over 65 years (10.2%) compared to younger patients (4.3%). The period to progression and survival were longer in patients over 65 years. Our analysis demonstrated that more favorable types and lower tumor grades were more frequent in breast cancer patients over 65 years of age which account for better disease outcomes compared to those below 65 years. The comparison of same histopathologic tumor types and grades in different age groups did not demonstrate any significant difference in metastasizing and survival. It may be concluded that the prognosis and treatment of female breast cancer should be based primarily on disease stage and histology/biology of the tumor and that the patient age is less important.
Capecitabine in the treatment of metastatic colorectal cancer in elderly patients

The study was designed to evaluate efficacy and toxicity of oral capecitabine in the treatment of metastatic colorectal cancer in elderly patients. A total of 17 patients with colorectal cancer (14 colon and 3 rectum) were included in the study (14 men and 3 women); median age was 73 years (range, 65-81 years). Since all the patients were presented with advance disease (liver metastases in 11 patients - confirmed by US and/or CT, lung metastases in 2 patients - confirmed by RTG and/or CT, liver and lung metastases in 3 patients and subcutaneous metastases in 1 patient). No prior chemotherapy was administered. All the patients received systemic chemotherapy with capecitabine 2500 mg/m² per os day 1-14, every 3 weeks. A total of 78 cycles of chemotherapy were delivered (range, 3-9 cycles), with average 6 cycles. Complete response was achieved in 1 patient (5.8%). Partial response in 6 (35.3%), stable disease in 4 (25.3%), and in additional 6 patients (35.3%) progression of disease after the third cycle of chemotherapy was observed. “Hand and foot” syndrome grade I was observed during 18/78 (23.1%) cycles in 4 patients grade II during 1/78 (1.3%) cycles in 1 patient and grade III during 11/78 (14.1%) cycles of chemotherapy in 3 patients. Diarrhea grade I was registered during 6/78 (1.3%) cycles in 1 patient and grade II during 10/78 (12.8%) cycles of chemotherapy in 2 patients. There was no evidence of presence of other toxicity effects of this chemotherapy regimen in our group of patients. Four patients are still in follow up and 13 died with median survival of 8.8 months (range, 3-16 months). We may conclude that therapeutic efficacy is in accordance with literature data. Also, the toxicity of this chemotherapy regimen was acceptable and we have no cessation of therapy for that reason.

Localisation, clinical and pathological characteristics of the colon cancer patients aged up to 40 years and over 65 years

Colorectal cancer is predominantly a disease of older population, but occasionally it appears in the younger patients, in whom very often diagnosis is overseen and the treatment begins late. Considering former results in detection and treatment of the colorectal cancer, we have decided to analyze clinical and pathological characteristics and localization of the colorectal cancer in patients aged up to 40 years and over 65 years. The group of 9 patients under 40 years was analyzed from 1997 to 2001. Patients with family genetic and the inflammatory diseases of colon were not included. Another group included 28 patients aged over 65 years with the colorectal cancer, treated at Institute for Oncology and Radiology of Serbia at the same time as the previous group. Arithmetic mean, standard deviation, Fisher’s test, Student t test were used in the statistical processing. There was no difference among the tested groups regarding localization of the malignant tumor. The most frequent localization was on the rectum and the left half of the colon. At diagnosis in the group of patients under 40 years of age, besides the metastatic process in the liver and lymph nodes, colorectal cancer infiltrated also in duodenum, stomach, right kidney capsule in one patient and in adnexa in two patients. In the patients over 65 years of age only liver metastases were noticed. When analyzing the tumor histopathological forms in both groups of patients, we found that invasive cancer type was predominant. Tubular and mucinous forms were present in patients up to 40 years of age, while only one patient over 65 years had tumor with mucinous component. Analyzing patients by Duke’s disease stage, the following results were obtained: in the group of patients up to 40 years, stages were as follows: Dukes B 1.5%, Dukes C 72.5% and Dukes D 26%, while in the group of patients over 65 the staging was as follows: Dukes B 1.5%, Dukes C 84.5% and Dukes D 14%. When compared the tumor grade we found that incidence of III grade was 36.8% in the patients up to 40 years, in relation to 17.8 diseased in the group of patients over 65 years of age. Five-year survival in the group of patients up to 40 years was 57%, while 30% of patients over 65 years of age survived 5 years. Obtained results show that there is no difference in the clinical symptomatology and the tumor localization in the both groups of patients. Incidence of the aggressive tumors was greater in younger persons and it did not influence 5-year survival and with early detection and more aggressive treatment approach, besides surgery, radiotherapy and chemotherapy, it enables significant improvement of the former survival.