Undertreatment or overtreatment – how far from each other in geriatric oncology?

Niedoleczenie czy nadmierne leczenie – jak daleko jedno od drugiego w onkologii geriatrycznej?

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KEY WORDS:

- cancer
- elderly
- aged
- mortality
- incidence
- survival
- healthcare burden
- undertreatment
- overtreatment

ABSTRACT

The mortality due to cancers of older patients, in age above 65 years of life, in comparison to younger is higher in majority of these diseases. It has been also reported that seniors are frequently denied the treatment according to current standards of therapy, thus suffer from undertreatment. There is solid evidence from controlled trials that older patients may tolerate pharmacological therapies in some cancers as well as young, providing they are under good supportive care. At the same time aggressive multimodal treatment may cause immediate or delayed side effects and exhaustion of reserves of the vital organs in elderly. This may cause a general deterioration, a decompensation of comorbidities, an evolution of geriatric syndromes and premature death, not directly caused by cancer. Such situation in aged cancer patients should be called the overtreatment. In diseases with better prognosis, with effective screening methods and large choice of treatment options like breast cancer, survival is getting better, although not in the eldest. The worse prognosis in old breast cancer patients may be caused to some extent by undertreatment. More fatal tumors like NSCLC await further optimization of cancer therapy towards better toxicity profile to avoid overtreatment.

SŁOWA KLUCZOWE:

- choroby nowotworowe
- rak
- starsi
- umieralność
- zapadalność
- przeżycie
- obciążenie chorobą systemu opieki zdrowotnej
- niedoleczenie
- nadmierne leczenie

STRESZCZENIE

Umieralność osób starszych, w wieku powyżej 65 roku życia, z powodu chorób nowotworowych jest wyższa niż u młodszych w większości przypadków. Istnieją doniesienia, że u seniorów nie stosuje się leczenia zgodnie z aktualnymi standardami, czyli są oni ofiarami niedoleczenia. Wiele silnych dowodów z badań kontrolowanych przemawia za tym, że starsi pacjenci mogą tolerować leczenie farmakologiczne w niektórych przypadkach tak samo jak pacjenci młodsi, pod warunkiem, że są oni otoczeni dobrą opieką wspomagającą. Z drugiej jednak strony, wielokierunkowe, agresywne leczenie skojarzone może spowodować natychmiastowe, bądź opóźnione efekty uboczne i wyczerpanie u osób starszych rezerw narządów istotnych dla życia. Następuje pogorszenie ogólnego stanu sprawności, zdekompensowanie się chorób współistniejących, rozwinięcie się zespołów geriatrycznych i przedwczesną śmierć, niekoniecznie w wyniku postępu choroby nowotworowej. W takich sytuacjach mówi się o nadmiernym leczeniu. W przypadku chorób o lepszym rokowaniu, w przypadku których istnieją efektywne metody badań przesiewowych i duży wybór metod leczniczych, przeżycie całkowite poprawia się, aczkolwiek nie u najstarszych pacjentek. Ich gorsze rokowanie może być spowodowane w pewnym stopniu przez niedostateczne leczenie. Nowotwory bardziej śmiertelne, jak niedrobnokomórkowy rak płuca, oczekują na dalszą optymalizację leczenia, z uwzględnieniem działań niepożądanych tak, aby uniknąć zbędnego nadmiernego leczenia.

Epidemiology

Cancer incidence culminates in younger age groups although deaths rise linearly in association with age in Poland. Mortality Incidence Ratio (MIR) is generally used as a high-level comparative measure to identify inequities in cancer outcomes. MIR is a cruder estimate but much easier measurable than 5- or 10-years survival. It relies on deaths number and new cases of diseases and these data are quite well accessible in the national registry (1). MIR for invariably fatal neoplasms, like central nervous system tumours, is comparable among age groups. However, other mostly fatal diseases like the pancreatic cancer and the lung cancer tend to be more severe in aged patients. This trend

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is even more evident in diseases prognostically more favorable like colon, prostate or breast cancers (Fig. 1) (2). MIR greater than 1 would indicate that more people died from a particular cancer rather than were diagnosed in a given year. In fact, while comparing periods distant recently a decade, the epidemiological situation of elderly suffering from central nervous system tumors has worsened. Whilst MIR in the period 2012-2016 is lower for some younger age groups, it is admittedly higher in older patients, comparing to the period of 2000-2004. Here, the crude mortality and incidence rates ratios are presented (Fig. 2) (2). There are no new environmental exposures that influence the incidence and it is stable or even lower comparing analyzed periods, especially in the eldest – 85+. The increase in MIR in older age groups results from the rising mortality (Fig. 3) (2). It is frustrating after the decade of development in standards of treatment of central nervous system tumors and fund rising in national healthcare system. On the opposite, the MIRs of breast cancer have a tendency to decrease over the time. Nonetheless, there is no such trend only in eldest group of age (85+) and, strikingly, in young girls 15-19 years old (Fig. 4) (2). This young age group is not offered the screening since the risk of cancer development is very low. The downward trend in MIR between periods compared depends mainly on the rise in incidence. Again, there is no change in environmental exposures that could explain this growth, except growing risk related to obesity. Notwithstanding, there is a huge spring in the breast cancer incidence in age groups 60-64 and 65-69. Luckily it does not translate to comparable rise in the mortality (Fig. 5) (2). The incidence growth may be attributed to growing prevalence of screening in this group where accumulation of life-risk is significant. Mammography detects early invasive cancer, thus raising the incidence but also increasing the chance for cure, so decreasing mortality. It is not the case in older age groups. One reason for that is that older women are not offered the screening mammography, so their disease is detected by clinical signs, in a higher clinical stage. This raises the incidence of treatment failure. Secondly, older women may be undertreated. We have recently analyzed utilization of cancer treatment procedures in the whole breast cancer population in Poland as registered by National Health Fund. We have found some significant but slight differences in healthcare burden imposed by both populations. However, we have noted 37% difference in MIR between age groups below and above 65 years. Underutilization of treatment modalities seems not to be a major cause of higher mortality of older patients (3). It is not a case for central nervous system tumors. Here, the underutilization of medical procedures in age group above 65 years of life differs tremendously from younger (data not shown).

Since the end-of-life care imposes the highest burden on healthcare, measures should be taken to decrease mortality through adequate prophylaxis, optimal treatment and supportive care in the elderly. Most frequent cancers are treated with standardized sequence of therapy modalities. The standards proposed by international bodies are recognized in Poland. In perplexity, standards of management in elderly are scarce due to inability to aggregate level 1 evidence. Individual approach is stained with hesitation and based on extrapolation from studies pertaining general population or fragmented data from observations in older subgroups. Use of surgery, radiotherapy and pharmacological therapies depends on clinical and pathological stage of the disease that is associated with the risk of recurrence and fatality due to the cancer in remaining life. Predictive factors are used in drug selection for hormonotherapy, immunotherapy and recently, for targeted therapy in the framework of precision oncology. There is still little data on treatment results in elderly. This may lead to hesitation and neglect in use of some more aggressive, toxic or expensive therapies in aged patients due to the fact that may be frail and have usually several concomitant diseases. These patients may not gain clinical benefit from standard treatment (so called overtreatment) but refraining from guidelines towards restraining therapy (so called undertreatment) may also hamper the outcomes (4, 5, 6). Herein, the treatment guidelines are reviewed in the context of striking right

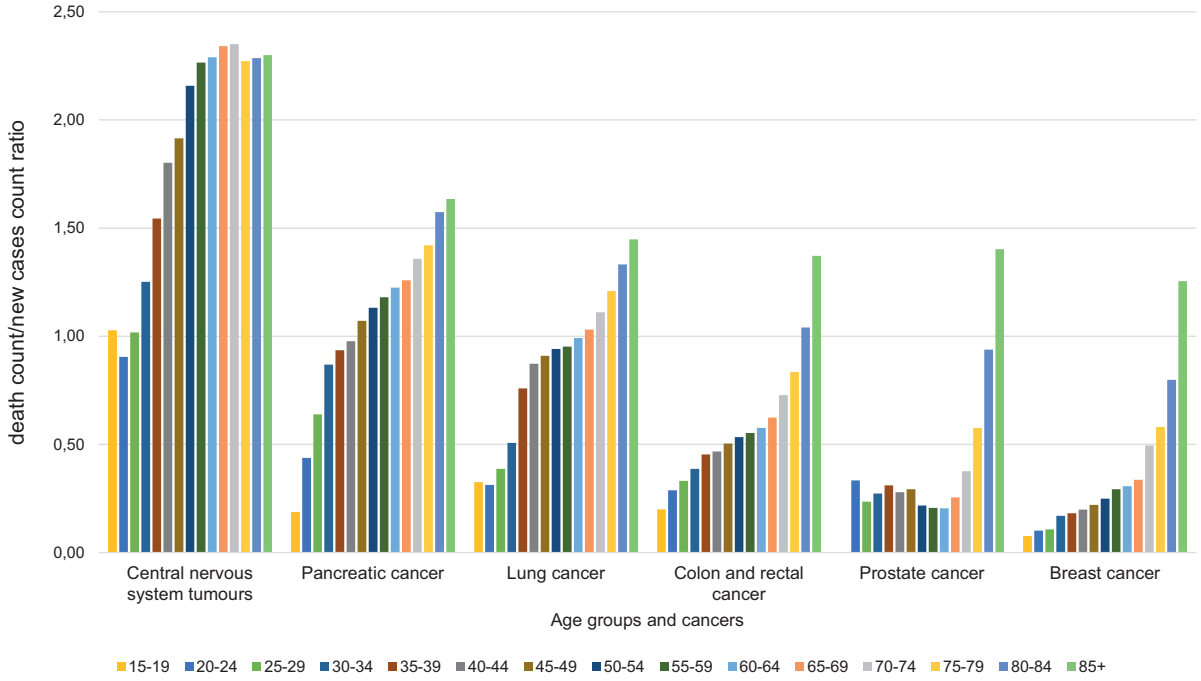

Fig. 1 Mortality/Incidence Ratio estimated for different cancers in years 1999-2016 in Poland.
Source: Cancer new cases and deaths in Poland. National Cancer Register, Maria Skłodowska-Curie Center of Oncology – Institute. Available at website: http://onkologia.org.pl/raporty/ access at: Dec 18,2019, own elaboration.

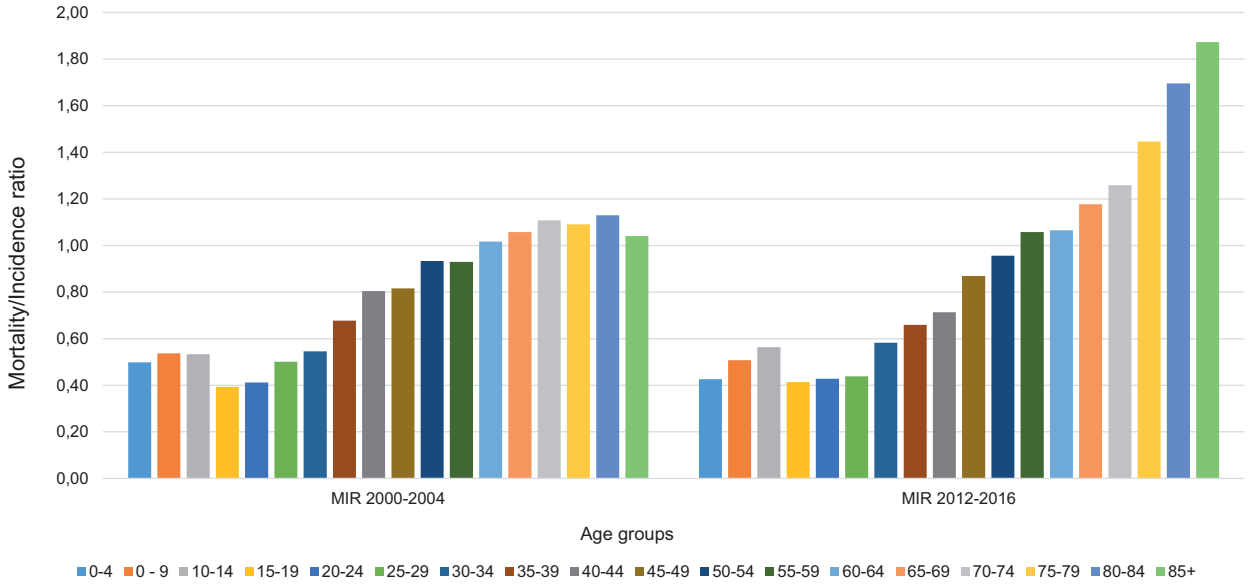

Fig. 2 Central Nervous System Tumours; Mortality/Incidence Ratio in age groups in periods 2000-04 and 2012-2016.
Source: Cancer new cases and deaths in Poland. National Cancer Register, Maria Skłodowska-Curie Center of Oncology – Institute.
Available at website: http://onkologia.org.pl/raporty/ access at: Dec 18,2019, own elaboration.

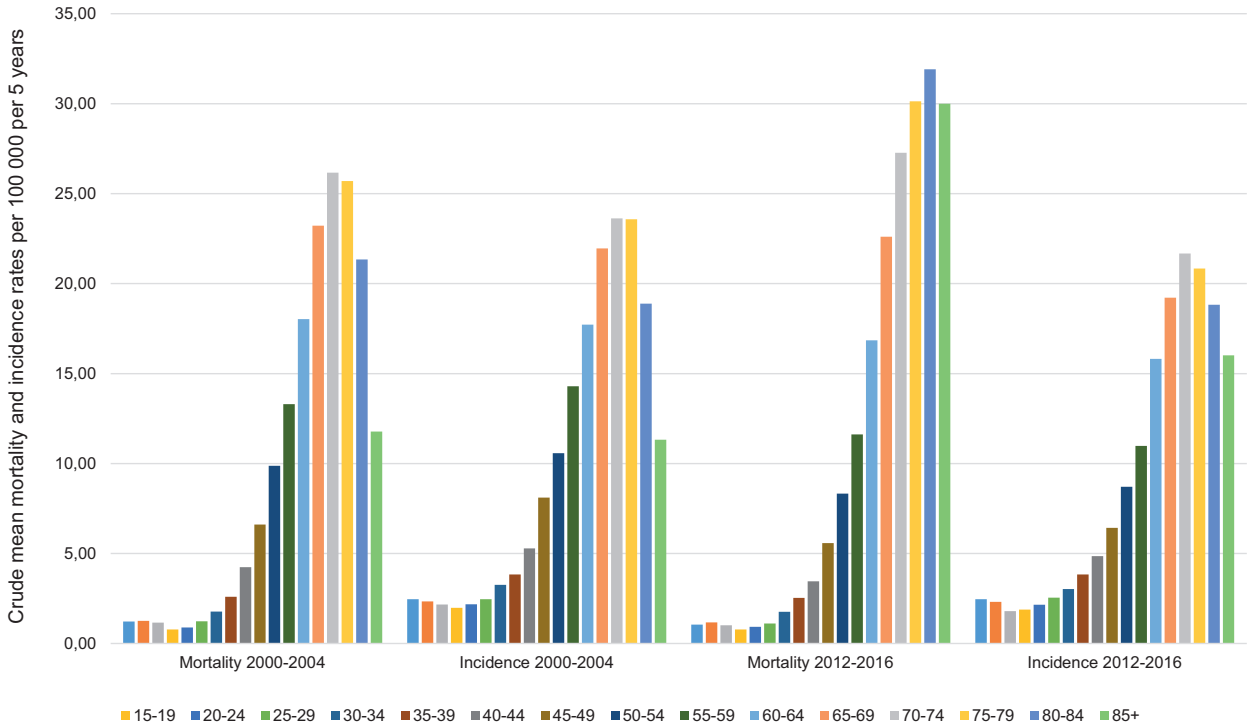

Fig. 3 Central nervous system tumours – comparison of mortality and incidence in age groups in years 2000-05 and 2012-16.
Source: Cancer new cases and deaths in Poland. National Cancer Register, Maria Skłodowska-Curie Center of Oncology – Institute.
Available at website: http://onkologia.org.pl/raporty/ access at: Dec 18,2019, own elaboration.

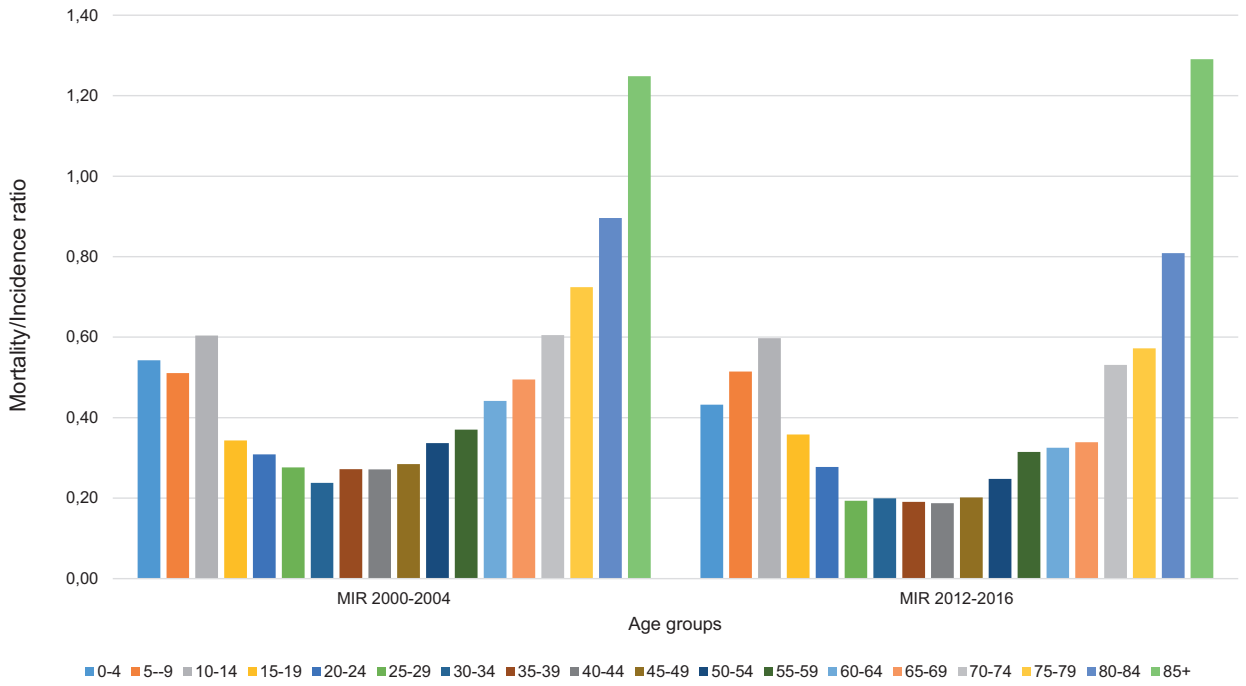

Fig. 4 Breast cancer in Poland. Comparison of mortality/incidence ratios between periods 2000-04 and 2012-2016.
Source: Cancer new cases and deaths in Poland. National Cancer Register, Maria Skłodowska-Curie Center of Oncology – Institute. Available at website: http://onkologia.org.pl/raporty/ access at: Dec 18,2019, own elaboration.

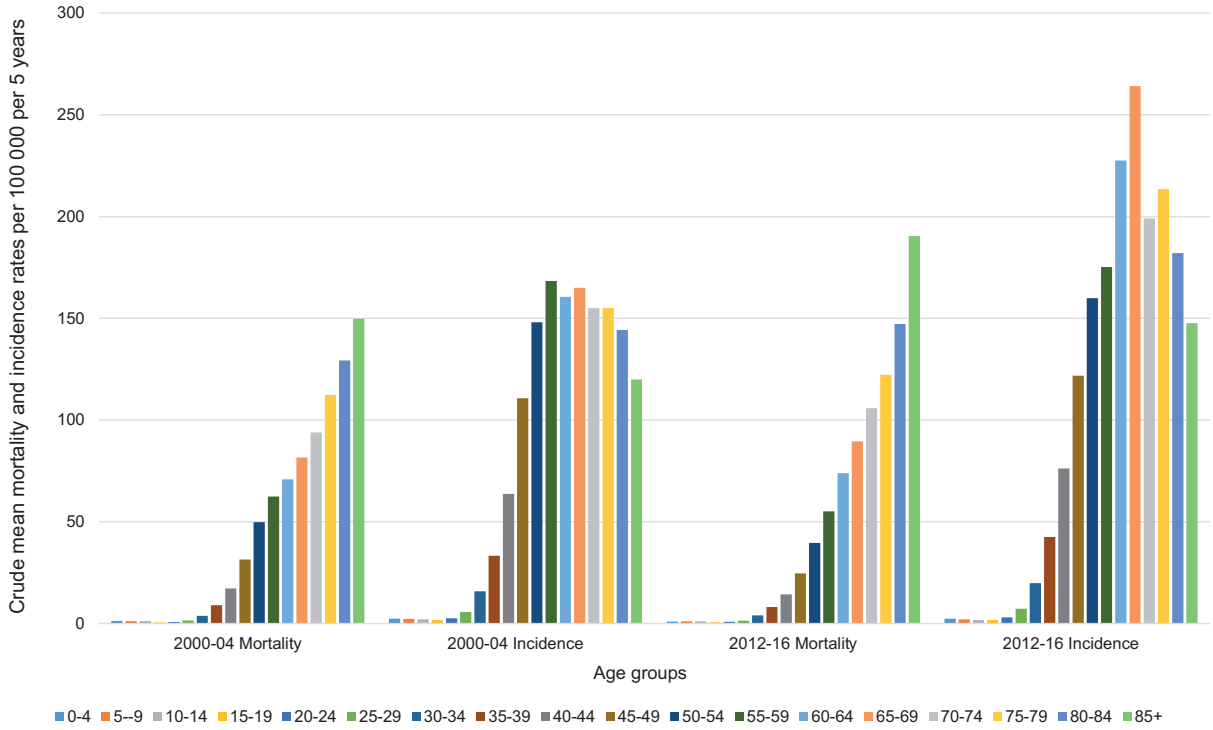

Fig. 5 Breast cancer in Poland Mortality and incidence in periods 2000-04 and 2012-2016.
Source: Cancer new cases and deaths in Poland. National Cancer Register, Maria Skłodowska-Curie Center of Oncology – Institute. Available at website: http://onkologia.org.pl/raporty/ access at: Dec 18,2019, own elaboration.

balance in care for breast cancer – the disease with rather good prognosis and many treatment options – in older patients. The concepts of undertreatment and overtreatment are intertwined. For the sake of good illustration, some information is provided on the changing approach to care in more fatal disease, the lung cancer, where we have noted significant progress in selection of less aggressive therapies.

Breast cancer

The biology of the breast cancer may be favorable in older women. Proliferation is slow and there is higher frequency of Grade 1 tumor, wider prevalence of favorable prognostic hormone receptors expression and lower probability of HER expression that is associated with poor survival (7). Having that, there is perception that sparing some aggressive or toxic interventions, that are shown to effectively prolong survival in younger patients, does not hamper treatment results in elder ones. On the other hand, worse survival in aged breast cancer patients was consequently shown in several studies in last years. It is argued to be associated with constraining use of available treatment modalities that have shown benefit in general breast cancer population (4, 6, 8, 9). Standards are being refined currently to strike the right balance between harm from aggressive therapies and clinical benefits for aged breast cancer patients.

Surgery

Breast conserving therapy or mastectomy are standard procedures offered to patients of all ages with early and locally advanced breast cancer. Poorer survival outcomes were observed in those countries where breast surgery was more frequently omitted in advanced stages as it is shown in another recent observational study (10).

Benefit is similar for all ages and exchange of surgery to endocrine therapy hampers the outcomes. Surgery followed by hormonotherapy had advantage over hormonotherapy in crucial endpoints like progression free survival and cancer related survival but also prolonged overall survival (11). On the other hand, outcomes of surgery are still much poorer than in younger patients and the complications such as pneumonia, cardiac arrest, hypertension, coronary artery disease in American Society of Anesthesiology class IV are independently associated with thirty-day mortality (12).

Some authors claim that favorable biology of breast cancer in elder women allows omission of conventional surgery or adjuvant therapies. In their retrospective one database study elderly undertreated patients generally fared as well as the appropriately treated elderly. Moreover, 44% undertreated elderly died without disease recurrence compared to 29% of the appropriately treated patients ($P < 0.001$). Therefore, it seems that less treated elderly experienced outcomes comparable to younger patients presumably because their cancers had better prognostic features (e.g. generally smaller, better differentiated, estrogen receptor positive, and with less nodal involvement) and not because sparing direct or delayed therapy related deaths (9). However, there is also evidence that early tumors in elderly are more frequently poorly differentiated with a higher tumor grade and Ki67, similar to their younger counterparts (13). Moreover, increased nodal involvement is mainly seen with smaller tumors, suggesting that more aggressive small tumors in older women may still cause distant metastases.

Sentinel node biopsy brings important prognostic information about tumor spreading potential but strong prognostic predictors are also partly available from primary tumor features. In older patients, the sentinel node positivity is as low as 15% and mathematical models are proposed to predict it and omit the sentinel node biopsy (14, 15). US Society of Surgical Oncology, in its 2016 Choosing Wisely campaign, suggests that surgeons "do not routinely use sentinel lymph node biopsy in clinically node negative women older than 70 years of age with hormone receptor positive invasive breast cancer" (16). Some studies have shown that axillary sentinel node macrometastases, even not treated, do not influence survival by themselves. The survival may be even slightly longer when the axillary nodes are not dissected (17). Therefore, axillary lymph nodes dissection is proposed to be refrained even in sentinel node positive instances although it may be endangered with higher rate of axillary recurrence (18). Radiotherapy is used as an alternative to lymphadenectomy with far lower frequency of lymphatic edema than after surgery (19). It is not obvious whether this is true for tumors larger than 5 cm and neoadjuvant treatment. New studies are set to answer these important questions and hopefully older patients will be fairly represented (20).

Radiotherapy

The risk of local recurrences declines with age. There is strong discussion on the possibility of omission of radiotherapy in the context of PRIME 2 study (Post-operative Radiotherapy In Minimum-risk Elderly – Phase II), an international, randomized, controlled Phase III trial. The study has been set out to address the question of whether whole breast radiation therapy (WBRT) could be omitted in carefully defined groups of older patients. Although the rate of recurrence is significantly larger and DFS shorter in those who are not irradiated, the overall survival is not changed. Therefore, it seems that at least if the risk of local recurrence is low (T1–T2, node-negative, grade 1 tumors, HR-positive) after BCT with a clear excision margin a postoperative radiotherapy can be omitted in old patients (21). The 5-year recurrence risk is 4% when omitting adjuvant radiotherapy vs. 1% in case of providing it (22). Alternations in adjuvant radiotherapy like hypofractionation, convenient for older patients, should also be considered.

Adjuvant pharmacological therapies

The standards issued by international expert groups do not allow to relieve older patients from exhaustive regime of adjuvant therapy tailored to stage of disease, prognostic and predictive factors. The benefits are similar in all groups.

Studies in neoadjuvant chemotherapy are conflicting and these drugs are far more toxic than hormones. Since comparisons are inconclusive in the neoadjuvant setting, hormone therapy is more often prescribed over chemotherapy, preferably in postmenopausal patients with HR-positive breast cancer. Although toxicity of adjuvant chemotherapy is high, there is no evidence to support omission of drugs and dose reductions in older patients compared with younger ones. In CALGB study, in case of monotherapy with capecitabine 3 years, relapse-free survival (RFS) and overall survival were significantly lower in comparison to standard chemotherapy (RFS 68% vs 85%; overall survival 86% vs 91%, respectively), mostly in estrogen-negative disease cases (23). Most

probably the data about advantage of chemotherapy in singular setting will not emerge. Studies are being closed due to poor accrual. Chemotherapy in adjuvant setting is most questionable modality due to its low therapeutic index or expected clinical benefit. The latter is being defined differently for older patients in terms of sustained or improved quality of life with life prolongation relegated to a secondary priority. In opposite to these goals, chemotherapy incurs immediate worsening of quality of life with blurred advantage.

Non-Small Cell Lung Cancer

Early lung cancer

In patients with an early peripheral lung cancer, up to the stage II according to the American Joint Committee on Cancer (AJCC), it is possible to avoid thoracotomy, especially in case when a patient is not eligible to the surgery. The mediastinal nodes should be assessed by PET-CT and, if PET is negative for metastases in mediastinum, stereotactive ablative radiotherapy (SABR) may be used. Recent data suggests that tumors abutting the proximal airways are at high risk for severe complications, when subjected to SABR. Dose-volume limits need to be identified to predict complications involving central structures such as the proximal airways, heart, esophagus, and great vessels, especially in older patients (24). SABR provides a long-term local control and survival for peripheral stage I NSCLC with a low toxicity (25).

Capturing the lung nodule in early phase of development a screening should be considered. Even more laborious screening methods, like Low Dose Computed Tomography (LDCT), are laden with a low predictive value. The health cost of screening is high since a detected lung nodule must be verified with CT assisted biopsy, bronchoscopy that draw along a significant discomfort and serious complications, dangerous for elder patients. Therefore, currently the US Preventive Services Task Force recommends LDCT yearly in patients 55 to 80 years old, that have the history of 30 years of smoking or ceased it not later than 15 years ago. Old patients should be screened until they develop a major health problem that is expected to limit their life in short time (26).

Advanced lung cancer

Adjuvant pharmacological treatment

Adjuvant pharmacological treatment is recommended after surgical removal of the NSCLC in stage II/III. The data is emerging that targeted agents may be more effective as chemotherapy in adjuvant setting. The study ADJUVANT/CTONG1104 shows that adjuvant gefitinib led to 28.7 months (95% CI 24.9-32.5) of disease-free survival, compared with 18.0 months (13.6-22.3) with vinorelbine plus cisplatin in patients with completely resected stage II–IIIA (N1-N2) EGFR-mutant non-small-cell lung cancer (NSCLC) [hazard ratio (HR) 0.60, 95% CI 0.42-0.87; p = 0.0054] (27).

However, this study had many caveats as discussed by other authors (28). Finally, both the gefitinib and chemotherapy group have similar 3-year disease-free survival. The BR19 trial compared gefitinib with placebo in patients with completely resected stage IB-IIIA NSCLC, demonstrating a worse overall survival for the gefitinib-treated group, with an HR for disease-free survival of 1.22.

Nevertheless, it is interesting for older patients that in ADJUVANT/CTONG1104 the level 3 toxicity in case of gefitinib was low (2%) and non-hematological (liver) while toxicity frequency of chemotherapy was significant (34%) and mainly hematological. Serious adverse events were incomparable – 7% for Gefitinib and 23% for chemotherapy. It is very important to use therapy with benign toxicity profile in adjuvant setting having very low effectiveness of this approach (5%).

Chemoradiotherapy

According to NCCN, in an unresectable stage IIIB NSCLC, concomitant chemoradiotherapy is recommended, followed by adjuvant targeted agent therapy with durvulumab. Unfortunately, there are fundamental differences in treatment of patients below and above 70 years of life. The elder have two time more chance to get no treatment at all; 1.4 more chance for the palliative radiotherapy and three times more chances to get only radiotherapy instead of chemoradiotherapy (29). There is littla data whether combined chemoradiotherapy improves overall survival in elderly patients with locally advanced non-small-cell lung cancer (NSCLC). In a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301), median overall survival for the chemoradiotherapy and radiotherapy alone groups were 22·4 months (95% CI 16·5-33·6) and 16·9 months (13·4-20·3), respectively (hazard ratio 0·68, 95·4% CI 0·47-0·98, p = 0·0179). More patients had grade 3-4 haematological toxic effects in the chemoradiotherapy group than in the radiotherapy alone group, but incidences of grade 3-4 pneumonitis and late lung toxicity were similar between groups and the toxic deaths were more frequent in radiotherapy group (4% vs. 3%). The authors concluded that for a select group of elderly patients with locally advanced NSCLC, combination chemoradiotherapy provides a clinically significant benefit over radiotherapy alone and should be considered for this population (30). These results were confirmed in a larger study. Treatment with chemoradiation was associated with improved OS versus that with radiation [hazard ratio (HR) = 0.66, 95% confidence interval (CI): 0.64-0.68, p <0.001]. Strikingly, when related to the concurrent chemoradiation, the sequential chemoradiation was associated with a 9% reduction in the risk for death (HR = 0.91, 95% CI: 0.85-0.96, p = 0.002) (31).

This fact alleviates the treatment aggressiveness demand. It seems that further augmentation of local therapies seems to make no sense and leads to overtreatment. There are no benefits from chemoradiotherapy preceded by induction chemotherapy in comparison to radiotherapy for those older than 70 years. There were no significant differences in overall survival, local recurrence rate and distant metastases while, there was a poorer tolerance and higher incidence of acute esophagitis in a more intensively treatment group (32).

Pharmacological therapy

The greatest chance for overtreatment seems to be related to chemotherapy in metastatic NSCLC. The greater intensity of cytotoxic drugs use does not provide clinical benefit. For example, the phase III trial that aimed to confirm the superiority of weekly docetaxel and cisplatin over docetaxel monotherapy in elderly patients with advanced non-small-cell lung cancer (NSCLC) has shown in the first interim analysis, that OS of the doublet arm was insignificantly inferior to that

of the monotherapy arm [hazard ratio (HR), 1.56; 95% CI, 0.98 to 2.49], which led to early study termination (33). ECOG 4599 trial with biological agent added to the doublet chemotherapy: bevacizumab + paclitaxel/carboplatin vs. paclitaxel/carboplatin has shown a small survival prolongation in elderly patients (OS 12.3 vs 10.3 months – hazard ratio for death, 0.79; P = 0.003) but with clinically significant bleeding were 4.4% and 0.7%, respectively (P <0.001), including deaths from pulmonary hemorrhage (34). In PS 2 or frail patients monotherapies with vinorelbine and pemetrexed regimens, are more tolerable. Data support single agent chemotherapy for the elderly on the basis of acceptable toxicity.

In contrast to the cytotoxic drugs, excellent responses have been observed with immune-checkpoint inhibitors, and targeted treatments for those tumors with "druggable" mutations, resulting in a paradigm shift in the treatment approach for older patients. Due to improved tolerability therapies, inclusion of older patients in clinical trials has increased, and sub-group analyses are possible. Four trials with TKIs (gefitinib and erlotinib), IPASS, IFUM, EURTAC, and OPTIMAL, included elderly patients of more than 65 years old. Due to reduced lean body mass, there is greater plasma concentration of erlotinib in elderly patients (0.5- to 2-fold higher than in younger patients). This results in greater toxicity and dose reductions in older patients. It seems that body composition measurements may be helpful in targeted dose titration in future (35).

Immunosenescence, the age-related decline of immunity, may affect the immune responses of non-small cell lung cancer (NSCLC) patients. Recently, immune checkpoint inhibitors have shown survival advantage over chemotherapy in the treatment of advanced non-small cell lung cancer (NSCLC). Analyses in age subgroups are awaited. Currently, the meatanalysis of 7 trials (n = 3867) has been published. Anti-PD1/PD-L1 therapies (nivolumab, pembrolizumab, atezolizumab) resulted in better OS {HR 0.72 [95% confidence interval (CI) 0.63, 0.82; P <.00001]}, PFS [HR 0.84 (95% CI 0.72, 0.97; P <.02)], and ORR [odds ratio (OR) 1.52 (95% CI 1.08, 2.14; P <.02)] in comparison to chemotherapy in advanced NSCLC. Improved safety was observed with anti-PD1/PD-L1 therapies [OR 0.31 (95%CI 0.26, 0.38; P <.00001)]. Subgroups analysis revealed that all factors assessed were associated with better overall survival except the two. Age above 75 and mutant KRAS status favored chemotherapy over immunotherapy (36).

In another analysis of four studies that included 2,192 NSCLC patients PD-1 inhibitors significantly prolonged the OS in both younger group (<65-year-age) (HR: 0.64, 95% CI: 0.54-0.75, P = 0.000) and older group (≥65-year-age) (HR: 0.68, 95% CI: 0.54-0.81, P = 0.001) comparing chemotherapy. Among patients aged over 75, no significantly longer OS was observed (HR: 1.02, 95% CI: 0.35-1.69, P = 0.971) compared with chemotherapy (37).

Conclusions

Mortality/Incidence ratio (MIR) is a measure shown to adequately reflect cancer survival. Worrying gap in survival between young and old persists or is even greater in inevitably fatal diseases like central nervous system cancers. In diseases with better prognosis, with effective screening methods and large choice of treatment options like breast cancer survival in getting better, although not in eldest. The worse prognosis in old breast cancer patients may be caused to some extent by undertreatment, defined as restriction of some therapy modalities or lower access to medical assistance. On the other hand, studies show that sparing selected interventions may not hamper the outcome. More fatal tumors like NSCLC await further optimization of cancer therapy towards better toxicity profile to avoid overtreatment.

Abbreviations:

BCT – breast conserving therapy,
MIR – mortality/incidence ratio,
NHF – National Health Fund,
NCCN – National Comprehensive Cancer Network,
NSCLC – Non-Small Cell Lung Cancer,
PET-CT – Positron Emission Tomography – Computed Tomography,
OS – Overall Survival.

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