IL TUMORE DEL POLMONE NELL'ANZIANO
LE TERAPIE FARMACOLOGICHE

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Primary lung cancer is the leading cause of human cancer deaths worldwide.

It has been the most important cause of cancer mortality in men since the 1960s, it has equaled breast cancer as a cause of mortality in women since the 1990s (reaching a plateau for women in most European countries and in the US, where lung cancer death rates in women are approaching those of men).

Lung cancer deaths in women are expected to increase (+7%) in the EU in 2012.

The median age at diagnosis is between 63 and 70 years, depending on whether patients with only a “clinical” diagnosis or with “histological-cytological” proof.

(Cancer, 2010; Drugs Aging, 2011; Annals of Oncology, 2012)
Non-small cell lung cancer (NSCLC) accounts for 80–85% of primary lung cancers and Small cell lung cancer (SCLC) represents 15-20%.

For newly diagnosed NSCLC cases, 47% were patients > 70 years of age and 14% were > 80 years; whereas for SCLC, 32% were patients > 70 years of age and 10% were > 80 years.

Smoking is the main cause, responsible for 80% of cases. Other risk factors: exposure to asbestos, arsenic, radon, and non-tobacco-related polycyclic aromatic hydrocarbons.

In recent times, an increase in the proportion of NSCLC patients who are never smokers has been observed, particularly in Asian countries. These epidemiological data have resulted in ‘non-smoking-associated lung cancer’, considered a distinct disease entity.

*(Annals of Oncology, 2012)*
Screening for lung cancer.


BACKGROUND: This is an updated version of the original review published in The Cochrane Library in 1999 and updated in 2004 and 2010. Population-based screening for lung cancer has not been adopted in the majority of countries.

SELECTION CRITERIA: Controlled trials of screening for lung cancer using sputum examinations, chest radiography or chest CT.

MAIN RESULTS: 9 trials (8 randomised controlled studies and 1 controlled trial) with a total of 453,965 subjects:

- in a large study that included both smokers and non-smokers comparing annual chest x-ray screening with usual care there was no reduction in lung cancer mortality (RR 0.99, 95% CI 0.91 to 1.07)

- non-statistically significant trend to reduced mortality from lung cancer when screening with chest x-ray and sputum cytology was compared with chest x-ray alone (RR 0.88, 95% CI 0.74 to 1.03)

- one large methodologically rigorous trial in high-risk smokers and ex-smokers (those aged 55 to 74 years with ≥ 30 pack-years of smoking and who quit ≤ 15 years prior to entry if ex-smokers) comparing annual low-dose CT screening with annual chest x-ray screening. In this study the relative risk of death from lung cancer was significantly reduced in the low-dose CT group (RR 0.80, 95% CI 0.70 to 0.92)

AUTHORS’ CONCLUSIONS: The current evidence does not support screening for lung cancer with chest radiography or sputum cytology. Annual low-dose CT screening is associated with a reduction in lung cancer mortality in high-risk smokers but further data are required on the cost effectiveness of screening and the relative harms and benefits of screening across a range of different risk groups and settings.
Nessun beneficio mediante lo screening annuale con RX torace

Low-dose TC =

Studi dimostrano una riduzione del 20% della mortalità da cancro, MA il numero di soggetti da screenare per prevenire 1 decesso per carcinoma polmonare è di 320

La maggior parte dei noduli rilevati alla TC sono benigni

Elevata incidenza di noduli falsamente positivi (circa 24%)

Rimane poco rilevante il problema delle radiazioni, mentre è maggiore quello delle complicanze delle manovre invasive per ottenere biopsie

The National Lung Screening Trial ha mostrato una riduzione del 20% nella mortalità per carcinoma polmonare in soggetti ad alto rischio mediante l'uso di TC a basse dosi di radiazioni. Molti interrogativi rimangono aperti (chi screenare, quanto frequentemente e per quanto tempo), con la necessità di nuove LG. Inoltre, il carico dei costi e benefici sul sistema sanitario rimane ancora non chiaro (American Journal of Roentgenology, 2014)
Pathological diagnosis concerning *small biopsy samples and cytology* should generally be made according to the World Health Organization and the International Association for the Study of Lung Cancer classification.

Adoption of these recommendations is strongly advised.

Specific subtyping of all NSCLC is now necessary for therapeutic decision-making and should be carried out wherever possible.

Obtaining adequate tissue material for histological diagnosis and molecular testing is important to allow individual treatment decisions.

Re-biopsy at disease progression should be considered.

Larger biopsies facilitated molecular testing. The benefits of molecular-guided therapy dramatically outweigh the risk of biopsy. The elderly benefit even more than younger patients from the improved therapeutic index of less-toxic and more effective target therapy.

Genetic alterations that are key oncogenic events have been identified in NSCLC, with 2 of these to date offering the chance of selective pathway-directed systemic therapy:

**Activating (sensitizing) epidermal growth factor receptor (EGFR) mutations**

The incidence of EGFR mutations in the Caucasian population is $\sim 10\%$ and is higher in never-smokers, the adenocarcinoma subtype, in women, and in East-Asian patients. An EGFR mutation status should be systematically analyzed in advanced NSCLC with a nonsquamous histology. These mutations are predictive for response to the EGFR tyrosine kinase inhibitors (TKIs) Gefitinib and Erlotinib and result in an improved response rate and progression-free survival in combination with better tolerability of treatment and a better QoL.

**The EML4-ALK fusion gene** is an oncogenic driver; it is encountered more frequently in never-smokers, the adenocarcinoma subtype and in younger patients, representing $\sim 5\%$ of adenocarcinoma. ALK activity can be efficiently targeted by the TKI Crizotinib.
A complete history including smoking history and comorbidities, weight loss, performance status, and physical examination.

Laboratory: routine hematology, renal and hepatic function, and bone biochemistry tests. The routine use of serum markers (such as CEA) is not recommended.

CT scan of the chest and upper abdomen.

Imaging of the central nervous system is reserved for patients with neurological symptoms or signs. Brain imaging should be performed in patients eligible for a loco-regional treatment.

MR imaging is more sensitive than CT scan.

Bone scan or local bone imaging (including MRI) is required in the presence of clinical suspicion of bony lesions not evaluable on CT scan.

PET-CT scan offers the highest sensitivity for mediastinal lymph nodes and distant metastasis assessment.

Cardio-respiratory evaluation, brain imaging, PET and, if needed for decision-making, invasive mediastinal node analysis are indicated for the evaluation of resectability or the suitability of radiotherapy with curative intent in the context of a solitary brain or adrenal lesion or oligometastatic disease confined to the lungs.

(ESMO Clinical Practice Guidelines - Annals of Oncology, 2012)
Treatment strategy

- The treatment strategy should take into account the histology, molecular pathology, age, PS, comorbidities, and patient's preferences.

- Treatment decisions should be discussed within a multidisciplinary tumor board.

- Systemic therapy should be offered to all stage IV patients with PS 0–2 [I, A].

- In any stage of NSCLC, smoking cessation should be highly encouraged because it improves the outcome.
ECOG – PERFORMANCE STATUS

- **0**: paziente completamente attivo; in grado di effettuare tutte le performance pre-morbose senza restrizioni; non analgesici

- **1**: paziente attivo ma limitato nelle attività intense; in grado di camminare ed effettuare lavori sedentari e con bassi sforzi; terapia autologa

- **2**: paziente in grado di camminare e autonono nella cura della persona, ma non in grado di lavorare; a letto o seduto per meno del 50% del tempo di veglia

- **3**: paziente parzialmente autonono nella cura di sé; a letto o seduto per più del 50% del tempo di veglia

- **4**: paziente completamente disabile; a letto per il 100% del tempo di veglia

- **5**: paziente deceduto
**POPOLAZIONI “SPECIALI” IN ONCOLOGIA**

- **Pazienti con Performance Status 2-3:**
  - Spesso esclusi dai clinical trials
  - Rappresentano il 30-40% dei casi

- **Età media alla diagnosi di 65-70 anni**
  - Normalmente nei clinical trial oncologici i 70 anni sono considerati il punto di riferimento per la definizione di “anziano”
  - I casi di K polmonare >70 anni sono circa il 33%
  - **Sotto-representati nei clinical trials** (negli anni Novanta solo una percentuale < 15% tra i soggetti arruolati nei clinical trials per la valutazione di nuovi farmaci oncologici aveva un’età > 70 anni)

*Caratteristiche comuni:*

- Pochi trial dedicati

- La maggior parte delle analisi dei trial comprendono sottogruppi con Performance Status PS 0-2 e/o di età più giovane.
The goals of treatments can be quite different between elderly specific trials and trials with unspecified upper age limit:

- Overall Survival benefit is the gold-standard outcome criterion for younger patients.

- In the older population groups, the emphasis may shift towards functional independence and quality of life.

- Improved survival at the expense of significant increased toxicity, hospitalisation and long-term dependence is unlikely to be the preferred option for the majority of older cancer patients.
MODIFICAZIONI BIOLOGICHE CORRELATE ALL'ETA'

- Aumento del grasso corporeo
- Riduzione del contenuto d'acqua corporeo
- Riduzione delle riserve di funzioni epatica e renale
- Comorbidità ed elevato uso di farmaci
- Modificazioni farmacocinamiche, soprattutto per i farmaci che richiedono l'attivazione a metaboliti attivi
- Aumentata tossicità dei chemioterapici
Assessment

- Nei pazienti affetti da cancro >70 anni è raccomandato l'uso della Valutazione Geriatrica Multidimensionale (*Raccomandazione B-positiva forte*)

- Definizione di FRAGILITA' in Oncologia Geriatrica (Balducci - Oncology, 2000):
  - almeno 1 Sindrome geriatrica (delirium, cadute, vertigini, sincope, incontinenza urinaria, debolezza muscolare, rallentamento motorio, stanchezza, scarsa attività fisica, perdita di eso involontaria)
  - dipendenza in almeno 1 BADL
  - 3+ comorbilità
  - età >85 anni

Vari sono i test di screening per individuare pazienti fragili o a rischio di eventi avversi (usati in quelle situazioni in cui la VGM non è praticabile): Vulnerable Elderly-13 Survey (VES-13), G8, Short Portable Performance Battery (SPPB) (*Raccom. B-positiva debole*)
ASSESSMENT GERIATRICO MULTIDIMENSIONALE
Quali strumenti in ambito oncologico

**Abbrevited CGA:** 15 item (3 domande su BADL, 4 domande su IADL, 4 domande su MMSE e 4 domande su GDS)

**Senior Adult Oncology Program (SAOP-2 Screening Tool):** domande di valutazione su stato funzionale, cognitivo, depressione + QoL, stato soggettivo di salute, cadute, nutrizione, sonno, farmaci, stato economico-sociale

**Vulnerable Elders Survey 13 (VES-13):**
cut-off >3

<table>
<thead>
<tr>
<th>Sensibilità</th>
<th>Specificità</th>
</tr>
</thead>
<tbody>
<tr>
<td>84-96%</td>
<td>81%</td>
</tr>
<tr>
<td>100%</td>
<td>40%</td>
</tr>
<tr>
<td>73%</td>
<td>86%</td>
</tr>
</tbody>
</table>

*(European Society Oncological Medicine – Handbook of Cancer in the Senior Patient, 2010)*
Predictive model for the probability grade 3-5 toxicity among elderly receiving chemotherapy.

An 11-item scale includes:

- age
- cancer type
- n° chemotherapy drugs
- anemia
- renal function
- hearing
- n° of falls
- ability to take medication without help
- ability to walk 1 block
- decreased social activity for physical or emotional diseases
La comorbilità nell'anziano si associa a una ridotta autonomia funzionale e a perdita di peso corporeo-malnutrizione, ma si osserva che la comorbilità da sola rappresenta un fattore prognostico negativo indipendente dallo stesso Performance Status e dall'età del paziente.

Non solo è necessario conoscere le problematiche mediche dell'anziano con carcinoma polmonare, ma è fondamentale ottimizzarne i trattamenti.

Le comorbidità più frequenti sono le malattie cardiovascolari, la BPCO, l'anemia e la riduzione della riserva midollare ossea.
La conoscenza sulla farmacologia anti-tumorale è molto limitata nei soggetti > 75 anni ed è praticamente inesistente negli ultra-80enni.

- Il ricorso a modificazioni della dose sulla sola età non è giustificato.
- Nel soggetto anziano in buone condizioni generali, è indicato il dosaggio standard (Evidenza 2-).
- La riduzione di dose in pazienti anziani fragili deve seguire informazioni farmacocinetiche e farmacodinamiche. Valutare sempre la funzione epato-renale (Evidenza 3).
- Considerare il rallentamento dell'assorbimento gastrico, soprattutto dopo gli 85 anni (Evidenza 4).
- Considerare i valori di Hb, poiché alcuni farmaci sono legati alle emazie e, in caso di anemia, può aumentare la frazione libera del farmaco con aumentata tossicità. Necessario correggere anemia (Evidenza 4).
- Correggere eventuali squilibri idroelettrolitici e deficit nutrizionali (Evidenza 3).
MODIFICAZIONI BIOLOGICHE CORRELATE ALL'ETA' – In particolare:

Funzione renale

- La nefrotossicità da Cisplatino è dose-limitata, potenzialmente irreversibile e si verifica principalmente durante la 1° settimana (controindicato se GFR <60ml/min/1.73m2). L'idratazione pre- e post-somministrazione di Cisplatino sono di fondamentale importanza (circa 2L di sol.Fisiologica). Il Carboplatino è meno nefrotossico e più maneggevole, sebbene leggermente inferiore in termini di efficacia.

- Per la Gencitabina non sono necessari aggiustamenti di dose, sebbene possa presentare una maggior tossicità in pazienti già con insufficienza renale.

- L'Ac.Zoledronico (utilizzato per l'ipercaleemia paraneoplastica) può indurre Necrosi tubulare acuta, soprattutto nei soggetti >80y con pre-esistente insufficienza renale (controindicato se GFR <30ml/min/1.73m2).
Tossicità ematologica

- La tossicità ematologica dei chemioterapici è più spiccata nell'anziano, pertanto sono frequentemente necessarie modificazioni delle dosi. La tossicità si manifesta principalmente durante il 1° ciclo di terapia.

- La riduzione della posologia dei farmaci nel trattamento del NSCLC permette di contenere la tossicità ematologica dei pazienti anziani rispetto ai più giovani.

- La risposta ai fattori stimolanti le colonie di granulociti (G-CSF) è mantenuta.

- L'uso profilattico di G-CSF permette la somministrazione di più alte dosi di chemioterapici, riducendo l'incidenza di neutropenia, neutropenia febbrile e delle infezioni.
Variabili da considerare:

- ADL (strumentali e di base)
- Stato cognitivo-demenza
- Stato nutrizionale
- Performance motorie
- Cadute
- Disponibilità di caregiver
- Maltrattamento

Comorbidità, stato cognitivo, disturbi neuropsichiatrici, supporto sociale e stato nutrizionale influenzano la QoL, la tossicità e gli outcome del paziente anziano con cancro, ma non vengono adeguatamente considerati e documentati.

In particolare, il CALO DI PESO si associa a perdita di massa muscolare, immunodepressione, depressione e incremento delle complicanze associate alla malattia e ai trattamenti, con conseguente maggior mortalità.
Table 5: Elements of a comprehensive geriatric assessment

<table>
<thead>
<tr>
<th>Parameter assessed</th>
<th>Elements of the assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Performance status, ADL, IADL</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Number of comorbid conditions, Severity of comorbid conditions, Comorbidity index</td>
</tr>
<tr>
<td>Socioeconomic conditions</td>
<td>Living conditions, Presence and adequacy of a caregiver</td>
</tr>
<tr>
<td>Cognition</td>
<td>Folstein’s minimental status, Other tests</td>
</tr>
<tr>
<td>Emotional conditions</td>
<td>Geriatric depression scale (GDS)</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>Number of medications, Appropriateness of medications, Risk of drug interactions</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Mini-nutritional assessment (MNA)</td>
</tr>
<tr>
<td>Geriatric syndromes</td>
<td>Dementia, Delirium, Depression, Falls, Neglect and abuse, Spontaneous bone fractures</td>
</tr>
</tbody>
</table>

Group 1:
Functionally independent
Without serious comorbidity

Group 2:
Dependent in one or more IADLs
And/or 1 or 2 comorbid conditions

Group 3:
Frail patients

Balducci L. Oncologist 2000;5:224-237
<table>
<thead>
<tr>
<th>STADI</th>
<th>DESCRIZIONE</th>
<th>TRATTAMENTO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primo (Robusto-Fit)</td>
<td>Non limitazioni delle normali attività di vita.</td>
<td>Terapia standard con adeguata terapia di supporto.</td>
</tr>
<tr>
<td></td>
<td>Non comorbilità.</td>
<td></td>
</tr>
<tr>
<td>Intermedio (Vulnerabile)</td>
<td>Dipendente in 1+ IADL.</td>
<td>Terapia come 1° stadio dopo riabilitazione.</td>
</tr>
<tr>
<td></td>
<td>Comorbilità di grado moderato.</td>
<td>Precauzionalmente terapia a dosaggio ridotto.</td>
</tr>
<tr>
<td>Breve spettanza di vita</td>
<td>Aspettativa di vita &lt; 3 mesi.</td>
<td>Sola terapia sintomatologica di supporto.</td>
</tr>
<tr>
<td></td>
<td>Assenza di riserva funzionale.</td>
<td></td>
</tr>
</tbody>
</table>
Ci sono pochi dubbi anche in ambito oncologico che la FRAGILITA' esista e che sia una problematica fondamentale da considerare nel paziente anziano con cancro.

Oncologi e Geriatri, utilizzando talvolta diverse definizioni di “fragilità” e diversi strumenti di assessment, possono individuare differenti tipi di pazienti.

La Fragilità può essere in alcuni casi correggibile e gli oncologi hanno il dovere di individuare i fattori potenzialmente modificabili, soprattutto in ambito nutrizionale, di ridotta mobilità, incontinenza e delirium.

La sola definizione di “anziano fragile” non deve rappresentare un criterio di esclusione da trattamenti potenzialmente curativi o di miglioramento dell'aspettativa di vita.

FRAGILITA' - CONCLUSIONI
TRATTAMENTI
CONCLUSION

Early stage NSCLC
- Surgery seems to be the optimal treatment
- Radiation as primary therapy is a viable option for patients >80y who cannot undergo surgery
- No data supporting the use of adjuvant chemotherapy after surgery for octogenarians

Advanced NSCLC
- It is currently incurable in all age groups
- Chemotherapy and EGFR-inhibitors seem to be safe with similar toxicity in respect of younger patients
- Treatment may decrease cancer-related symptoms and prolong survival in fit octogenarians

SCLC
- Very little data exist for octogenarians
- Very small series indicate that therapy is safe in selected patients and may benefit in term of symptoms and improving outcomes
Are we treating enough Elderly Patients with Early stage Non-Small Cell Lung Cancer?

Pallis AG, Scarci M. (Lung Cancer, 2011)

- Surgery is the treatment of choice for Stage I, II and subsets of stage IIIA NSCLC, and is the only therapeutic strategy that offers a significant chance of cure.

- Patients age at presentation should no longer influence access to radical surgery.

- Although surgical resection is the “gold-standard” for Early-stage NSCLC, some subjects are denied surgery due to age, comorbidity or patients refusal. In these patients, Radiotherapy can be administered with curative intent, but with lower survival.

- Adjuvant Radiotherapy after surgical resection had failed to demonstrate an overall survival benefit.

- No prospective data exists on Adjuvant chemotherapy after surgical resection in older population with Early-stage NSCLC. Conclusions are extrapolated from retrospective subgroup analyses involving younger patients. These data support evidence that adjuvant chemotherapy confers an overall survival benefit in subjects > 70y, without a significant increase in toxicity rate (also with lower total doses of drugs or fewer cycles in respect of younger subgroups). Even poor PS should not pose an absolute contraindication to appropriate therapy.
The Elderly Patient with Operable Lung Cancer

The literature on Video-Assisted Thoracoscopic Surgery (VATS) lobectomy in older patients consistently demonstrates low morbidity, low mortality, and shorter hospital stays. Such results hold even in octogenarians, including low rates of postoperative confusion.

The fit elderly patient with surgically resectable disease should undergo surgery, with consideration of adjuvant chemotherapy.

The Elderly Patient with Nonoperable Lung Cancer (IIIA or IIIB NSCLC)

The fit elderly patient with unresectable or stage III disease should be considered for chemo-radiotherapy, preferably concomitant chemo-radiation.

For less fit patients, sequential chemotherapy followed by radiation therapy or radiation therapy alone may be considered.
We found that people with advanced NSCLC that had chemotherapy and best supportive care lived longer than those who had best supportive care: After 12 months, were alive
- 29 out of 100 who were given chemotherapy + best supportive care
  VS
- 20 out of 100 who just had best supportive care.

Some patients and doctors may be concerned that the side effects of chemotherapy outweigh the benefits of receiving it. However, 3 of the trials included in this project reported that for those patients who received chemotherapy, QoL was either the same or better than those that did not receive chemotherapy.

This study showed that chemotherapy in addition to supportive care helped some patients to live longer, even the elderly and less fit.
Locally Advanced Disease

The risk-benefit ratio is less favorable for locally advanced disease, especially in the elderly. The chance of cure is lower, and the risk of mortality and debilitating toxicity is higher in subjects older than 70 years compared with younger (in particular, esophageal and hematologic toxicity).

Metastatic Disease

Palliative Radiation = single-fraction RT for bone metastases and short-term hypofractionated thoracic RT are appropriate considered in selected patients.

Chemotherapy = Platinum-doublet therapy is the standard of care, but it remains controversial in the elderly. The recommendations are using:
- a regimen of Carboplatinum+Paclitaxel or other Carboplatin-based combination in fit elderly patients
- a single-agent chemotherapy in those with a poor PS, comorbidity or at risk to undergo more toxicity.

Target therapy = provide effective treatment with less toxicity than conventional chemotherapy

BUT
- Bevacizumab (antivascular endothelial GF recombinant monoclonal antibody) does not improved overall survival, with a higher incidence of grade 3-5 neutropenia, bleeding, and proteinuria in the elderly compared with younger patients
- Erlotinib (tyrosine-kinase inhibitor that targets epidermal GF receptor) has more adverse effects (> grade 3)
Patients aged 70-89 years with a PS score 0-2 could be treated with use of monthly carboplatinum + weekly paclitaxel (Platinum-based Dublets therapy), but the toxicity is not negligible and subjects must be monitored carefully. There are not sufficient studies to promote second-line therapy. 

(ESMO Clinical Practice Guidelines - Annals of Oncology, 2012) 

(Drugs Aging, 2011. Optimal Pharmacotherapy for Elderly Patients with Advanced NSCLC)
**KEY POINTS**

**Single Agent Chemotherapy**
Vinorelbina, Pemetrex, Docetaxel hanno dimostrato benefici su progression-free survival, miglioramento di anoressia, fatigue e QoL, anche in pazienti anziani. Sono indicati come opzioni terapeutiche sia come first-line sia in trattamenti successivi. La scelta del farmaco deve basarsi sulla funzione d’organo e comorbilità.

**Combination Chemotherapy**
*Non-platinum* = nessun vantaggio rispetto alla monoterapia in termini di sopravvivenza e QoL, con maggior rischio di effetti collaterali. NON INDICATI
*Platinum-based* (cisplatino+paclitaxel, cisplatino+gemcitabina, cisplatico+docetaxel, carboplatino+paclitaxel) = rappresentano lo standard di cura, MA pazienti >70y presentano > tossicità. Nei > 75-80y gli effetti collaterali superano i benefici su sopravvivenza. Da utilizzare solo negli anziani *robusti*. Carboplatino meglio tollerato del Cisplatino.

*Quoix, Lancet 2011*

**Target therapy**
*Epidermal GF-receptor* (Erlotimib) = come second line-therapy, ma importante tossicità (rash, diarrea) e sospensione
*Vascular endothelial GF* (Bevacizumab) = scarsi studi
Carboplatin and weekly Paclitaxel Doublet-chemiotherapy compared with Monotherapy in Elderly patients with Advanced NonSmall-Cell Lung Cancer

Quoix, et al. (Lancet, 2011)

RCT con 451 pazienti con PS 0-2 di 70-89y affetti da NSCLC
  – Carboplatino+Paclitaxel
  – Monoterapia con Vinorelbina o Gemcitabine

Sopravvivenza > nella Doublet-chemiotherapy = 10.3 vs 6.2 mesi
  HR 0.64, \( p < .0001 \); a 1 anno 44.5% vs 25.4%.

Tali risultati sono stati confermati anche per i soggetti > 80y con PS =2
Terapia di Associazione vs Monoterapia

Exploratory Sub-group analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>327</td>
<td>0.631 (0.494-0.806)</td>
<td>0.0002</td>
</tr>
<tr>
<td>2-3</td>
<td>123</td>
<td>0.626 (0.431-0.910)</td>
<td>0.0141</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≤80 yr</td>
<td>337</td>
<td>0.676 (0.533-0.857)</td>
<td>0.0012</td>
</tr>
<tr>
<td>&gt;80 yr</td>
<td>114</td>
<td>0.534 (0.357-0.799)</td>
<td>0.0022</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ADC</td>
<td>229</td>
<td>0.734 (0.546-0.986)</td>
<td>0.0397</td>
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<tr>
<td>Squamous-Other</td>
<td>222</td>
<td>0.517 (0.347-0.762)</td>
<td>0.000009</td>
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<tr>
<td>Smoking status</td>
<td></td>
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</tr>
<tr>
<td>Never smoker</td>
<td>94</td>
<td>0.650 (0.400-1.050)</td>
<td>0.0818</td>
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<tr>
<td>Smoker</td>
<td>356</td>
<td>0.621 (0.495-0.778)</td>
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<tr>
<td>Weight loss</td>
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<td></td>
<td></td>
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<tr>
<td>≤5%</td>
<td>203</td>
<td>0.610 (0.443-0.839)</td>
<td>0.0023</td>
</tr>
<tr>
<td>&gt;5%</td>
<td>241</td>
<td>0.726 (0.553-0.953)</td>
<td>0.0209</td>
</tr>
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<td>ADL score</td>
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<tr>
<td>≤6</td>
<td>88</td>
<td>0.650 (0.419-1.008)</td>
<td>0.0541</td>
</tr>
<tr>
<td>6</td>
<td>350</td>
<td>0.997 (0.471-2.075)</td>
<td>0.000017</td>
</tr>
<tr>
<td>Mini Mental score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤23</td>
<td>67</td>
<td>0.817 (0.490-1.364)</td>
<td>0.4395</td>
</tr>
<tr>
<td>&gt;23</td>
<td>374</td>
<td>0.610 (0.487-0.765)</td>
<td>0.000018</td>
</tr>
</tbody>
</table>

OS – The univariate hazard ratio was derived from a Cox model with a single treatment covariate

(Quoix E. et al, Lancet 2011)
Doublet therapy was superior to a single third-generation cytotoxic agent as first-line therapy for elderly patients with advanced NSCLC, in terms of overall survival, time to progression, overall response rate, and 1 year survival rate. But more hematologic toxicities and neurotoxicity were observed with doublet therapy.

Such results should be interpreted cautiously.

The optimal dosage and schedule of platinum-based doublet should be investigated in future prospective clinical trials.

Gemcitabine-based doublet therapy seemed less efficacious than Platinum-based Doublet, but it could be considered for elderly patients who were not suitable for platinum-based chemotherapy, because of its tendency to improve overall survival and 1-year survival rate.
For fit, chemotherapy-naive, nonelderly patients with advanced NSCLC not amenable to chemoradiotherapy, platinum-based doublets are considered the standard first-line treatment. Single-agent therapy (Gemcitabine and Vinorelbine) has long been recommended for first-line chemotherapy in elderly patients (>70 years). However, subgroup analyses suggested that patients aged >70 years derived similar benefits from a Platinum-based Doublet as their younger counterparts.

In 2006, it was conducted a phase III study comparing single-agent therapy (Gemcitabine or Vinorelbine) to Carboplatin and weekly Paclitaxel in elderly NSCLC patients. There was considerable benefit derived from the Carboplatin-based doublet compared with the single-agent therapy in terms of overall survival.

These results led to a modified paradigm of first-line treatment in performance status 0–2 elderly patients with advanced NSCLC, as illustrated by the recently published National Comprehensive Cancer Network recommendations.

(Quoix. European Respiratory Journal, 2014)
At the present time, three drugs (docetaxel, pemetrexed and erlotinib) have been authorised for second-line therapy in advanced NSCLC patients, previously treated with at least one line of a platinum-based combination chemotherapy.

In particular, the BR21 study showed that Erlotinib significantly increased overall survival compared with best supportive care for nonselected advanced NSCLC.

Subgroup analysis of elderly patients included in the BR21 study showed that there was no differential effect of Erlotinib according to age >70 versus <70 years. Due to its good tolerability profile, Erlotinib was chosen as systematic second-line therapy.

(Quoix. European Respiratory Journal, 2014)
Use of TKIs (NB: STUDI PREVALENTI NEL PAZIENTE <70y):

• First-line treatment with a TKI (Erlotinib or Gefitinib) should be prescribed to patients with tumors bearing an activating (sensitizing) EGFR mutation [I, A].

• Patients with EGFR mutation and PS 3–4 may also be offered an EGFR TKI [II, A].

• In EGFR WT patients, EGFR TKIs are not recommended as first-line therapy, being inferior to chemotherapy [I, A].

• Patients with NSCLC harboring an ALK rearrangement should be considered for Crizotinib, a dual ALK and MET TKI, during the course of their disease.

(ESMO Clinical Practice Guidelines - Annals of Oncology, 2012)
Second-line therapy in elderly patients with Advanced nonsmall cell lung cancer
Elisabeth Quoix, et al. (European Respiratory Journal, 2014)

The reason for undergoing second-line therapy was disease progression for 93.8% (95.1% in the single-agent arm and 92.6% in the doublet arm), excessive chemotherapy toxicity for 4.1% (2.8% and 5.4%, respectively) and other reasons in 2.1% of cases.

Multivariate analysis of overall survival revealed that performance status 0–1, never having smoked, adenocarcinoma and weight loss < 5% were all favourable independent prognostic factors, whereas the randomisation arm showed no significant impact.

Of the 292 patients who received Erlotinib, 20.5% experienced grade 3–4 toxic effects: 19.4% in the single-agent arm and 21.6% in the doublet arm. The most frequent toxic effects were rash, asthenia, anorexia, and diarrhoea.
## TABLE 1 Results of univariate and multivariate logistic regression analyses assessing the eligibility to receive erlotinib as second-line therapy (L2) according to baseline patient characteristics (prior to induction therapy)

(Quoix. Eur Resp J, 2014)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients receiving L2 n (%)</th>
<th>Univariate analysis*</th>
<th>Multivariate analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Treatment arm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doublet chemotherapy</td>
<td>144 (64.3)</td>
<td>1.14 [0.77–1.69]</td>
<td>0.5073</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>148 (67.3)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>210 (64.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>82 (69.5)</td>
<td>1.26 [0.80–1.98]</td>
<td>0.3201</td>
</tr>
<tr>
<td><strong>Age years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤80</td>
<td>217 (65.4)</td>
<td>0.93 [0.59–1.47]</td>
<td>0.7572</td>
</tr>
<tr>
<td>&gt;80</td>
<td>75 (67.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Performance status</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>234 (72.9)</td>
<td>2.97 [1.93–4.57]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥2</td>
<td>58 (47.6)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA–IIIB</td>
<td>47 (56.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>245 (68.1)</td>
<td>1.67 [1.03–2.72]</td>
<td>0.0364</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous or other</td>
<td>142 (65.1)</td>
<td>1.06 [0.71–1.56]</td>
<td>0.7841</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>150 (66.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>68 (72.3)</td>
<td>1.47 [0.89–2.43]</td>
<td>0.1317</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>224 (64.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MMS examination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤23</td>
<td>34 (52.3)</td>
<td>1.92 [1.12–3.27]</td>
<td>0.0169</td>
</tr>
<tr>
<td>&gt;23</td>
<td>250 (67.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ADL score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>42 (48.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6</td>
<td>239 (69.7)</td>
<td>2.41 [1.49–3.90]</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>CCI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>226 (67.7)</td>
<td>1.40 [0.89–2.18]</td>
<td>0.1426</td>
</tr>
<tr>
<td>&gt;2</td>
<td>66 (60.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMI kg·m⁻²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>32 (61.5)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>20 to ≤26</td>
<td>156 (63.7)</td>
<td>1.10 [0.59–2.03]</td>
<td>0.7718</td>
</tr>
<tr>
<td>&gt;26 to ≤30</td>
<td>70 (72.2)</td>
<td>1.62 [0.79–3.31]</td>
<td>0.1850</td>
</tr>
<tr>
<td>&gt;30</td>
<td>34 (68.0)</td>
<td>1.33 [0.59–3.00]</td>
<td>0.4953</td>
</tr>
<tr>
<td><strong>Weight loss before randomisation %</strong></td>
<td>144 (72.4)</td>
<td>1.73 [1.15–2.59]</td>
<td>0.0081</td>
</tr>
</tbody>
</table>

MMS: mini-mental state; ADL: activities of daily living questionnaire; CCI: Charlson’s comorbidity index; BMI: body mass index. *: n=444; †: n=421; ‡: six patients who had not received L2 had an initial World Health Organization performance status of 3; §: patients who completed first-line therapy.
Treatment of Small-Cell Lung Cancer in Elderly Patients
Pallis AD, Shepherd FA, Lacombe D, Gridelli C.

(Cancer, 2010)

The purpose of this review is to focus on the management of SCLC in the elderly population. The issues that will be covered are radiotherapy and chemotherapy for limited-stage (disease limited to 1 hemithorax, with hilar and mediastinal nodes that can be encompassed within 1 tolerable radiotherapy portal) and extensive-stage SCLC.

Management of Limited-Stage SCLC
The standard of care for patients with good performance status and limited-stage disease is combined concurrent chemo-radiotherapy. Patients should receive 4 to 6 cycles of a platinum-based chemotherapy doublet combined with early radiotherapy (with Cycle 1 or 2).

Sintesi degli studi:
- older age = > mortality
- overall survival rate at 5 years < in patients >80 years
- very old patients received < local radiotherapy
- 47% of these patients did not receive any kind of local therapy
- in all studies, elderly patients received less intensive treatment in terms of chemotherapy dose or number of cycles
- radiotherapy was either less intensive in the elderly (dose reductions, less frequent use)
- some studies reported higher toxicity for the elderly, whereas others did not
- overall 2-year survival rates were significantly lower with advancing age: <65y 37%, 66-74y 22%, >75y 19% (P.003) = median survivals 17, 12, and 7 months
- on multivariate analysis, age and Charlson comorbidity scores were not significantly associated with treatment response and survival
Chemotherapy versus best supportive care for extensive Small cell lung cancer
Alvarez MP.
Cochrane Lung Cancer Group. Published Online: 27 NOV 2013.

Two small RCTs from the 1970s suggest that first-line chemotherapeutic treatment (based on ifosfamide) may provide a small survival benefit (<3 months) in comparison with supportive care or placebo infusion in patients with advanced SCLC.

Platinum-based combination chemotherapy regimens have been shown to increase complete response rates when compared to non-platinum chemotherapy regimens with no significant difference in survival, and so these are currently the standard first-line treatment for patients with SCLC.

Second-line chemotherapy at relapse or progression may prolong survival for some weeks. Nevertheless, the impact of first-line chemotherapy on quality of life, older patients, women and patients with poor prognosis is unknown and the benefits of second-line chemotherapy are also unclear for older people. Globally, the evidence on which these conclusions are based is very scarce and of uncertain or low quality, which calls for well-designed, controlled trials to further evaluate the trade-offs between benefits and risks of different chemotherapeutic schedules in patients with advanced SCLC.
Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Treatment of oligometastatic NSCLC

- Stage IV NSCLC patients presenting with solitary metastases, if localized to brain, adrenals, or lung, can be treated with curative intent.
- In the case of solitary brain metastasis, surgical resection followed by WBRT or alternatively radiosurgery ± WBRT might be beneficial. Further options include surgical resection of the primary lung combined with systemic chemotherapy [II; B], or definitive chemoradiotherapy, preferred in the case of locally advanced primary, such as solitary station N2 disease [III; B].
- In cases of solitary—histological proven—adrenal metastasis, prolonged survival after resection of the adrenal and the primary tumor has been suggested in selected patients [II; B].
- Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous secondary primary tumors and treated, if possible, with surgery and adjuvant chemotherapy (if indicated), definitive radiotherapy or chemoradiotherapy [II; A].

Follow-up

- Close follow-up, at least every 6 weeks after first-line therapy, is advised but should depend on individual retreatment options [III; B].
- Radiological follow-up should be considered every 6–12 weeks to allow for early initiation of second-line therapy.
TERAPIE DI SUPPORTO e TERAPIE PALLIATIVE
Role of minimally-invasive procedures in stage IV NSCLC

- In case of symptomatic major airway obstruction or post-obstructive infection, endoscopic debulking by laser, cryotherapy, or stent placement may be helpful [III; C].
- Endoscopy is useful in the diagnosis and treatment (endobronchial or by guiding endovascular embolization) of hemoptysis [III; C].
- Vascular stenting might be useful in NSCLC-related superior vena cava compression [II; B].

Role of palliative surgery in stage IV NSCLC

- Recurrent pleural effusions can be managed by pleurodesis.
- The preferred sclerosing agent is talc, which is more effective than bleomycin or tetracycline [II, B]; thoracoscopic insufflation with talc (poudrage) is more effective than talc slurry sclerosis [II, B].

Role of radiotherapy

- Radiotherapy plays a major role in symptom control in the case of bone and brain metastases and is also effective in treating pain related to chest wall, soft tissue, or neural invasion.
- Neurological symptoms from spinal compression can be relieved by early radiotherapy.
- Radiotherapy is indicated in cases of hemoptysis, symptomatic airway compression or obstruction, and following CNS and, sometimes, bone surgery [II; B].
Nutrizione

✔ La valutazione dello stato nutrizionale deve considerare: lo stato nutrizionale prima della malattia, istotipo e sede della neoplasia, tossicità dei trattamenti, perdita di peso, BMI, apporto alimentare, PCR, albumina.

✔ I supplementi nutrizionali orali (proteico/calorici e a base di vitamine e aminoacidi) dovrebbero essere utilizzati in pazienti anziani oncologici in caso di malnutrizione (*Raccomandazione B-positiva debole*).

✔ Non vi sono evidenze che dimostrino l'efficacia del supporto nutrizionale enterale e parenterale nell'aumentare la massa magra sulla sopravvivenza e sulla QoL. La NET o NPT dovrebbero essere prese in considerazione in pazienti con breve aspettativa di vita e in cui la cachessia è dovuta a ostruzioni del tratto gastrointestinale (*Racc.C-positiva debole*).

✔ Il Megesterolo Acetato ha dimostrato un miglioramento del peso corporeo, dell'anoressia e della QoL, ma con aumentato rischio tromboembolico e di mortalità nel lungo periodo (*Raccomandazione C-negativa debole*).
Role of bisphosphonate
- Zoledronic acid reduces skeletal-related event (pathologic fracture, radiation/surgery to bone, or spinal cord compression) and is recommended in stage IV bone metastatic disease [II; B].
- Denosumab is not inferior [I; A], and shows a trend toward superiority, to zoledronic acid in lung cancer in terms of skeletal-related event prevention [II; B].

Role of palliative-care early intervention
Early palliative-care intervention is recommended, in parallel with standard oncologic care [I; A].

Response evaluation
- Response evaluation is recommended after 2-3 cycles of chemotherapy using the same initial radiographic investigation
- Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity.
Lung cancer is the 6° most frequent malignancy responsible for Pulmonary Embolism.

Of all Non-small cell lung cancers, adenocarcinoma is currently considered to be the most thrombogenic tumor.

**Incidence and Risk Factors**

- Overall incidence of PE = 3.6% (0.2 – 17%) [misdiagnosis for respiratory distress in a patient with lung cancer is often attributed to pneumonia, disease progression, or pleural effusion]
- 1.5% in patients who underwent lung cancer resections vs 2.7% in nonsurgical candidates receiving chemotherapy → directly a result of the fact that patients with advanced stages are not operative candidates
- The mean time from the diagnosis of lung cancer to the diagnosis of PE was 185 days (174 - 3,609 days)
- As many as 85% of PEs are found within the 1° year after the lung cancer diagnosis.
**Effect on Mortality**
- In a case-control study comparing 40 patients with PE and 80 patients without PE, the same mortality rate was found (median survival 15.3 versus 11.4 months).
- In another smaller study of 24 patients, a reduced survival time was found when lung cancer was diagnosed, but not in those with PE diagnosed after the diagnosis of cancer.
- 80% of patients with the concomitant diagnosis of PE and lung cancer died in less than 8 months.

**Prophylaxis**
- Advantages of utilizing VTE prophylaxis is the reduced number of episodes of PE and the increase in survival rate post-operatively. The drawback of VTE prophylaxis may be the risk of postoperative intrathoracic bleeding and potential neurologic complications in patients with epidural catheters for postoperative analgesia.
- In medically treated patients, low molecular weight heparin is deliberately used for prophylaxis. The benefits, even for patients who are receiving chemotherapy, remain unknown.
- Data on VTE prophylaxis, studies pertaining to PE treatment duration, and the cost effectiveness are underreported.
Antifibrinolytic therapy to reduce haemoptysis from any cause
Cochrane Tobacco Addiction Group.  
Published Online: 18 APR 2012

Antifibrinolytic agents (tranexamic acid, aminocaproic acid, nafamostat and aprotinin) are drugs that act by inhibiting the process that dissolves clots, thereby reducing bleeding.

We identified two trials. Both of them evaluated the use of tranexamic acid, one for haemoptysis caused by tuberculosis and the other for haemoptysis from a variety of causes.

Tranexamic acid significantly reduced the bleeding time, but it did not make any difference to the number of patients who were still suffering from haemoptysis when it was evaluated at seven days after the start of treatment. Severe adverse effects were not reported and mild side effects were not different between patients receiving tranexamic acid and those not receiving tranexamic acid.

*There is insufficient evidence to judge whether antifibrinolytics should be used to treat haemoptysis from any cause, though limited evidence suggests they may reduce the duration of bleeding.*
1) Aging is associated with physiologic changes in organ function that could alter drug pharmacokinetics, with an impact on cytotoxic chemotherapy tolerability and toxicity.
2) Aging is associated with a significant prevalence of comorbid diseases.
3) Comorbidities have an impact on patient performance status and on patient ability to tolerate treatment, influencing overall survival.
4) Treatment decisions should be based on physiological rather than chronological age.
5) Aging is a highly individualized process.
6) Although several biological parameters have been used to predict functional status and outcome in elderly patients, none have been prospectively validated.
7) Comprehensive Geriatric Assessment (CGA) is one of the procedures developed to evaluate elderly patients’ functional status for the purpose of improving treatment outcomes. Data concerning CGA and its ability to detect covert health problems in the elderly cancer population are consistent.
8) Much of data currently available are based on age-specific retrospective analyses of trials that have enrolled patients without an age limit. These trials, however, are highly likely to suffer from selection bias, as only elderly patients considered “healthy enough” would have entered those studies.
9) Results from clinical trials conducted in younger patients cannot be extrapolated to the general elderly population. Prospective, elderly specific clinical trials are mandatory to provide evidence-based recommendations.

(Pallis, Cancer 2010)
TAKE-HOME MESSAGES PER I GERIATRI

✔ Osare di più
✔ Proporre più pazienti a oncologi e radioterapisti, dopo un'accurata selezione in base alla valutazione multidimensionale
✔ Considerare che la chemioterapia e la raditerapia rappresentano cure palliative anche nelle forme avanzate di carcinoma polmonare
✔ Anche pazienti > 70 anni con parziale disabilità (PS >2) possono beneficiare di trattamenti chemioterapici in monoterapia, in associazione o target-therapy
✔ Soprattutto in pazienti anziani è più utile effettuare esami bioptici, al fine di impostare trattamenti specifici con minor tossicità
✔ I cicli di chemioterapia dovrebbero essere il più prolungati possibile, se la malattia è controllata e gli effetti collaterali sono tollerabili