Combining radiation therapy and chemotherapy: Feasible in the elderly?

Jean-Claude Horiot
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- Are they reliable data justifying contra-indications of combinations of radiotherapy and chemotherapy in the elderly?
- What to do prior treatment to enhance tolerance to radio-chemotherapy schedules?
- Are they reliable indications of combined RT/CT per tumor site?
- Which management adjustments to recommend if needed?
- Is there a role for modern radiotherapy techniques?
- Which prospective research?
Are they reliable data justifying contra-indications of combinations of radiotherapy (RT) and chemotherapy (CT) in the elderly?  

(1)

- There is a considerable amount of data supporting that chemoradiotherapy schedules (neoadjuvant, concomitant or adjuvant CT) is more toxic (mostly acute toxicity) than radiotherapy alone.

- Most of the data from research trials refer to healthy (WHO 0,1,2) non-geriatric population

- Although, not based on a level one evidence, it seems logical to expect that such differences should be larger in elderly patients
Are they reliable data justifying contra-indications of combinations of radiotherapy (RT) and chemotherapy (CT) in the elderly?

(2)

- Reasons for expecting a worse toxicity in elderly:
  - Less WHO 0,1,2 in the elderly population
  - Increased risk for co-morbidities (hepatic, renal, cardiovascular etc..)
  - Increased risk of bone marrow depletion
  - Lower acceptance of aggressive, long-lasting and multiple-session/courses treatment
  - Specific psychological issues
Comorbidity, Disability, and Geriatric Syndromes in Elderly Cancer Patients Receiving Home Health Care
(S.M. Koroukian & al)

- **PATIENTS AND METHODS:** Ohio Cancer Incidence Surveillance System, 65 years of age or older with incident breast (n = 952), prostate (n = 324), or colorectal cancer (n = 1,276) from August 99 through Nov 2001.

- **RESULTS:** The proportion with no comorbidity, disability, or geriatric syndromes was:
  - 26.4% in breast cancer patients
  - 12.0% in prostate cancer patients,
  - 14.0% in colorectal cancer patients.

- The proportion of patients presenting all three entities at once was 11.7%, 24.7%, and 15.7%, respectively, in three cancer sites.

It is a common belief that a radio-chemotherapy scheme should only be proposed:

- To elderly patients in reasonably good general condition: This proportion will sharply decline beyond 70 years.
- In clinical situations for which a significant clinical benefit has been either demonstrated (rare) or is likely to occur in this age group.
- After comprehensive information of the patient and family.
- After adequate work-up and management of co-morbidities.
- In the frame of clinical research (unfortunately not so often).
As a result of all these well-known facts..

- The number of patients offered access to RT/CT schedule is astonishingly low!

- We should carefully reconsider this issue to make sure that a pessimistic behavior would not be detrimental to part of the elderly population with curable cancer.
  - By being proactive in restoring a better general condition
  - By exploring newer treatment modalities in upper age groups
Report on management of rectal cancer in France in 2000

From:

- Rapport rédigé pour la Direction Générale de la Santé (DHOS)
- Anne Marie Bouvier, Guy Lanois, Jean Faivre et le réseau FRANCIM
- Unpublished data.
A recent example: 2000 Data

- **From 12 French cancer registries:**
  - Bas-Rhin, Calvados, Côte d’or, Doubs, Haut-Rhin, Hérault, Isère, Loire Atlantique, Manche, Saône et Loire, Somme, Tarn.

- **Population of 8,419,000 (15 % of France)**

- **757 rectal cancers**
Methodology

- GCP’s and consensus statements available in all places.
- TNM Stage, pathology, treatment and follow-up data available.
- Rectosigmoid analysed with colon.
- Leaving only 25.3 % as rectal malignancies (787 cases)
- Sex ratio: male 62% female 38 %
- Age < 75: 64.5%
- Age > 75: 34.6 %
Surgical resection

- Overall, 84.7% of primary rectal cancers had a resection
- Complete 70.5% (6.5% endoscopic resection)
- <75 years: 89.7%
- >75 years: 75.1% (p<0.001)
Age, Radiotherapy (RT) and Chemotherapy (CT)

- **<75**

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>Range</th>
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<tbody>
<tr>
<td>Adjuvant RT</td>
<td>45.8 %</td>
<td>27-60</td>
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<tr>
<td>Palliative RT</td>
<td>14.1 %</td>
<td>6-20</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>51.9 %</td>
<td>31-66</td>
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</table>

- **>75**

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Adjuvant RT</td>
<td>26.7 %</td>
<td>6-38</td>
</tr>
<tr>
<td>Palliative RT</td>
<td>15.3 %</td>
<td>0-41</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>17.6 %</td>
<td>0-36</td>
</tr>
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</table>
Inclusion in a research trial (all patients)

- Yes: 5.3 % (range 0-14.6)
- No: 92.6 % (range 80.5-99.8)
- Unknown: 2.1 %
- Elderly: not indicated by likely to be near to ZERO
What to do prior to treatment to enhance tolerance to radio-chemotherapy schedules?

- A comprehensive geriatric assessment!
- To detect and treat reversible co-morbidities
- To restore as much as possible any physiological and biological imbalance before cancer treatment start
- Including psychological evaluation and preparation of the patient and close family.
Are they reliable indications of combined RT/CT per tumor site?

- Level one research data on the benefit of RT/CT over RT in cancers occurring frequently in elderly:
  - Carcinoma of the anus: a very interesting example since it can be extrapolated (regarding toxicity) to other tumor sites benefiting of concomitant RT/CT in S.C.C such as Head & Neck and uterine cervix cancers)
  - Head and neck cancers.
  - Cervix cancers
  - Hodgkin and NHL’s (never concomitant RT/CT)
  - Breast cancers (in fact very few concomitant except for inflammatory)
  - glioblastomas
RADIO-CHEMOTHERAPY IN LOCALLY ADVANCED ANAL CANCER
RESULTS: COLOSTOMY FREE SURVIVAL (P = 0.002)

Eligibility: up to 76.
In fact 22% only older than 60

Bartelink & al, JCO, 1997
Can this be extrapolated to H & N cancers in the elderly?

No!

Nearly all trials comparing RT to RT + cisplatin based regimens had upper age limits to 65-70.
Nine EORTC head & neck trials after issuing recommendation for no upper age limit

<table>
<thead>
<tr>
<th>Age limit</th>
<th>Trials (n)</th>
<th>Notes</th>
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<tbody>
<tr>
<td>70 years</td>
<td>3</td>
<td>Activated before 1995</td>
</tr>
<tr>
<td>75 years</td>
<td>2</td>
<td>1 before 1995; 1 EPO trial</td>
</tr>
<tr>
<td>No upper age limit</td>
<td>4</td>
<td>Trials 22954, 24954, 22962, 24001</td>
</tr>
</tbody>
</table>

- Of the trials with no upper age limit:
  - Total 574 patients
  - Only 15% >65 years
  - Only 1 patient aged >75 years
New (or revised) concepts in Head & Neck cancers in the past three years (2004-2007)

⇒ induction CT to be revisited
  • EORTC randomized trial PF vs TPF
    significantly improved survival with TPF

⇒ targeted therapies to be considered
  • XRT vs XRT + C225 randomized trial
    significantly improved survival with C225
EORTC 24971: revisiting neo-adjuvant CT: TPF vs PF

- Taxotere® + cisplatin + fluorouracil (TPF) versus cisplatin + fluorouracil (PF) in the treatment of inoperable, locally advanced SCCHN.
- Taxotere® 75 mg/m2 + cisplatin 75 mg/m2 + fluorouracil 750 mg/m2 (n=174) vs cisplatin 100 mg/m2 + fluorouracil 1000 mg/m2 (n=181)
- followed by RT (7wks later) +/- surgery for residual disease
- Selected inclusion criteria:
  - 18 to 70 years of age (10% > 65), WHO 1,2: in fact all but 1 (0.3% WHO 1, 0!)
  - Stage III-IV without distant metastases
  - hypopharynx, larynx, oropharynx, or oral cavity

*Vermorken & al: ASCO 2006, n engl j med 357;17; october 25, 2007*
EORTC trial (Vermorken et al. ASCO 2004)
Unresectable and previously untreated HNSCC

<table>
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<tr>
<th></th>
<th>PF</th>
<th>TPF</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Alopecia</td>
<td>0 %</td>
<td>11.5 %</td>
<td></td>
</tr>
<tr>
<td>Stomatitis/mucositis</td>
<td>11.2 %</td>
<td>4.8 %</td>
<td></td>
</tr>
<tr>
<td>Gr 3-4 tox</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR to CT</td>
<td>53.6 %</td>
<td>67.8 %</td>
<td>.007</td>
</tr>
<tr>
<td>CRR to CT</td>
<td>6.6 %</td>
<td>8.5 %</td>
<td>NS</td>
</tr>
<tr>
<td>ORR to CT-XRT</td>
<td>58.6 %</td>
<td>72.3 %</td>
<td>.008</td>
</tr>
<tr>
<td>CRR to CT-XRT</td>
<td>19.9 %</td>
<td>33.3 %</td>
<td>.004</td>
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**Progression Free Survival**
- Cox model (primary): p=0.006
- Hazard ratio 0.72
- 95% CI (0.56; 0.91)
- Unadjusted Logrank test: p=0.006
- Median: 12.7 mo (10.2, 14.2)
- Median: 8.4 mo (7.5, 9.6)

**Overall Survival**
- Logrank test: p=0.016
- Hazard ratio 0.73
- 95% CI (0.57; 0.94)
- Median: 18.6 mo (15.7, 24.1)
- Median: 14.5 mo (11.7, 18.8)
EORTC 24971 (results) TPF >PF

- O.S.: 18.6 vs 14.2 months, (29% mortality reduction risk HR:0.71, P=.005)
- PFS: 11.4 months vs 8.3 months (P=0.007)
- Overall response rate: 72.3% vs 58.6% (P=0.006)
- Toxicity profile: gr for gr 3,4 neutropenia 76 vs 53%, thrombocytopenia 5 vs 18 %, alopecia 11 vs none.
- Fewer deaths from toxic effects: (2.3% in the TPF group and 5.5% in the PF group)

Vermorken & al: ASCO 2006
<table>
<thead>
<tr>
<th></th>
<th>XRT (213 pts)</th>
<th>XRT + E (211 pts)</th>
<th>p</th>
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<tbody>
<tr>
<td>Gr 3-4 skin tox</td>
<td>18 %</td>
<td>34 %</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gr 3-4 mucositis</td>
<td>52 %</td>
<td>54 %</td>
<td>NS</td>
</tr>
<tr>
<td>1-yr LRC</td>
<td>59 %</td>
<td>69 %</td>
<td></td>
</tr>
<tr>
<td>2-yr LRC</td>
<td>48 %</td>
<td>56 %</td>
<td>.02</td>
</tr>
<tr>
<td>med survival</td>
<td>28 mos</td>
<td>54 mos</td>
<td></td>
</tr>
<tr>
<td>2-yr survival</td>
<td>55 %</td>
<td>62 %</td>
<td></td>
</tr>
<tr>
<td>3-yr survival</td>
<td>44 %</td>
<td>57 %</td>
<td>.02</td>
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</table>

**Locoregional control**

**Overall survival**
RT + a monoclonal antibody against EGFR, A progress in elderly with moderately advanced SCC of the Head & neck?

- With the exception of acneiform rash and infusion reactions, the incidence of grade 3 or greater toxic effects, including mucositis, did not differ significantly between the two groups.

- Eligibility: no upper age limit.

- Median age: 57 (range 34-82)

- Only 10% had a 60-70 Karnovsky score (90%, 80-100)

- Once more, just an interesting avenue to be further explored in elderly

NSCLC in elderly: radiochemotherapy?

- Considerable risk of unacceptable toxicity of concurrent radiochemotherapy.

- Multidisciplinary consultation with a surgical, radiation, medical oncologist, pneumologist, cardiologist, geriatrician, supportive care specialists...

- Elderly patients with medically inoperable stage I or II NSCLC, will in most cases be treated with XRT alone

- Elderly patients with inoperable stage III disease:
  - induction chemotherapy versus radiotherapy alone?
  - Elderly patients with acceptable PS should be offered chemotherapy, either combination platinum-based therapy or single-agent therapy (depending upon patient’s co-morbid conditions).
Can a conventional schedule of radiation therapy be administered to elderly patients with glioblastoma multiforme?

- 83 consecutive GBM (2001-2006). under 65 years (n=52) and ≥65 years old (n=31)
- 27/31 elderly patients (87.1%) had conformal radiotherapy (CRT, 59.40 Gy, 1.80 Gy/day with reduced TV after 39.6 Gy.
- Neurological acute toxicity was observed in 6/31 patients (19.4%), with grade 3 in two patients. In the under 65 group, 5/52 patients (9.6%) had neurotoxicity (Grade 3 in two patients) (n.s)
- At a median follow-up period of 28 months (range, 3-61), median PFS survival (PFS) was 11 months in the ≥65 group and 10 months in the under 65 group;
- OS was respectively 17 months and 22 months.
- 1-year survival was respectively 77.6% and 74.5%.

Conclusions: In our analysis age did not seem to be a limiting factor in patients with glioblastoma multiforme. Next logical step: RT + TMZ.

Tumor sites with no (or weak evidence) of benefit of first line combined RT/CT in younger patients

- Rectal cancers  (less local recurrences, no survival benefit)
- Prostatic cancers (emerging role of taxanes in hormone-refractory)
- Gynecological cancers (endometrium)

- In most of these cases, research trials results are either without elderly people or with very small sample subgroups
- Thus resulting in a very weak incentive to offer such combinations to the elderly population
A trial of special interest: 22921 on rectal cancer T3-T4: Pre-op RT+-CT, +-post-op CT (1011 pts)

- Originally upper age limit was 75
- Then extended to 80.
- 382 (38%) over 65
- 172 (17%) over 70
- 14 (1.4%) over 75
- More than half of the patients (56.4%) were over 65 years
Radiochemotherapy in curative management of rectal cancers

- Acute toxicity and outcome of concomitant radiochemotherapy for (selected) elderly patients with rectal cancer were comparable to those obtained in younger patients.

- These data suggests that elderly patients should be treated according to their functional status rather than age.
Concomitant radio-chemotherapy for elderly patients with stage II-III adenoCa.

- 98 patients > 65 years of age. March 2002 to Feb 2005
- Concomitant radiochemotherapy 50 Gy/5-6 wks + capecitabine 500 mg/sqm/day
- 78 patients received the entire planned treatment
- In 12, radiation dose was reduced to 30-44Gy
- 8 patients received only 1 week of capecitabine

Toxicity and Outcome (98 pts)

- grade 3-4 diarrhea in 20 patients
- vomiting and nausea in 28 patients
- grade 3-4 hematological toxicity in 19 patients.
- 68 pts had surgery and (with sphincter preservation in 37) Complete pathological response was achieved for 9 patients.
- inoperable patients, received a boost of 10 Gy on the tumor volume
- 82/98 patients are alive: 55 disease free, 18 local relapse, 9 metastatic disease. 11 patients died from cancer and 5 from co-morbidities.
Which management adjustments to recommend if needed (1)?

- The timing of the combination:
  - Concomitant RT/CT will almost always result in a higher acute toxicity and should only be proposed in situations where a benefit can be expected (e.g. in a curative treatment of an oropharyngeal cancer or as a pre-operative RT/CT in rectal cancer)
  - Neo-adjuvant CT may also reduce acute toxicity (compared to concomitant) e.g. in conservative management of laryngopharyngeal cancers
  - Adjuvant chemotherapy so far seems less well accepted and tolerated (e.g. in head and neck and rectal cancers)
Which management adjustments to recommend if needed (2)?

- **Dose reductions?**
  - For radiation therapy: not advisable
    - A dose reduction and/or an increased overall treatment time will increase the tumor failure risk
  - For chemotherapy: same recommendations as in the frail adults
  - Better to stop chemotherapy rather than taking the risk of an early radiotherapy interruption

- **Target Volume reduction?**
  - Acceptable in the elderly in areas of low risk of subclinical disease
  - Using better normal tissue sparing techniques (see later)
Is there a role for modern radiotherapy techniques?

- **Intensity modulated radiotherapy allows:**
  - A sharper coverage of the PTV (planned target volume)
  - A considerably better sparing of normal tissue and critical organs
  - Allowing tumor dose escalation trials (usually not in the elderly, except maybe in prostatic cancers…)
  - An improved acute tolerance of radiation therapy
    - Extending the range of indications of curative radiotherapy in Head and neck and pelvic cancers
    - Making concomitant RT/CT easier to deliver
  - Reducing the risk of late normal tissue damage
  - Enhancing durably quality of life (e.g. salivary gland sparing in head and neck cancers)
7 fields for T2 N2C oropharyngeal tumor sparing the parotid glands, the hard palate and the spinal cord delineated as organ at risk. Dose constraints for the parotids and for the palate were Dmean < 26 Gy. Dose constraints for the spinal cord was Dmax < 45 Gy.
Bilateral parotid sparing RT treatment planning with IMRT T2 pN0 tonsillar fossa S.C.C.
Experience of Dijon: 3D vs IMRT
Uterus intact
From where do we start with the inclusion of elderly in EORTC research trials with RT alone?

- The recommendation to delete age limits was followed in more than half (57%) of the protocols activated since 1995.
- About 30% of patients then entered were over 65.
- Most of them were 65-75 (92%).
- Very few over 80 (22 in 13 protocols).
- None of these protocols was specifically designed for elderly.
- Prostate, rectum are “good sites” for extending or cancelling upper age limits.
- In Head & neck, lung, the accrual of elderly was disappointing.
EORTC recommendations for RT research in the elderly

- Extending age limits to 80 (or no upper age limit) should be standard policy for most research trials when patients comply with other eligibility criteria.

- Specific trials should be designed for frail patients (regardless of age) and for patients over 80, whenever life expectancy seems consistent with the planned timing of analysis.

- The use of well-adapted scoring scales should become standard policy in master protocols.

- Together with the activation of such measures, the resistance and inertia due to old habits must be addressed by proper dialogue and information of investigators and patients.
Which prospective research for Radiochemotherapy? Two situations:

1) **Elderly patients fulfil eligibility criteria**
   - Extending the concept of « *no upper age limit* » to:
     - Phase III trials comparing radiotherapy alone to radiochemotherapy combinations
     - Phase III trials testing the addition of non-cytotoxic molecules to radiation therapy (e.g. C 225 in head and neck cancers)
   - Activating trials in elderly when a benefit of a RT/CT scheme has been demonstrated in non-geriatric adults (e.g. in glioblastomas)

2) **Specific protocols for frail patients**
   - Investigating innovative combinations of RT (high precision) and less toxic drugs
To conclude

- Although some improvement is observed, there are still major obstacles to overcome to offer a broader access to radiochemotherapy schemes to the elderly:
  - Scarce and low level of evidence of benefit
  - Resistance from the oncology community
  - Resistance from patients and their families
  - Optimal treatment preparation and delivery are more time consuming and may not be available everywhere

- However optimal management in elderly represents a growing challenge, an ethical problem and a scientific opportunity

- Hence… No choice left. We must tackle to that issue
Last recommendation!

Do not forget that when radiochemotherapy is not feasible, radiotherapy alone
- with adequate preparation of the patient after a comprehensive geriatric assessment
- and high accuracy treatment planning

is almost always feasible!!!