REZUMATUL TEZEI DE DOCTORAT

OPTIMIZAREA STRATEGIILOR CHIMIORADIOTERAPICE IN TRATAMENTUL COMBINAT MULTIMODAL AL CANCERULUI BRONHO-PULMONAR ”NON-SMALL CELL” AVANSAT LOCO-REGIONAL

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AUC = aria de sub curba
DSS = supravietuirea specifica de boala
Carbo=Carboplatin
cc = carcinom
ChT = Chimioterapie
ChRT = chimioradioterapie
Cis=Cisplatin
CR = raspuns complet
CT = Computer Tomografie
c = ciclu
2D-RT = radioterapie bidimensionala
3D-CRT = radioterapie conformationala tridimensionala
LC = control local
LRPFS = supravietuirea fara progresia loco-regionala a bolii
mS = supravietuirea mediana
mTTP = timpul median pina la progresia bolii
MTD = doza tolerate maximal
n = numarul
PFS = supravietuirea fara progresia bolii
PR = raspuns partial
PS = statusul de performanta
PD = progresia bolii
RR = rata de raspuns
RT = radioterapie
S = supravietuire
SD = boala stationara
TD = doza totala
Vrb=Vinorelbina
z = ziua

INTRODUCERE

Cancerul bronhopulmonar reprezinta o problema de sanatate publica prioritara in lume, privind datele epidemiologice. Este pe primul loc privind mortalitatea in multe tari, in special la barbati. Incidenta globala este in continua crestere si valorile cele mai mari cu 65.7 la 100,000 populatie se gasesc in Centrul si Estul Europei [2]. In Romania, incidenta a crescut constant in ultimele decade, atit pentru femei cit si pentru barbati, valorile fiind pe primul loc la barbati si pe locul patru la femei dupa cancerul de sin, col uterin, colon si rect. In ceea ce priveste mortalitatea, se situeaza de asemenea pe primul loc la barbati, urmat de cancerul de stomac colon, rect si ficat si pe locul patru la femei, dupa cancerul mamar, colorectal si col uterin [5, 12].

In contributia personala am ales drept obiectiv al studiului clinic, optimizarea strategiilor terapeutice in cancerul bronhopulmonar „non-small cell" stadiul III avansat locoregional, deoarece aceasta histologie reprezinta marea majoritate a cancerelor bronhopulmonare si mai mult de o treime prezinta la diagnostic boala avansata locoregional. Aceasta categorie cu tumori invazive, cu interesarea ganglionilor mediastinali, este heterogena, cu prognostic rezervat datorita controlului local modest si dezvoltarii metastazelor la distanta. Din aceasta cauza rezulta dificultatea de a stabili un consens terapeutic. In cadrul stadiului IIIA, un subgrup restrins este considerat potential operabil: cazurile T3N1, sau cu interesare N2 minimala, sau chiar unele categorii T4N0, dupa chimio- sau chimioradioterapie neoadjuvanta, desi unele studii nu au dovedit un beneficiu in supravietuire prin adaugarea chirurgiei dupa chimioradioterapie [54-56]. Restul cazurilor cu interesare ganglionara madiastinala masiva („bulky"), sau mai mult de doua statii ganglionare mediastinale, sau stadiul IIIB definit prin N3 (adenopatii mediastinale, hilare heterolaterale sau supraclaviculare), sau prin T4 (invazia tumorii primare in mediastin, trahee, vasele mari, cord, esofag sau vertebre), sint considerate adevaratele cazuri avansate locoregional, inoperabile, care beneficiaza de tratament combinat, multimodal. O subcategorie T4 cu colectii pleurale maligne, este de obicei exclusa din acest tratament combinat, nebeneficiind de iradiere si fiind cu prognosticul mai apropiat de boala metastatica. Avind in vedere aceasta heterogenitate in cadrul stadiului III, cu consecinte terapeutice diferite, a condus la necesitatea revizuirii sistemului de stadializare [41] propus pe 2009.

Desi in ultimele decade s-au depus eforturi uriase pentru imbunatatirea controlului local si la distanta, tratamentul optimal in cancerul bronho-pulmonar „non-small cell" stadiul III avansat loco-regional este inca dezbatut, multe intrebari raminind deschise, cu privire la cea mai buna combinatie de citostatice, secventialitatea cu radioterapia, utilizarea protectorilor, integrarea tehnicilor noi de radioterapie si a agentilor noi biologici.

La inceputul acestui mileniu, numeroase trialuri, majoritatea studii de faza a III-a [105-110], au comparat diferite regimuri de generatia a 3-a, dublete sau triplete, dar nici una din aceste combinatii de citostatice nu s-a dovedit net superioara. Mai apoi meta-analize ale acestor trialuri, au incercat sa raspunda la aceasta intrebare, dar rezultatele au fost controversate [111-115]. Avind in vedere ca tratamentul in cancerul bronho-pulmonar „non-small cell" avansat loco-regional este unul multimodal, iar chimioradioterapia concomitenta pare sa fie superioara tratamentului secvential intrebarea trebuie reformulata in sensul selectionarii celei mai bune combinatii de citostatice care poate fi administrata concomitent cu radioterapia din perspectiva eficacitatii ridicate si tolerantei acceptabile.

Contributia personala are drept obiectiv sa raspunda la unele dintre intrebarile formulate, si este structurata in doua studii clinice prospective care au decurs in mod logic una din alta.

Primul este un studiu de faza a II-a care si-a propus determinarea eficacitatii prin prisma ratei

de raspuns si a supravietuirii cit si a toxicitatii tratamentului concomitent cu vinorelbina si un compus de platina cu radioterapia, urmat de chimioterapia de consolidare cu acelasi regim de citostatice, in cancerul bronho-pulmonar „non-small cell" avansat loco-regional. Studii preclinice au indicat rolul radiosensibilizator al vinorelbinei cu efect la nivelul microtubulilor, cu blocarea ciclului celular in fazele cele mai radiosensibile, G2/M [41], conducind la utilizarea in clinica a combinatiei vinorelbina/cisplatin concomitent cu radioterapia.

Rezultatele preliminare ale primului studiu de faza a II-a au aratat ca este fezabil, bine tolerat, profilul de toxicitate fiind comparabil cu datele din literatura [91, 92, 97], iar rata de raspuns si supravietuirea fiind promitatoare.

Rata esecurilor loco-regionale fiind inca semnificativa, a fost evidenta necesitatea pe mai departe a unui tratament mai agresiv loco-regional si la distanta. A fost rindul radioterapiei de a creste randamentul terapeutic, realizat prin integrarea noilor tehnici de radioterapie conformationala tridimensionala. O noua strategie s-a dezvoltat prin integrarea secventei de chimioradioterapie concomitenta dupa chimioterapia de inductie si urmata de cea de consolidare. Expectanta de la chimioterapia de inductie a fost de reducere a volumului tumoral si in consecinta a volumului tinta tumoral pentru radioterapie cu escaladarea dozei de iradiere pentru cresterea probabilitatii ratei de control cu scaderea efectelor acute si tardive. Chimioterapia de consolidare s-a adugat ca urmare a rezultatelor primului studiu la care rata de raspuns a fost semnificativ mai buna cind s-au administrat 5 sau 6 cicluri de chimioterapie.

Astfel contributia personala este structurata in doua studii prospective, cu diferita integrare a secventei de chimioradioterapie concomitenta: in primul studiu este urmata de chimioterapia de consolidare, iar in al doilea studiu este precedata de chimioterapia de inductie si urmata de chimioterapia de consolidare si cu incorporarea tehnicilor moderne de radioterapie conformationala tridimensionala, care au permis escaladarea dozelor de iradiere, intr-un studiu de faza I-II modificat. Intre timp rezultatele primului studiu au ajuns la maturitate.

A. PRIMUL STUDIU PROSPECTIV

REZULTATE PE TERMEN LUNG CU CHIMIORADIOTERAPIA CONCOMITENTA CU VINORELBINA SI UN COMPUS DE PLATINA URMAT DE CHIMIOTERAPIA DE CONSOLIDARE PENTRU CARCINOAMELE BRONHO-PULMONARE „NON-SMALL CELL" STADIUL III AVANSATE LOCO-REGIONAL - UN STUDIU DE FAZA A II-A

Obiectivele acestui studiu prospectiv de faza a II-a a fost determinarea eficacitatii, toxicitatii si supravietuirii dupa chimioradioterapia concomitenta cu vinorelbina si un compus de platina, urmata de chimioterapia de consolidare cu acelasi regim de citostatice in carcinoamele „non-small cell" stadiul III avansate loco-regional.

Pacienti si metode. Cincizecisiopt de pacienti au fost inclusi in studiu, in perioada 16.11.2000 si 26.02.2004, cu o virsta mediana de 56 ani, variind intre 44 si 71 ani, barbati/femei 50/8, cu indicele de performanta 1/2 = 27/31, stadiul IIIA/ IIIB 11/47, cu urmatoarele histologii: carcinoame scuamoase 45, adenocarcinoame 7, carcinom adenoid chistic 1, carcinoame cu celule mari 7.

Tratamentul a constat in 2 cicluri de chimioterapie cu vinorelbina si un compus de platina, administrate concomitent cu radioterapia, urmate de inca 2-4 cicluri de chimioterapie de consolidare cu aceleasi citostatice. Dozele au fost reduse cind au fost administrate concomitent cu radioterapia: vinorelbina 15 mg/m^2 iv. in perfuzie de 30 min, in ziua 1 si 8, la

interval de 21 zile si cisplatin 80 mg/m^2 in perfuzie iv. de 2 ore, cu hidratare in ziua 1, sau Carboplatin AUC 3 in perfuzie iv. in 30 de minute, ziua 1, la interval de 21 zile. Dozele au fost cele clasice cind s-au administrat ca si chimioterapie de consolidare: vinorelbina 25 mg/m^2 iv. in perfuzie de 30 min, in ziua 1 si 8, la interval de 21 zile si cisplatin 100 mg/m^2 in perfuzie iv. de 2 ore, cu hidratare, in ziua 1, sau Carboplatin AUC 5 in perfuzie iv. in 30 de minute, ziua 1, la interval de 21 zile. Premedicatia cu dexametazona si antiemetice s-a facut de rutina. Amifostina, (ethyol WR-2721)**,** un tiofosfat organic, chiomio-radioprotector, a fost administrat inainte de chimioterapie in perfuzie iv. 740 mg/m^2, ziua 1, 8, la 21 zile, la primii 22 pacienti.

Rezultate: **Toxicitatile,** evaluate la toti pacientii, (dupa criteriile RTOG), au fost preponderent de grad 1 si 2. Toxicitatile severe au fost: esofagita de grad 3 si 4 cu o rata de 19 %, comparabila cu datele publicate in literatura, neutropenia cu 19% si toxicitatile digestive cu 17% au fost mai scazute decit datele raportate. De asemenea am observat o rata mai scazuta de esofagite severe, 14%, la pacientii care au primit amifostina, fata de 22%, la cei care nu au beneficiat de acest chimioradioprotector, dar diferenta nu a fost statistic semnificativa. O rata scazuta de 7% din pacienti au prezentat anemie severa, care a fost corectabila.

Cu toate ca rata toxicitatilor acute a fost acceptabila, comparabila cu datele din literatura, a avut un impact asupra compliantei chimioterapiei (64%) si radioterapiei (80%). S-a semnalat un singur deces toxic prin soc septic, dar **toxicitati tardive** semnificative, nu s-au raportat**.**

Rata raspunsurilor evaluata la toti pacientii, (considerind criteriile RECIST), a fost promitatoare: la 13 pacienti (22.41%) s-a obtinut un raspuns complet (CR), la 24 (41.38%) un raspuns partial (PR) cu o rata de raspuns obiectiva (RR = CR+PR) de 64% (95% CI 52-76). Sasesprezece pacienti (27.59%) au avut boala stabila (SD) si 5 (8.62%) au dezvoltat progresia bolii (PD).

Supravietuirea specifica de boala (DSS) cu valori la 1, 2, si 3 ani a fost de 59%, 32% si respectiv de 21%, cu supravietuirea mediana de 15.1 luni. Rezultatele obtinute sint comparabile cu datele din literatura (bratul cu chimioradioterapie concomitenta din studiul lui Zatloukal [92] si studiul francez al lui Fournel [91]). Supravietuirea fara progresia bolii (PFS) a atins la 1- 2- si 3-ani valori de 38%, 18% si respectiv 7%, cu o mediana pina la progresia bolii de 10.3 luni. Supravietuirea fara progresia loco-regionala (LRPFS) a aratat la 1, 2 si 3-ani valori de 54%, 35% si respectiv 21%, reperzentind un control local relativ bun dupa definitia lui Green [198]. Totusi rata esecurilor locoregionale de 60% reprezinta un argument pentru necesitatea unui tratament mai agresiv in al II-lea studiu prospectiv.

In analiza uni si multivariata nici unul din factorii legati de pacient, cum ar fi virsta, genul, histologia, stadiul sau indicele de performanta, sau legati de tratament, ca numarul de cicluri de chimioterapie, doza totala sau etalarea in cazul radioterapiei nu au influentat semnificativ supravietuirea sau progresia bolii.

Avind in vedere ca DSS a fost influentata semnificativ doar de raspunsul la tratament, 31% la trei ani pentru CR+PR vs 5% pentru SD+PD, $p<0.01$, am considerat modelul logistic multivariat avind drept obiectiv raspunsul la tratament si care a aratat semnificatie doar pentru numarul de cicluri administrate, ($p=0.02$).

B. AL II-LEA STUDIU PROSPECTIV

CHIMIOTERAPIA DE INDUCTIE CU VINORELBINA SI UN COMPUS DE PLATINA URMATA DE CHIMIORADIOTERAPIA CONCOMITENTA SI CHIMIOTERAPIA DE CONSOLIDARE PENTRU CARCINOAMELE BRONHO-PULMONARE „NON-SMALL CELL" STADIUL III AVANSATE LOCO-REGIONAL - UN STUDIU MODIFICAT DE FAZA I-II

Obiective: evaluarea fezabilitatii si eficacitatii integrarii chimioradioterapiei concomitente cu vinorelbina si un compus de platina, dupa chimioterapia de inductie si urmata de chimioterapia de consolidare, cu acelasi regim de citostatice, pentru carcinoamele bronho-pulmonare „non-small cell" stadiul III, avansate locoregional. Avind in vedere controlul loco-regional rezervat la aceasta categorie de pacienti, odata cu introducerea radioterapiei conformationale tridimensionale, s-a evaluat posibilitatea de escaladare a dozei de iradiere.

Pacienti si metode: Saptezecisitrei de pacienti au fost inclusi in perioada 05.02.2004 - 24.01.2008 cu o virsta mediana de 58 ani (39–75), barbati/femei = 67/6, cu un indice de performanta 1/2=41/32, stadiu IIIA/IIIB=11/62, carcinoame scuamoase 57, cu celule mari 5, adenocarcinoame 4, carcinoame„non-small" 7. Tratamentul a constat din 2 c de chimioterapie (ChT) de inductie cu Vrb (25 mg/m², z1, 8, q21) si Cis (100 mg/ m², z1, q21), sau Carbo (AUC 5, z1, q21), urmate de inca 2 c cu doze reduse: Vrb 15 mg/ m², z1, 8, q21, Cis 80 mg/ m², z1, q21 sau Carbo AUC 4, z1, q21, administrate concomitent cu radioterapia (RT) si inca 2 c de ChT de consolidare cu aceleasi citostatice in doze complete. Iradierea s-a efectuat la acceleratorul liniar (15MV) pina la o doza totala de 60-70 Gy/30-35 fractiuni/ 6-7 saptamini. Doua tehnici de iradiere au fost utilizate, cea clasica bidimensionala, ultimii 33 pacienti beneficiind de Radioterapie conformationala tridimensionala (3D-CRT). Douazecisiopt pacienti care au indeplinit contringerile histogramelor doza-volum (Doza maxima pentru maduva spinarii ≤ 48Gy, V20 pentru ambii plamini < 35% si Dozele de toleranta cu risc de complicatii 5% din tabelul lui Emami [192] pentru 1/3, 2/3 respectiv 3/3 din volumul esofagului si cordului) au fost supusi escaladarii dozelor in patru cohorte la: 64Gy, 66Gy, 68Gy, 70Gy.
Patru cicluri de ChT au fost completate de 90% din pacienti, 5 sau 6 c de 71%. Trei patrimi (75%) din pacienti au primit ≥ 60 Gy.

Rezultate: saptezecisitrei de pacienti au fost evaluati pentru **toxicitati** care au fost preponderent usoare, de grad 1 si 2. Toxicitatile severe, de grad 3 si 4 au avut o rata scazuta, chiar mai scazuta decit in primul studiu de faza a II-a considerat « perioada de invatare » : neutropenia la 12 pacienti (16%), anemia si esofagita la cite 6 pacienti e (8%), greturi si varsaturi la 5 (7%) pacienti. Radiopneumonita severa de grad 3 a fost prezenta la 5 (7%) pacienti.

Escaladarea dozei de iradiere, in cele patru cohorte: 64Gy, 66Gy, 68Gy si 70Gy, in administrare concomitenta cu chimioterapia, in limitele permise de histogramele doza volum sus amintite, a fost posibila la 28 dintre cei 33 de pacienti cu RT conformationala tridimensionala cu o rata acceptabila de toxicitati acute severe. Este de mentionat faptul ca toxicitatile severe au aparut cu preponderenta la pacientii la care nu s-a escaladat doza de iradiere, deoarece datele din histogramele doza-volum pentru organele critice nu le-au permis. Avind in vedere ca doza de maxima toleranta nu a fost atinsa studiul va fi continuat in perspectiva. Cu toate acestea, exista un risc potential pentru toxicitati severe tardive. Singura toxicitate tardiva notabila, strictura esofagiana, a fost observata in cazul clinic prezentat, desi

la acest pacient, fiind intre primii cu 3D-CRT, nu s-a escaladat doza peste 60 Gy, V20 fiind la limita de 35%. Trebuie mentionat ca parametrii dosimetrici au fost acceptabili, si toleranta in timpul si dupa perioada de iradiere a fost apparent buna, fara semne acute de esofagita. Din aceasta cauza o urmarire riguroasa pe termen lung si studii in continuare sint necesare pentru acumularea de experienta in acest sens.

Raspunsurile, evaluate la toti pacientii, cu RR de 66%, cu 29% CR, 37% PR, 20% SD si 14% PD, de asemenea au fost comparabile cu datele din literatura si ceva mai bune decit in primul studiu. Nici unul din criteriile legate de pacient ca virsta, sexul, statusul de performanta, histologia sau stadiul clinic, nu au influentat semnificativ rata de raspuns. Dimpotriva toti factorii legati de tratament, ca numarul de cicluri administrate (cu ambele valori prag 4 si respective 5 cicluri), doza totala, precum si etalarea iradierii, au influentat semnificativ RR.

Cu o mediana de urmarire de 11.9 luni, **DSS** la 1 an a fost 66% (95%CI:53-78%) si de asemenea a fost comparabila cu datele din literatura (supravietuirea la un an de 64% in bratul 3 al studiului LAMP [99] si supravietuirea la un an de 69.2% in studiul ceh a lui Zatloucal [92]). Supravietuirea mediana nu a fost atinsa inca. **PFS** la un an a fost de 47%, cu o mediana pina la progresia bolii de 11,2 luni. LRPFS la un an a fost de 64%. Desi nu se pot compara rezultatele celor doua studii prospective efectuate, nefiind randomizate, supravietuirile au fost mai bune in al II-lea studiu, explicatia constind in tratamentul mai agresiv aplicat.

In analiza univariata, singurul factor legat de pacient care a influentat semnificativ DSS (p=0.01) si PFS (p=0.02) a fost indicele de performanta. In ceea ce priveste factorii legati de tratament, DSS a fost influentat semnificativ de doza totala pentru ambele valori prag, 60 Gy (p=0.01), si 64 Gy respectiv (p=0.02). PFS a fost influentata semnificativ cind s-au administrat mai mult de 4 cicluri de ChT (p=0.01) si cind s-au administrat cel putin sau mai mult de 60 Gy (p=0.01). Valoarea p s-a apropiat de semnificatia statistica cind s-au administrat mai mult de 5 cicluri (p=0.07) si o doza mai mare sau egala cu 64 Gy (p= 0.06).

In analiza multivariata Cox, singurul factor semnificativ legat de tratament a fost doza totala mai mare sau egala cu 60 Gy. In ceea ce priveste PFS nici un factor preterapeutic sau terapeutic nu s-a dovedit a fi semnificativ.

Utilizind **modelul logistic multivariat** pentru raspunsul la tratament ca si "endpoint", numarul de cicluri (p<0.01) si doza totala mai mare sau egala cu 60Gy (p=0.04) au fost semnificative si au permis stratificarea pacientilor in functie de **scorul prognostic al ratei de raspuns** in trei categorii: pacienti cu doza totala mai mare sau egala cu 60 Gy si care au primit 6 cicluri de ChT cu o RR de 85.71%, cei cu aceeasi doza totala dar care au primit 5 cicluri de ChT cu o RR de 76.47% si restul cu doza mai mica de iradiere si un numar mai mic de 5 cicluri, in diferite combinatii cu RR pentru aceasta categorie de numai 39.29%.

In final **DSS**, a fost semnificativ influentata de raspunsul la tratament, atingind la un an o rata de 95% pentru cei cu raspuns complet, 73% pentru cei cu raspuns partial, 53% pentru pacientii cu boala stabila si numai 12% pentru pacientii cu boala in progresie. Pentru **PFS la un an**, pacientii cu progresia bolii nu au fost considerati, rata fiind de 90% pentru pacientii ci raspuns complet, 31% pentru cei cu raspuns partial cit si pentru cei cu boala stationara. Deasemenea in cazul **LRPFS** la un an valorile au fost de 95% pentru pacientii cu raspuns complet, 63% pentru cei cu raspuns partial si 60% pentru cei cu boala stationara (p<0.01).

Avind in vedere ca imbunatatirea controlului loco-regional ar creste supravietuirea in cancerul bronho-pulmonar „non-small cell" avansat loco-regional, strategia escaladarii dosei de iradiere trebuie explorata in continuare.

CONCLUZII FINALE SI PERSPECTIVE

1. Importanta subiectului rezulta din datele epidemiologice care situeaza cancerul bronhopulmonar pe primul loc din punct de vedere al incidentei si mortalitatii in majoritatea tarilor, cu valorile cele mai ridicate in Centrul si Estul Europei. In Romania incidenta si mortalitatea sint pe locul intii pentru barbati si pe locul patru pentru femei, dupa cancerul mamar, de col uterin, colon si rect.

2. Optimizarea strategiilor terapeutice in carcinoamele bronho-pulmonare "non-small cell stadiul III avansat loco-regional, reprezinta o provocare pentru clinician, in aceasta categorie heterogena, privind alegerea celui mai bun regim de citostatice in combinatie cu RT prin prisma eficacitatii si profilului de toxicitate, integrarea tehnologiilor noi in radioterapie, spre exemplu RT ghidata imagistic, tehnicile conformationale tridimensionale, dispozitivele pentru reducerea miscarilor de organ si verificarea erorilor de pozitionare.

3. Obiectivele studiului au fost dezvoltarea unei strategii terapeutice pentru imbunatatirea rezultatelor generale exprimate prin: RR, DSS, PFS, LRPFS cu un profil de toxicitate si calitatea vietii acceptabile.

4. Structura studiului este organizat in 2 etape: primul studiu prospectiv de faza a II-a a avut drept scop evaluarea fezabilitatii si rezultatelor prin alegerea unui regim de citostatice care sa se poata administra concomitent cu RT cu tehnica clasica bidimensionala, urmata de chimioterapia de consolidare, cu acelasi regim de citostatice si un al doilea studiu modificat de faza I-II, derivat in mod logic din primul, cu escaladarea agresivitatii ambelor proceduri, prin adugarea chimioterapiei de inductie, care precede secventa de chimioradioterapie concomitenta si chimioterapia de consolidare si integreaza noile tehnologii de radioterapie conformationala tridimensionala, cu escaladarea dozei de iradiere, pentru cresterea probabilitatii de control loco-regional cu cit mai putina morbiditate.

5. Trebuie mentionat **ca experienta internationala** a aratat possibilitatea de a imbunatati prognosticul in carcinoamele bronho-pulmonare „non-small cell" stadiul III avansat loco-regional, prin combinarea ambelor metode chimio si radioterapia, dar nu exista un consens in ceea ce priveste alegerea citostaticelor, modatitatii de administrare, a technicilor de iradiere.
La Institutul de Oncologie „ Prof Ion Chiricuta" am dezvoltat o strategie pe termen lung, la inceput stabilind un regim de chimioradioterapie concomitenta care s-a dovedit superioara fiecarei modalitati terapeutice aparte, cu un profil de siguranta favorabil. Pasul urmator a constat in escaladarea agresivitatii ambelor modalitati prin adaugarea chimioterapiei de inductie si introducerea tehnicilor noi de radioterapie conformationala tridimensionala cu escaladarea dozelor de iradiere.

6. Concluziile finale pe baza rezultatelor obtinute au subliniat, in experienta noastra, ca vinorelbina si un compus de platina reprezinta o alegere buna pentru o administrare simultana cu radioterapia, din perspectiva profilului de siguranta si al eficacitatii. Rezultatele primului studiu au ajuns la maturitate, acumulind experienta. In al doilea studiu, avind in vedere ca la analiza univariata singurul criteriu legat de pacient care a influentat semnificativ DSS si PFS a fost indicele de performanta, iar intre criteriile legate de tratament, DSS a fost influentat de DT $\geq$ 60Gy si DT $\geq$ 64Gy, pe cind PFS a fost influentat de numarul de cicluri > 4 si DT $\geq$ 60Gy, am considerat ca in pacientii cu indice de performanta bun, este rezonabil a administra 5 sau 6 cicluri de ChT si doze mai mari de iradiere decit 60Gy, cind datele de histograma

doza-volum cu privire la organele critice o permit. Aceasta schema de terapie tip „sandwich", de integrare a secventei de chimioradioterapie concomitenta intre ChT de inductie si cea de consolidare, s-a dovedit a fi avantajoasa in mod special pentru reducerea volumului tinta tumoral pentru 3D-CRT, tinind seama ca mai mult de jumatate din pacienti au avut o rata de raspuns obiectiva dupa chimioterapia de inductie, facind posibila escalarea dozei in continuare. Astfel pacientii care raspund mai bine la ChT de inductie pot fi selectionati pentru tratamente mai agresive ca si chimioradioterapia concomitenta si 3D-CRT cu escaladarea dozei in siguranta, care poate fi continuata pina se obtine doza maxima tolerata. Rata scazuta a toxicitatilor pulmonare este de asemenea un argument pentru aceasta strategie. Scorul prognostic al RR de asemenea sustine acest design, obtinind pentru acesti pacienti o RR variind intre 76.47% si 85.71%, care s-a dovedit a influenta in continuare supravietuirea.

7. In perspectiva, ramin intrebari deschise in continuare in legatura cu alegerea celei mai bune combinatii de citostatice, cu cea mai mare eficacitate si cea mai buna toleranta in administrarea concomitenta cu RT.

De asemenea modalitatea optimala de administrare nu este bine definita, daca administrarea sistemica la 3 saptamini este mai buna sau cea saptaminala, cu doze scazute cu efect radiosensibilizator. Majoritatea studiilor au utilizat schema saptaminala de administrare [98, 99].

Gemcitabina este un potential radiosensibilizator dar doza tolerata in administrare concomitenta cu RT nu este bine stabilita.

Metaanaliza lui Douillard a dovedit superioritatea docetaxelului asupra alcaloizilor de vinca de generatia a II-a si a III-a luate la un loc [112], iar metaanaliza lui Grossi a aratat ca docetaxelul si gemcitabina reduc riscul de progresie a bolii cu 7 respectiv 12 % [113].

Un studiu de non-inferioritate, de faza a III-a randomizat, utilizind pemetrexed si cisplatin vs gemcitabina si cisplatin in carcinoamele bronho-pulmonare „non-small cell" avansate sau metastatice [200] a aratat o supravietuire similara, dar un beneficiu in mS pentru adenocarcinoame (12.6 vs 10.9 luni, p=0.033) si carcinoame cu celule mari (10.4 vs 6.7 luni, p=0.027).

Docetaxelul si pemetrexedul si-au dovedit activitatea in tratamentul de linia a II-a [201] dar au fost mai putin investigati in prima linie concomitent cu RT.

Se formuleaza de asemenea intrebari legate de parametrii de RT, privind escaladarea dozei, modificarile de fractionare, etalarea si volumul tinta tumoral, de data aceasta prin perspectiva tratamentului concomitent cu chimioterapia. Avind in vedere aceste intrebari, studiul nostru de escaladarea dozei de iradiere in concomitenta cu chimioterapia se continua pentru a acumula experienta in acest domeniu.

Odata cu aparitia erei moleculare, tratamentele tintite au fost integrate. Rezultatele promitatoare ale studiilor E4599 si AVAIL [148, 149], au lansat bevacizumabul in tratamentul de linia I-a in carcinoamele bronho-pulmonare „non-small cell" avansate in combinatie cu citostaticele de generatia a 3-a desi pentru un grup restrins de carcinoame non-scuamoase. Modalitatea in care tratamentele moleculare pot fi combinate cu RT si cu ChT in carcinoamele bronho-pulmonare „non-small cell" avansate urmeaza sa fie evaluata in viitor.

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- 15. 12th World conference on lung cancer, Seoul Korea, 2-6 sept 2007
- 16. ECCO 14 the European Cancer Conference, Barcelona 23-27 sept 2007
- 17. Conferinta Societatii Maghiare de Radioterapie 25-27 oct, 2007 Debrecin
- 18. The 7th Congress of B.U.O.N. 16-19 oct 2008 Izmir Turkey

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SUMMARY of the PhD thesis entitled

OPTIMIZING CHEMORADIOTHERAPY STRATEGIES IN THE COMBINED MODALITY TREATMENT OF LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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List of abbreviations in alphabetical order

AUC = area under the curve
DSS = Disease specific survival
cc = carcinoma
ChT = Chemotherapy
ChRT = chemoradiotherapy
CR = complete response
CT = Computer Tomographic scan
cy = cycle
d = day
2D-CRT = two-dimensional conformal radiotherapy
3D-CRT = three-dimensional conformal radiotherapy
Fig = Figure
HFRT = hiperfractionated radiotherapy
LC = local control
LRFS = loco-regional progression-free survival
mS = median survival
mTTP = median time to progression
MTD = maximal tolerated dose
n = number
NSCLC = Non-small cell lung cancer
PFS = progression-free survival
PR = partial response
PS = performance status
PD = progressive disease
RR = response rate
RT = radiotherapy
S = survival
SD = stable disease
Sq cell cc = squamous cell carcinoma
TD = total dose
ULN = upper limit of normal
y = year

INTRODUCTION

Epidemiology data place lung cancer on the priorities of health care worldwide, considering its incidence and mortality. It is the leading cause of cancer mortality, especially in men, in many countries. Globally the incidence is increasing and the highest rates for men are found in Europe, especially in Central and Eastern Europe with 65.7 per 100,000 population [2]. In Romania, incidence has been increasing constantly in the last decades for men and women as well, the figures situated it on the first place in men and on the forth place in women after breast, cervix uteri, colon and rectum cancer. In what concerns mortality in our country, lung cancer is on the first place for men, followed by stomach, colon and rectum and liver cancer. In women is also on the forth place after breast colorectal and cervix uteri cancer [5, 12]

The clinical study chose as purpose the optimization of treatment strategies in locally advanced stage III NSCLC, as it represents the vast majority of lung cancers with more than one third presenting locally advanced disease at diagnosis. This category is a very heterogeneous group with locally extensive tumours and invasion of the mediastinal lymph nodes, with low overall survival due to modest local control and development of distant metastases. Therefore is difficult to find a consensus concerning treatment in this heterogeneous setting.

Within stage IIIA, a small soubgroup might be potentially operable: T3N1, or with minimal N2, and even some of the T4 (e.g. satelite nodules in the same lobe) N0 tumours, after neoadjuvant chemotherapy or chemoradiotherapy, although some studies didn't show any substantial benefit by adding surgery**,** **[**54-56]. The rest with bulky mediastinal lymph nodes, or more than two stations involved or stage IIIB defined by either N3 (heterolateral mediastinal or supraclavicular lymph nodes) or T4 (invasion of the mediastinum, heart, great vessels, tracheea, carina, esophagus or vertebral body), are considered the main locally advanced inoperable NSCLCs and benefit of combined modality chemoradiotherapy as the standard approach. Patients with malignant pleural effusions („wet IIIBs") are usually excluded, as they cannot benefit of radiotherapy and their prognosis is more alike to metastatic disease. This heterogeneity with therapeutical consequences lead to the neccessity of the revision of the last Staging System [41] which is avaited for 2009.

Although in the last decades big efforts have been done in this field, to improve local and distant control, the optimal therapy for locally advanced, stage III NSCLC is still debated, many questions are waiting for answers concerning the best drug combinations, the sequencing issue with RT, the use of protectors, integration of new RT techniques, and, new biological agents.

At the beginning of the 3rd millennium, numerous trials, most of them phase III studies [105-110], compared different regimens of 3rd generation doublets or triplets, but none of these chemotherapeutic regimens has clearly emerged as the most efficacious. Then meta-analyses of some of these trials, tried to answer this question, but results were controversial [111-115].

As combined modality treatment is the standard approach in locally advanced NSCLC and it seems that there is evidence for even better results with concurrent approach for fit patients the question should be formulated as which is the best chemotherapy regimen to be combined with RT in the perspective of efficacy and toxicity profile.

The personal contribution was aimed to answer to some of the formulated questions and became structured in two prospective clinical studies which emerged logically from one to another.

The first prospective phase II study started with the purpose to determine the efficacy, toxicity and survival of concurrent therapy with vinorelbine and a platinum compound with radiotherapy, followed by consolidation chemotherapy with the same drugs, for locally advanced non small cell lung cancer (NSCLC). Preclinical studies, indicating a role for vinorelbine as radiosensitiser, based on the antimicrotubule effect with subsequent cell cycle arrest in G2/M, the most radiosensitive cell cycle phases [13], have led to the use of vinorelbine /cisplatin combination with RT

As the preliminary results of the first phase II study showed that it is feasible, well tolerated, and the toxicity profile compared favorably with other similar studies [91, 92, 97] and the effect on the response rate and survival was promising it warranted further clinical evaluations in a second prospective study, which emerged from the first one. As the rate of loco-regional failures was still high, it was obvious that there is a need for more agressive loco-regional treatment. It was the turn for radiotherapy to increase the therapeutic ratio and as there was the possibility to integrate new radiotherapy techniques, like three-dimensional conformal radiotherapy, a new strategy developed of the combined treatment with induction chemotherapy followed by the concurrent chemoradiotherapy and followed by consolidation chemotherapy. It was the expectation from the induction chemotherapy to reduce the tumour volume, allowing thus the reduction of the target volume for radiotherapy and leading consequently to dose escalation for achieving a higher probability of tumour control with less acute or late side effects. The treatment scheme incorporated at the end consolidation chemotherapy as the results of the first phase II study demonstrated significantly better response rate when 5 or 6 cycles of chemotherapy were given.

Thus the personal contribution is structured in two prospective studies, with different integration of the concurrent chemoradiotherapy sequence: in the first is followed by consolidation chemotherapy and in the second is preceeded by induction chemotherapy and followed by consolidation chemotherapy and with the introduction of the new technique of three dimensional radiotherapy with dose escalation. In the meantime the first phase II study grew to mature results.

A. FIRST PROSPECTIVE STUDY

LONG TERM RESULTS OF CONCURRENT CHEMO-RADIOTHERAPY WITH VINORELBINE AND A PLATINUM COMPOUND FOLLOWED BY CONSOLIDATION CHEMO-THERAPY FOR UNRESECTABLE STAGE III NON-SMALL CELL LUNG CANCER (NSCLC) – A PHASE II STUDY

Purpose: The aim of this prospective phase II study was to determine the efficacy, toxicity and survival of concurrent therapy with vinorelbine and a platinum compound with radiotherapy, followed by consolidation chemotherapy with the same drugs, for loco-regionally advanced non small cell lung cancer (NSCLC).

Patients and methods: Fifty-eight patients with stage III NSCLC were included: median age 56 years (range 44-71), males / females 50/8, performance status 1/2 = 27/31, stage IIIA/ IIIB 11/47, squamous cell carcinoma 45, adenocarcinoma 7, adenoid cystic carcinoma 1, large cell carcinoma 5. Treatment consisted of 2 cycles of ChT with vinorelbine and a platinum compound concurrently with RT, followed by 2-4 more cycles of consolidation ChT with the same drugs. When given concurrently with RT the drugs were administered at lower doses: vinorelbine 15 mg/m^2 given as an iv. infusion over 30 min, on day 1 and 8, every 21 days and cisplatin 80 mg/m^2 iv. infusion over 2 h with hydration on day

1, or carboplatin at an area under the plasma concentration time curve (AUC) 3, iv. infusion over 30 min on day 1, every 21 days. When given as consolidation chemotherapy the doses were: vinorelbine 25 mg/m^2 on day 1 and 8, every 21 days; cisplatin 100 mg/m^2, on day 1, or carboplatin AUC 5, on day 1, every 21 days. Premedication with dexamethasone and antiemetics was administered routinely. An organic thiophosphate radio-chemoprotector amifostine (ethyol WR-2721) was administrated before chemotherapy as a 30 min iv. infusion at a dose of 740 mg/m^2, on days 1 and 8, every 21 days in the first 22 patients

Results: Toxicities, evaluated in all pts, were preponderently mild, grade 1 or 2. Severe grade 3 and 4 esophagitis with a rate of 19% was comparable with the data published in the literature but digestive .toxicity and neutropenia with 17 % and 19% were lower. Also we observed a trend of lower severe esophagitis rates among patients who received amifostine, 14% vs 22% in patients without amifostine, but statistical significance was not reached.
A low rate of patients (7%) had severe anemia which was manageable.
Still the **acute toxicity rates** were acceptable, manageable and comparable with the data in the literature, they had an impact on the compliance for chemotharapy (64%) and radiotherapy (80%) as well. There was only one patient with septic death and no significant **late toxicities** have been reported.

The responses in the intent-to-treat patients were promising: 13 patients (22.41%) achieved CR, 24 patients (41.38%) achieved PR for an overall RR (CR+PR) of 64% (95% CI 52-76). Sixteen patients (27.59%) had stable disease (SD) and 5 (8.62%) developed progressive disease (PD).

Also the 1, 2, and 3-year **DSS** rates of 59%, 32% and 21% respectively, with **mS** of 15.1 months were comparable with the data in the literature (concurrent arm of the czech study, as well as with the concomitant arm of the french trial)**.** The **PFS** showed 1- 2- and 3-year values of 38%, 18% and 7%, respectively, with a mTTP of 10.3 months. **LRPFS** showed at 1, 2 and 3-years values as 54%, 35% and 21% respectively, witnessing a rather good LC. Still the LR failure rate of 60% was an argument for more aggressive treatment in the second prospective study.

In the **univariate or multivariate analyses** none of the patient related factors such as age, gender, histology, stage or PS nor the treatment related factors like number of cycles, total dose and total number of days of radiotherapy delivery had any significant effect on survival or progression

As DSS was influenced significantly only by response to treatment, 31% at three years for CR+PR vs 5% for SD+PD, $p<0.01$, we considered a multivariate logistic model with response to treatment as endpoint which showed significance only for the number of cycles administrated ($p= 0.02$).

C. SECOND PROSPECTIVE STUDY

INDUCTION CHEMOTHERAPY WITH VINORELBINE AND A PLATINUM COMPOUND FOLLOWED BY CONCURRENT CHEMORADIOTHERAPY AND CONSOLIDATION CHEMO-THERAPY WITH THE SAME DRUGS FOR STAGE III NON-SMALL CELL LUNG CANCER (NSCLC) – A MODIFIED PHASE I-II STUDY

Purpose: to evaluate safety and efficacy of integration of concurrent ChRT with Vinorelbine (Vrb) and a Platinum compound after induction ChT and followed by consolidation ChT with the same drugs, for stage III NSCLC. As local control rates are poor

in this cathegory dose escalation using three-dimensional conformal radiotherapy has been chosen as strategy to improve local control and survival.

Patients and methods: 73 patients (pts) were included from 05.02.2004 to 24.01.2008: median age 58(39–75), M/F=67/6, PS 1/2=41/32, stage IIIA/IIIB=11/62, squamous cell cc 57, large cell cc 5, adenocc 4, „non-small"carcinoma 7. Treatment consisted of 2 cycles (c) of induction ChT with Vrb (25 mg/sqm, d1, 8, q21) and Cis (100 mg/sqm, d1, q21), or Carbo (AUC 5, d1, q21), followed by 2 more c with reduced doses: Vrb 15 mg/sqm, d1, 8, q21, Cis 80 mg/sqm, d1, q21 or Carbo AUC 4, d1, q21, given concurrently with RT and 2 c of consolidation ChT with the same drugs, in full doses. RT (15MV) has been administrated to a total dose of 60-70 Gy/30-35 fractions. Two techniques of RT have been used: the classical bi-dimensional and the last 33 pts benefited of 3D-CRT. Twenty-eight patients with 3D-CRT who fulfilled the DVH constraints (maximal dose for the spinal cord ≤ 48Gy, V20< 35% and the TD5% for the esophagus and heart for 1/3, 2/3 and 3/3 respectively of the volume of organ from the table of Emami [192]) underwent dose escalation in four cohorts 64Gy, 66Gy, 68Gy, 70Gy.
For each dose level of RT up to 7 patients were enrolled to have at least five assessable patients for toxicity. Dose escalation from one dose level to the next could occur if no more than two grade 3 toxicities or only one grade 4 toxicity occurred during the course of RT and the following 8 weeks. If one grade 3 and one grade 4 toxicity occured, further expansion by five assessable patients at the same dose level was applied with similar rules for dose escalation to these additional patients [193,194].
90% of pts completed at least 4 c, 71% completed 5 or 6 c of ChT. 75% of pts received ≥ 60Gy.

Results: In the73 evaluable pts for **toxicities** these were preponderantly mild, of grade 1 and 2. Severe grade 3 and 4 toxicities were even lower than in the first phase II study considered the "learning period": neutropenia in 12 pts (16%), anemia and esophagitis in 6 patients each (8%), nausea and vomiting in 5 (7%) patients. Grade 3 acute radiation pneumonitis was present in 5 (7%) of the patients.

Dose escalation of RT with concurrent ChT, within the planning constraints outlined in this population in four cohorts : 64Gy, 66Gy, 68Gy, 70Gy, was possible with acceptable acute toxicities As no MTD was reached during dose escalation this strategy has to be continued. However there is also a potential risk of severe late toxicities, as witnessed in the clinical case presentation, in tissues which good classical dosimetric parameters, which exhibited initially apparent good tolerance during treatment and in the immediate post irradiation period. Therefore a long-term follow-up and further studies in this field are needed.

Responses with an overall RR of 66%, with 29% CR, 37% PR, 20% SD and 14% PD also were comparable with the data in the literature and slightly better than in the first study.
None of the patient related criteria such as age, sex, performance status, histology, or stage influenced significantly the RR. On the contrary all the treatment related factors influenced significantly the objective RR: such as number of cycles (with both thresholds: 4 and 5 cycles), total dose and total number of days of delivery of RT.

With a median follow-up of 11.9 months, the 1-year **DSS** rate was 66% (95%CI:53-78%) and was comparable with the data in the literature :1-year survival rate of 64% of arm3 of the LAMP study [99] and the 1-year survival rate of 69.2% in the Czech study [92]. The **mS** has not been reached yet. The **PFS** rate at 1 year was 47%, with a mTTP of 11,2 months. LRPFS showed at 1 year 64%. Although not comparable, as not randomized the results of the second study are slightly better as more aggressive treatment has been delivered.

In univariate analyses the only patient related factor that influenced significantly DSS (p=0.01) and PFS (p=0.02) was PS.
Concerning the treatment related factors, DSS was influenced significantly by total dose, for both threshold doses considered, 60 Gy (p=0.01), and 64 Gy respectively (p=0.02). PFS was influenced significantly when more than 4 cycles of ChT were given (p=0.01) and when more or at least 60 Gy were administrated (p=0.01). The p value approached to the statistical significance when more than 5 cycle were given (p=0.07) and when more or at least 64 Gy were administrated (p= 0.06)

In multivariate Cox regression analyses, the only significant treatment related factor is the total dose greater or equal with 60Gy. The same steps have been done for PFS but none of the pretreatment or treatment related factors were found significant.

Using the **multivariate logistic model** with response to treatment as endpoint, the number of cycles (p<0.01) and the total dose more or equal with 60 Gy (p=0.04) were significant, permitting the stratification of patients according to the **prognostic score of RR** in three categories: patients with total dose higher or equal with 60 Gy and who received 6 cycles of ChT with a RR of 85.71%, those with the same total dose but with 5 cycles who attained a RR of 76.47% and the rest of the patients who had or lower dose of RT or lower nr of cycles in different combinations, with a RR for this category of only 39.29%.

Finally **DSS**, was significantly influenced by treatment response, achieving at 1 year a survival rate of 95% for complete responders, 73% for partial responders, 53% for patients with stable disease and only 12% for patients who progressed. As patients with progressive disease were not considered for the 1-year **PFS**, the rates were 90% for complete responders, 31% for patients with partial response as well as for stable disease. Somewhat similar was the 1-year LRPFS according to response rate: 95% for complete responders, 63% for partial responders and 60% for patients with stable disease (p<0.01).
Because improvements in loco-regional control could improve survival in advanced NSCLC, the strategy of dose-escalated radiotherapy needs to be further explored

FINAL CONCLUSIONS AND PERSPECTIVES

5. The importance of the topic is emphasized by the epidemiology data which situate lung cancer mortality and incidence on the first place in many countries, with the highest figures in Central and Eastern Europe. In Romania incidence and mortality are on the first place for men and on the fourth place for women after breast, cervix uteri, colon and rectum cancer.

6. Optimization of treatment strategies in locally advanced stage III NSCLC represents **a challenge for the clinician** in this heterogeneous setting, concerning the best chemotherapy regimen to be combined with RT in the perspective of efficacy and toxicity profile and the integration of new technologies in radiotherapy like image guided radiotherapy, 3D-CRT, devices to overcome organ motion and set-up errors.

7. The **objectives of the study** were to develop a multidisciplinary treatment strategy to improve the general outcome: RR, DSS, PFS, LRPFS with an acceptable toxicity profile, quality of life.

8. The **structure of the study** is organized in 2 steps: the first prospective phase II study aimed to evaluate feasibility and outcome by choosing a basic chemotherapy regimen to be combined with classical 2DRT technique in concurrent setting and followed by consolidation chemotherapy and the second one, a modified phase I-II study with the escalation of the

aggressiveness of both modalities by adding induction chemotherapy preceding the concurrent chemoradiotherapy and consolidation chemotherapy and by integrating the new technology of 3D-CRT, with dose escalation in order to achieve a higher probability of tumour control with less morbidity.

5**. Specific remarks** would emphasize that **i**nternational experience has shown the possibility to improve prognosis in locally advanced stage III NSCLC by combining both modalities chemo and radiotherapy but there is no consensus regarding the choice of the drugs, modalities of delivery, irradiation techniques.
At the Institute of Oncology „ Prof Ion Chiricuta" we developed a long term strategy, first by establishing a concurrent chemoradiotherapy regimen that proved to be superior to either treatment alone and with favorable safety profile. The next step was to escalate the agressiveness of both modalities by adding the induction chemotherapy and introducing the new technology of three-dimensional conformal RT with dose escalation.

6. The final conclusions of our results were that in our experience vinorelbine and a platinum compound is a good candidate for combining with simutaneous radiotherapy in the perspective of safety profile and efficacy. The results of the first study grew to mature, long term results, and more experience has been accumulated. In the second study, as in the univariate analysis the only patient related criteria that influenced significantly DSS and PFS was PS and among treatment related criteria DSS was influenced by TD≥60 Gy and TD≥64 Gy, wherease PFS was influenced by n of cy >4 and TD≥60 Gy, we consider that in fit patients with good PS there is a good reason to administrate 5 or 6 cycles of ChT and higher doses than 60Gy of RT. This „sandwich" schedule, of integrating the concurrent setting between induction and consolidation ChT, prooved to be appropriate especially for reducing the Target Volum for 3D-CRT, as more than half of the patients had a RR after the induction ChT making possible further dose escalation. Thus „good responders" after induction chemotherapy can be selected for more agressive treatment as concurrent chemoradiotherapy with the integration of conformal techniques which allow safely dose escalation, which is to be continued untill MTD is attained. The low rate of pulmonary toxicity is also an argument in this view for this strategy.
The prognostic score of RR also sustains this design, obtaining for these patients a RR ranging between 76.47% and 85.71%, which proved to have further significant influence upon survival.

7. **In the perspectives** there still remain questions to be answered, regarding the best drug combination to be chosen, with the highest efficacy and best toxicity profile, that can be combined safely with RT.
Also the optimal mode of administration, is not well defined: wether systemic, at 3 weeks is better, than weekly low dose with radiosensitising effect. Most of the studies used the weekly schedual of administration [98, 99].
Gemcitabine is a potent radioinhancer but tolerated doses in concomitant setting have not been well established.
The Douillard metaanalysis proved the superiority of Docetaxel upon second and third generation vinca alcaloid compounds [112]. and the metaanalyses of Grossi emphasised that Docetaxel and Gemcitabine reduces the risk of progression of the disease with 7 and 12 % respectivelly [113].
A non-inferiority randomized Phase III trial of Pemetrexed and Cisplatin vs Gemcitabine and Cisplatin in Locally Advanced or Metastatic NSCLC [200] showed similar overall survival, but a benefit in mS in adenocarcinomas (12.6 vs 10.9 months, p=0.033) and large cell carcinomas (10.4 vs 6.7 months, p=0.027).
Docetaxel and Pemetrexed prooved their activity in second line therapy [201] but were less

investigated in first line and in concurrent setting with RT.
There are also questions with the most effective parameters of RT concerning dose escalation, altered fractionation, overall treatment time, and treatment volume, for this time in the perspectives of combined simultaneous ChT. Regarding this our dose-escalation study is continued to find answers in this field.
Since the advent of molecular era targeted treatments have been integrated. The promissing results of the E4599 and AVAIL study launched Bevacizumab in the first line of advanced non squamous NSCLC, in combination with 3rd generation drug doublets [148, 149], although for a restricted group of non-squamous cell carcinoma. How molecular treatments can be combined with RT in locally advanced NSCLC has to be evaluated in the future.

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- junior doctor, 1983-1986, Districtual hospital Cluj
- general practitioner, 1986-1988, Health unit Unguras, Cluj county and Clinical Hospital of Pulmonary Diseases "Leon Daniello".
- resident in oncological radiotherapy, 1988-1991, Institute of Oncology "Prof. Ion Chiricuta" Cluj-Napoca
- specialist in oncological radiotherapy since 1991
- senior radiation oncologist, Institute of Oncology "Prof. Ion Chiricuta" Cluj-Napoca since 1996
- specialist in general oncology and chemotherapy since 2000
- PH.D. candidate in medicine, scientific coordinator Prof. dr. N.Ghilezan, at the University of Medicine and Farmacie "Iuliu Hatieganu" Cluj-Napoca, since october 2003

Professional titles:

- graduate in oncological radiotherapy since 1991
- researcher in oncology since 1991
- first- degree in oncological radiotherapy since 1996
- graduate in general oncology and chemotherapy since 2000

Positions hold in professional organizations or societies:

Member in:

- Romanian Society of Oncological Radiotherapy
- Romanian Society of Cancer
- European Society for Therapeutic Radiology and Oncology (ESTRO)
- European Society of Medical Oncology (ESMO)
- Balkan Union of Oncology (BUON)
- member of the Editorial Board of the Journal of BUON
- Christian association of health " Solatium"- president of the board
- International Association for the Study of Lung Cancer (IASCL)

- J.L.Moreno Society of Psichodrama

Postgraduate studies:

- residency in radiation oncology, course of general oncology and chemotherapy, 1988-1991, Cluj
- course on general oncology, 1990 Timisoara
- course on descriptive biostatistics, 1991, Cluj
- course on computer tomography, 1991, Cluj
- new perspectives in cancer treatment – farmorubicin high dose, Farmitalia Carlo Erba, 08. 05.1991
- course on Clinical Imunology, 26.10.- 20. 11. 1992, Institute of Haematology, Budapest
- ESO course on "Breast and Lung cancer" 21-22.10. 1993, Cluj
- ESO course on " Molecular Biology : Fundamental & clinic", 1995, Cluj
- course on Paliativ Care, 16-17.06. and 26-27.11. 1995 Budapest
- course of Systemic Psychotherapy 25.05- 28.05. 1995,Cluj
- Medical Oncology Workshop 23-24.05.1996 Iasi
- Salzburg – Cornell Seminar "Oncology", 27.07-02.08. 1997, Salzburg
- satellite courses "Meet the professor" at the 8th World Conference on lung cancer, 10-15.08.1997
- AAMP International Scientific course on " the Physics of Radiation Therapy 10-14.06.1999
- ESTRO teaching course on " Imaging for target volume determination in radiotherapy, 24-28.06.2001, Krakow
- Multidisciplinary approach in Oncology & Treatment Planning, the 11th Interuniversity Symposium, organized by the "Aristotelis " Institute 29.08. –01.09. 2001, Thessaloniki
- Aromasin, hormonal therapy in breast cancer- Pharmacia Enterprises –symposia 31.05-02.06.02 Mamaia
- The third international symposium on " Target Volume Definition in Radiation Oncology based on Sentinel Node Procedure" Limburg 29-31.05.2003
- Satelyte symposia of the 10th World Conference on Lung Cancer 10-14.08.2003, Vancouver
- Satelyte symposia of the 8th Central European Lung Cancer Conference, 1-3 sept 2002 Wienna
- Satelyte symposia of the 21st ESTRO Meeting 17-21 sept , 2002 Praga
- Satelyte symposia of ECCO 12, 21-25 sept, 2003, Copenhaga
- Training in psihodrama – 14-15.02; 04-05.04; 20-22.06.03;03-05.10.03 ; 13-14.02.04 ; 16-17.04.04 ; 04-05.06.04 ; 03-04.09.04 ; 06-07.11.2004
- Course on Bronchoscopy , 01.11.03-01.02.2004, Bucharest
- Satelyte symposia of the 23rd ESTRO Meeting 24-28 oct , 2004 Amsterdam
- Satelyte symposia of the 29th ESMO Congress 29oct- 2 nov 2004 Wienna
- ESMO Scientific & Educational Conference (ESEC) Budapest, Hungary 2-5 June 2005-11-15
- Satelyte symposia of the 11th World Conference on Lung Cancer 3-6.07.2005, Barcelona, Spain
- Study programme at the Instituto Europeo di Oncologia , Dept of Radiotherapy Milan 20.06.- 20.09.2005
- ESO Course of Advances in Radiation Therapy, Milan, 15-17.02.2006
- First Course on Deliniation of Target Volumes and new thechniques in radiotherapy, IOCN, 24-26.03.2006

- Postuniversity course on: Progresses of the year 2005 in the management oncological patients, a post ASCO/ESMO/ESTRO meeting under the auspices of UMF & IOCN, 7-8. 04. 2006
- Course-Conference of the 10th Central European Lung Cancer Conference, 18-21,2006 Prague Czech Republic
- Course on: New technologies in clinical radation oncology: implementation in Romania in colaborare cu William Beaumont Hospital Royal Oak USA, 26-28 sept 2006 Cluj
- Simpozionul "Intre consens si realitate in tratamentul Cancerelor digestive" " 6 dec 2006
  cu ocazia zilelor UMF "Iuliu Hatieganu"
- Curs postuniversitar "Tendinte noi in controlul cancerului", 22-23 iunie 2007,
- ECCLU, Lugano iulie 2007
- Satelyte symposia of the, 12th Wold Conference on Lung Cancer, Seoul Korea, 2-6 sept 2007
- Satelyte symposia of the ECCO 14 the European Cancer Conference, Barcelona 23-27 sept 2007
- Conference of the Romanian Society of Radiotherapy and Oncology (SRRO) oct 2007
- Zilele Universitatii de Medicina si Farmacie Iuliu Haiteganu, Cluj 03.12.2007
- 9th European Congress: Perspectives in Lung Cancer Torino,12-15 march 2008
- ESMO Conference Lugano 3-6 july 2008
- 33rd ESMO Congress, Stockholm 12-16 sept 2008
- ESMO supported course: Breast cancer Management: A European Perspective, 2-4 october 2008

Scientific activity:

62 papers, 47 papers first author, 18 (15 first author) presented at international Conferences:

1.The 4th Central European Conference, sept 1996, Gdansk, Poland,

2. Conference on Lung Cancer, 09-11.11.1996 Creta, Greece,

3. The 7th European Interuniversity symposium at "Aristotelis" Institute, 1997 Thessaloniki, Greece,

4. The 8th World Conference on Lung Cancer, august, 1997 Dublin Ireland,

5. The 18th UICC International Cancer Congress, 30 june-5 july, 2002, Oslo, Norway,

6. The 4 th Congress of the Balkan Union of Oncology.22-23. nov 2002 Athens, Greece,

7. The 10th World Conference on Lung Cancer 10-14 august, 2003 Vancouver, Canada,

8. ECCO 12, 21-25 sept 2003, Copenhagen,

9. The 5th Congress of BUON, 14-17 oct. 2004 Belgrade,

10.The 23rd ESTRO Meeting, 24-28 oct, 2004 Amsterdam,

11. The 29th ESMO Congress, 29oct-2 nov 2004 Wienna,

12. 11th World Conference on Lung Cancer, 3-6.07.2005, Barcelona, Spain,

13. The 6th Congress of the Balkan Union of Oncology 13-16 sept 2006, Sofia Bulgaria

14. ESTRO 25 Meeting October 9-12, 2006, Leipzig, Germany

15. 12th World Conference on lung cancer Seoul Korea, 2-6 sept 2007

16. ECCO 14 the European Cancer Conference, Barcelona 23-27 sept 2007

17. The Conference of Hungarian Society of Radiotherapy, 25-27 oct, 2007 Debrecen

18. The 7th Congress of B.U.O.N. 16-19 oct 2008 Izmir Turkey

30 abstracts and 11 articles(9 first author)

Topics: Local and distant control in advanced breast cancer, prognostic significance of axillary involvement in breast cancer, chemoradiotherapy strategies in "non-small and small lung cancer, clinical value of tumour markers (Cyfra 21-1) in lung cancer.

List of the titles of the scientific papers:

1. The evolution of diagnosis procedures in Lung Cancer (Evolutia procedurilor de diagnostic in neoplasmul bronho-pulmonar); G. Petrescu, N. Culcitchi, V. Georgescu, L. Toader, P. Rusu; Consfatuirea interjudeteana cu tema cancerul bronhopulmonar 29.05.1987 Sibiu.
2. Local and distant control in advanced breast cancer, (Controlul local si la distanta in cancerul mamar avansat) C.Vitoc, P.Rusu, A.Rancea, N. Ghilezan, National Oncology Conference, oct 1992, Craiova
3. Prognostic significance of axillary involvement in operable breast cancer, (Semnificatia prognostica a invaziei axilare in cc mamar operat)

P. Rusu, S.Cipaian, V.Muntoiu, C. Vitoc, N. Ghilezan, National Oncology Conference, 23-24.09. 1993 Bucuresti.

4. Adjuvant treatment in breast cancer in the experience of Oncology Institute Cluj (Indicatiile si rezultatele tratamentului adjuvant in cancerul mamar ; experienta Institutului Oncologic Cluj), N.Ghilezan, C. Pap, C.Vitoc, N.Todor, P.Rusu, A.Rancea, N.Galatar, A.Rusu, National Oncology Conference, 23-24.09, 1993, Bucharest.
5. Cost-benefit evaluation in the diagnosis and treatment of advanced Breast Cancer (Bilantul preterapeutic si tratamentul CMALR-Analiza cost beneficiu), C.Vitoc, P.Rusu, G. Crisan, N. Ghilezan, H. Hancu, Simpozion de Oncologie, 2-3 iunie 1994, Baile Felix, Oradea
6. Prognostic significance of axillary involvement after neoadjuvant chemotherapy in advanced breast cancer, (Valoarea prognostica a axilei dupa chimioterapie neoadjuvanta in CMALR), C. Vitoc, G.Crisan, P.Rusu, A. Rasinaru, A. Rancea, N.Todor, N. Ghilezan, National Oncology Conference, 14-16 oct, 1994, Bucharest
7. Alternatives in chemotherapy in advanced NSCLC (Alternative pentru utilizarea chimioterapiei in carcinoamele bronho-pulmonare"non-small cell" avansate), TE Ciuleanu, N. Ghilezan, N.Todor, D.Cernea, A.Ioan, P. Rusu- Scientific session " Zilele IMF" 1995, Cluj- Napoca
8. Cyfra 21-1 , a new marker in Lung Cancer (Cyfra 21-1, un nou marker in cancerul bronho-pulmonar). Petronela Rusu. Cancerul nr 13, 1996.
9. Prognostic factors in advanced non-small cell Lung Cancer-a multivariat analysis (Carcinoamele bronho-pulmonare nonmall cell locoregional avansate-analiza multivariata a factorilor de prognostic), TE Ciuleanu, N.Ghilezan, N. Todor, E.Cvitkovic, H de

Cremoux, J.P. Armand, P. Ruffie, N. Azli, J.C.Saltiel, I.Momet, S.Voisin, A.Ioan, D.Cernea, P.Rusu, I. Radulescu,C.Cebotaru, M. Albiter, National Oncology Conference, 23-25 oct 1996, Poiana Brasov.

10. Chemo-radioterapy strategies in small cell Lung Cancer (Rezultatele unor strategii de tratament asociat chimio-radioterapic in cancerul bronho-pulmonar cu celule mici), P.Rusu, N.Ghilezan, T.E.Ciuleanu, D.Cernea, C.O.Ordeanu,A.Ioan, M.Albiter, N.Todor, National Oncology Conference, 23-25 oct 1996, Poiana Brasov
11. Radiotherapy in advanced NSCLC (Radioterapia in tratamentul cancerului bronho-pulmonar non- small avansat locoregional), D.Cernea, C.Ordeanu, A.Ioan, P.Rusu,T.Guttman, National Oncology Conference, 23-25 oct 1996, Poiana Brasov
12. A multivariate regression analysis for advanced non-small cell lung cancer patients treated with multidisciplinary approach including chemotherapy, Ciuleanu TE, Ghilezan N, Todor N, Cvitkovic E, De cremoux H, Armand JP, Ruffie P, Azli N, Saltiel JC, Monnet I, S Voisin, A Ioan, D Cernea, P Rusu, I Radulescu, C Cebotaru, M Albiter, Proc 4th Central European Conference on Lung Cancer, sept.1996, Gdansk
13. Accordance between clinical and pathological staging in NSCLC, A.Ioan, N.Ghilezan, T.E. Ciuleanu, T.Guttman, D.Cernea, P.Rusu, the 4th Central European conference, sept 1996, Gdansk
14. Multimodality therapy in resectable NSCLC, A. Ioan, N.Ghilezan, T.E.Ciuleanu,D.Cernea, P.Rusu, Conference on Lung Cancer, 09-11.11.1996, Creta, Greece
15. Noninvasive diagnostic work-up correlated, with operative findings in NSCLC. Recent advances in diagnostic imaging and supportive care in oncology, Guttman T, Ciuleanu TE, A Ioan, P Rusu, Todor N, Barsan M, Ghilezan N, Book of Abstracts of The 7th European Interuniversity symposium at "Aristoteles" Institute, 1997 Thessaloniki, Greece, P19, p51.
16. Cyfra 21-1: clinical value in lung cancer, P.Rusu, Lung cancer 1997,V 18, supl1: p 162, abstract of the 8th World Conference on Lung Cancer, 10-14 august, 1997 Dublin Ireland.
17. Therapeutic guide: Lung Cancer (Ghid terapeutic: Cancerul bronhopulmonar), TE Ciuleanu, Gutulescu N, Donea S, Pop S, C Cebotaru, P Rusu, Radioterapie & Onc Med, (5), nr 1, 1999: 8-19.
18. Cyfra 21-1: clinical value in lung cancer, P.Rusu, Radioterapie & Onc Med 1999, V 3: 252-260.
19. Recent advances in the management of stage III non-small cell lung cancer, P.Rusu, Radioterapie & Onc Med 1999, V 3: 185-194.
20. External Radiotherapy in lung cancer (Radioterapia externa in Cancerul Bronhopulmonar, P.Rusu , "Zilele Oncologice Clujene" 9-12 noiembrie 2001, Cluj- Napoca
21. External Radiotherapy in lung cancer, P Rusu. Radioterapie & Oncol Med, 2000,VI,4: 364-374
22. Current chemoradiotherapy strategies in advanced NSCLC (Noi strategii in tratamentul chimio -radioterapic al cancerelor bronho-pulmonare "Non-small cell avansate loco-regional") teaching lesson"–P. Rusu – National symposium 31 may- 1 june 2001, Iasi

23. PCI 99-EULINT 1-eligibility and noneligibility criteria (Trial International de iradiere craniana profilactica)-P. Rusu, T.E. Ciuleanu, D. Cernea, C. Cebotaru, D. Iancu, T.Guttman, N. Ghilezan . National Oncology Conference, 23-24 nov, 2001, Bucharest

24. Radiochimioterapia concomitenta cu Navelbine si Cisplatine in carcinoamele bronho-pulmon "non-small cell avansate loco-regional, staudiu de faza a II-a, rezultate preliminare, P.Rusu, TE Ciuleanu, D.Cernea, C. Cebotaru, D.Iancu, D.Roman, N.Todor, N.Ghilezan, abstract book, National Oncology Conference, 23-24 nov, 2001, Bucharest

25. Ameliorarea prognosticului pacientilor avind un carcinom bronho-pulmonar localizat localizat, printr-un abord pluridisciplinar,Ciuleanu TE,Rogociu R, Ioan A, Barsan M,Guttman T, Rusu P, Ghilezan N. Oncology Conference, 23-24 nov, 2001, Bucharest

26. Chemo-Radiotherapy strategies in Locally Advanced Non-Small Cell Lung Cancer. P. Rusu, Radioterapie & Oncologie Medicala 2002, 1: 22-29.

27.Chimio-radioterapia concomitenta urmata de chimioterapia de consolidare cu vinorelbina si cisplatin in carcinoamele bronhopulmonare « non-small cell « avansate loco-regionale– P. Rusu, T.E. Ciuleanu, D. Cernea, D. Pelau, V. Gaal C. Cebotaru, D. Iancu, T.Guttman, N. Todor, N. Ghilezan, - 1st National Conference on Medical Oncology, 11-14 april 2002, Craiova–Caciulata

28. Phase II study of vinorelbine and cisplatin with concurrent radiotherapy for unresectable stage III NSCLC, a preliminary analysis – P. Rusu, T.E. Ciuleanu, D. Cernea, D. Pelau, V. Gaal, C. Cebotaru, D. Iancu, T.Guttman, N. Todor, N. Ghilezan, - The 18th UICC International Cancer Congress 30 june-5 july 2002, Oslo-Norway Abstract book.

29. The evolution of chemoradiotherapy strategies in advanced NSCLC (Evolutia strategiilor radiochimioterapice in carcinoamele bronho-pulmonare "non-small cell", locoregional avansate experienta Institutului Oncologic Cluj) P.Rusu–"Zilele Oncologice Clujene" 9-12 noiembrie 2002, Cluj- Napoca

30. Radiochimioterapia concomitenta cu vinorelbina si cisplatin în carcinoamele bronhopulmonare "non-small cell" avansate locoregional, P. Rusu, T.E. Ciuleanu, D. Cernea, D. Pelau, V. Gaal C. Cebotaru, D. Iancu, T.Guttman, N. Todor, N. Ghilezan, -" Zilele Oncologice Clujene" 9-12 noiembrie 2002, Cluj-Napoca

31. Current issues in operable and marginally operable NSCLC (Actualitati in carcinoamele bronhopulmonare '' Non small cell'' (CBPNSC) operabile si marginal operabile)– P.Rusu, National Onclogy Conference with international participation: " Tendinte moderne in oncologie "07-10 nov 2002, Craiova- Caciulata

32. Advances in lung cancer, in the light of the 18th UICC International Cancer Congress 30 june-5 july,2002,Oslo, Norway, Petronela Rusu, Radioterapie & Onc Med, 2002.

33. Current issues in concurrent chemo-radiation for advanced non-small cell lung cancer - P.Rusu, The 4 th Congress of the Balkan Union of Oncology nov.22-23, 2002 Athens, Greece.

34. Optimized radiotherapy techniques in Lung Cancer (Optimizarea tehnicilor de radioterapie in cancerul bronhopulmonar), P.Rusu, Zilele medicale ale Institutului Oncologic "Prof Ion Trestioreanu" 9-11 mai 2003, Bucuresti

35. Concurrent chemoradiotherapy with Navelbine and Cisplatin for unresectable stage III NSCLC, a phase II study, P.Rusu , T.E. Ciuleanu, D. Cernea, D. Pelau, V. Gaal C. Cebotaru, D. Iancu, T.Guttman, N. Todor, N. Ghilezan,Lung Cancer vol 41, supl 2, S 241

(Abstracts of the 10th World Conference on Lung Cancer 10-14 august, Vancouver, Canada).

36. Concurrent chemoradiotherapy with Navelbine and Cisplatin for unresectable stage III NSCLC, a phase II study, P.Rusu , T.E. Ciuleanu, D. Cernea, D. Pelau, V. Gaal C. Cebotaru, D. Iancu, T.Guttman, N. Todor, N. Ghilezan, Radioterapie & Onc Med, 2003.
37. Molecular strategies in Lung Cancer, P.Rusu, The 2nd National Conference on Medical Oncology, 11-13.09.2003, Durău.
38. Navelbine and Cisplatin with concurrent radiotherapy for unresectable stage III NSCLC, P.Rusu T.E. Ciuleanu, D. Cernea, D. Pelau, V. Gaal C. Cebotaru, D. Iancu, T.Guttman, N. Todor, N. Ghilezan, EJC Supplement Abstract Book, of ECCO 12, 21-25 sept 2003, S241, Copenhagen, Denmark
39. Treatment in Lung Cancer-P.Rusu–Teaching lecture on Thoracic Tumours at the University of Medicine and Farmacy "Ĭuliu Haţeganu" Cluj Napoca 24-25 10. 2003.
40. Evaluation of toxicity in concurrent chemoradiotherapy in advanced "Non small cell lung cancer" –Petronela Rusu, T.E. Ciuleanu, D. Cernea, D. Pelau, V. Gaal C. Cebotaru, Aura Popescu, T.Guttman, N. Todor, N. Ghilezan, Conferința Națională de Oncologie şi Zilele Medicale ale Institutului Oncologic Bucureşti, 14-15. 05.2004
41. Timing and innovative Radiotherapy techniques in Limited Disease Small Cell Lung Cancer – Petronela Rusu, BUON meeting 14-17 oct 2004 Belgrade
42. Concurrent chemoradiotherapy with Navelbine and Cisplatin for unresectable stage III NSCLC, Petronela Rusu, T.E. Ciuleanu , Dana Cernea , Doris Pelau , Viola Gaal ,Cristina Cebotaru , Dana Iancu , T. Guttman , N.Todor , N.Ghilezan, The 23rd ESTRO Meeting 24-28 oct , 2004 Amsterdam,
43. Concurrent chemoradiotherapy with Navelbine and Cisplatin for unresectable stage III NSCLC, Petronela Rusu, T.E. Ciuleanu , Dana Cernea , Doris Pelau , Viola Gaal ,Cristina Cebotaru , Dana Iancu , T. Guttman , N.Todor , N.Ghilezan, The 29th ESMO Congress 29oct- 2 nov 2004 Wienna,
44. Strategii chimioradioterapice in carcinoamele bronho-pulmonare "non small cell"avansate loco-regional – experienta Institutului Oncologic "Prof Ion Chiricuta" Petronela Rusu, T.E. Ciuleanu, D. Cernea, C. Cebotaru, T.Guttman, N. Todor, N. Ghilezan. Zilele UMF "Iuliu Hatieganu -8 .12.2004
45. A phase II study of concurrent chemoradiotherapy with Navelbine and Cisplatin for unresectable stage III NSCLC, Petronela Rusu, T.E. Ciuleanu , Dana Cernea , Doris Pelau, Viola Gaal ,Cristina Cebotaru ,T. Guttman , N.Todor , N.Ghilezan, The 11th World Conference on Lung Cancer, Barcelona, Spain 3-6.07.2005
46. Radiation pneumonitis, risk factors and techniques to reduce irradiated lung volum Petronela Rusu, N.Ghilezan, Congresul XV al Societatii Romane de Radioterapie si Oncologie Medicala, 22-24.09.2005 Cluj-Napoca
47. Radioterapia conformationala – posibilitati si limite. G.Kacso, D Cernea, P.Rusu, V.Cernea, Zilele Universitatii de Medicina si Farmacie "Iuliu Hatieganu", 07.12.2005
48. Cinical basis of deliniation of Target Volumes , lymphatic drainage and treatment principles in NSCLC, Petronela Rusu, First Course on Deliniation of Target Volumes and new thechniques in radiotherapy, IOCN, 24-26.03.2006

49. Biological basis and evolution of combined chemo-radiotherapy strategies in locoregional advanced NSCLC, Petronela Rusu, Postuniversity course on: Progresses of the year 2005 in the management oncological patients, a post ASCO/ESMO/ESTRO meeting under the auspices of University of Medicine and Farmacy & IOCN, 7-8. 04. 2006

50. Concurrent chemoradiotherapy with Vinorelbine and a Platinum compound followed by consolidation chemotherapy for unresectable stage III Non-Small- Cell Lung Cancer (NSCLC), *Petronela Rusu[1], T.E. Ciuleanu [1,2], Dana Cernea [1], Doris Pelau [1], Viola Gaal [1], Cristina Cebotaru [1], Dana Iancu [1], T. Guttman [1], N.Todor [1], N.Ghilezan [1,]* presented as oral presentation at the 6th Congress of the Balkan Union of Oncology 13-16 sept 2006, Sofia Bulgaria

51. Induction chemotherapy with Vinorelbine and a Platinum compound followed by concurrent chemoradiotherapy and consolidation chemotherapy with the same drugs for stage III Non-Small-Cell Lung Cancer (NSCLC)-A phase II study, *Petronela Rusu[1], T.E. Ciuleanu [1,2], Dana Cernea [1], Doris Pelau [1], Viola Gaal [1], Cristina Cebotaru [1], Dana Iancu [1], T. Guttman [1], N.Todor [1], N.Ghilezan [1,2]* ESTRO 25 Meeting October 9-12, 2006, Leipzig, Germany

52. Severe vincristine induced neuropaty after small doses in a patient with Hodgkin's Lymphoma, Case report and review of the literature. V Tibre, Petronela Rusu, Carmen Cobzariu. Radioterapie & Oncol Medic, 2006, 1:77-81

53.Concurrent chemoradiotherapy with vinorelbine and a platinum compound followed by consolidation chemotherapy for unresectable stage III non-small cell lung cancer; preliminary results of a phase II study: *P. Rusu[1], T.E. Ciuleanu[1,2], D. Cernea[1], D. Pelau[1], V. Gaal[1], C. Cebotaru[1], T. Guttman[1], N. Todor[1], N. Ghilezan[1,]* Journal OF B.U.O.N. 2007;1,:33-39.

54. Predictive factors for lung toxicity in 3DCRT *Petronela Rusu[1], N.Ghilezan [1,2]* Teaching course: New trends in cancer control, Cluj-Napoca, 22-23 iunie 2007,

55. Long-term results of concurrent chemoradiotherapy with Vinorelbine and a Platinum compound followed by consolidation chemotherapy for advanced stage III Non-Small-Cell Lung Cancer (NSCLC) :Petronela Rusu[1], T.E. Ciuleanu [1,2], Dana Cernea [1], Doris Pelau [1], Viola Gaal [1],Cristina Cebotaru [1], Dana Iancu [1], T. Guttman [1], N.Todor [1], N.Ghilezan [1,2] J Thor Onc 2007;(2)8, S652 abstr: p2-205,(Supplement for the 12th World Conference on Lung Cancer, Seoul Korea sept 2-6, 2007

56. Induction chemotherapy with Vinorelbine and a Platinum compound followed by concurrent chemoradiotherapy and consolidation chemotherapy with the same drugs for stage III Non-Small-Cell Lung Cancer (NSCLC) - A phase II study. *Petronela Rusu[1], T.E. Ciuleanu [1,2], Dana Cernea [1], Doris Pelau [1], Viola Gaal [1], Cristina Cebotaru [1], Dana Iancu [1], T. Guttman [1], N.Todor [1], N.Ghilezan [1,2]*EJC, (5),4:383, poster 6584, supplement for ECCO14, European Cancer Conference 23-27 sept, 2007, Barcelona,

57. Recent advances in the chemoradiotherapy of unresectable locally advanced Non-Small-Cell Lung Cancer (NSCLC), the experience of the Istitute of Oncology „Prof. Ion Chiricuta" Cluj-Napoca *Petronela Rusu[1], T.E. Ciuleanu [1,2], Dana Cernea [1], Doris Pelau [1], Viola Gaal [1], Cristina Cebotaru [1], Dana Iancu [1], T. Guttman [1], N.Todor [1], N.Ghilezan [1,]*Oral presentation at The Conference of Hungarian Society of radiotherapy, 25-27 oct, 2007 Debrecin Hungary

58. Prognostic value of Lymph Node involvement and therapeutical implications in operable NSCLC,

the experience of Institute of Oncology "Prof. Dr. Ion Chiricuta" Cluj – Napoca. *Petronela Rusu, TE Ciuleanu, S Hica, D Cernea, c Cebotaru, T Guttman, I Hrab, L Grigore, N Todor, N Ghilezan,oral presentation at The conference of University of Medicine and Farmacie" Iuliu Haiteganu", 03.12.2007*

59. Updated treatment strategies in advanced non-small cell lung cancer *Petronela Rusu*, teaching lecture, Post ASCO/ECCO teaching course , Cluj 26-27.06.2008

60. Induction chemotherapy followed by concurrent chemoradiotherapy and consolidation chemotherapy with Vinorelbine and a Platinum compound for stage III NSCLC – A phase II study, oral presentation at The 7th Congress of B.U.O.N. 16-19 oct 2008 Izmir Turkey

61. Three-Dimensional Conformal-Radiotherapy in Combined-modality Treatment for advanced Non-small cell lung cancer- A Clinical Case Presentation. *Petronela Rusu*[1], *Nicolae Ghilezan*[1,2] Journal of Radiotherapy & Medical oncology. 2008;(14),3:172-182

62. Optimizing treatment strategies in advanced non-small cell lung cancer. Petronela Rusu. Teaching lecture at the University of Madicine and Farmacy Iasi 4-6 dec 2008