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Hellenic Surgical Oncology

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CONTENTS

ΤΟ ΟΝΕΙΡΟ

«Αν μπορείς να το ονειρευτείς,
μπορείς να το κάνεις.»
Walt Disney (1901-1966)

Αγαπητά Μέλη της Ελληνικής Εταιρείας Χειρουργικής Ογκολογίας (ΕΕΧΟ),
Αγαπητοί Συνάδελφοι και Φίλοι της Εταιρείας,

Σήμερα η Εταιρεία μας, αλλά και η χειρουργική εκπαίδευση στην Ελλάδα, διανύουν μια ιστορική καμπή. Το όνειρο πολλών χρόνων, που ήταν η επίσημη αναγνώριση της εξειδίκευσης στη Χειρουργική Ογκολογία έγινε πραγματικότητα, και η 238η ολομέλεια του Κεντρικού Συμβουλίου Υγείας (ΚΕΣΥ) στις 6/12/2012, με την υπ' αριθμόν 13 απόφαση, όπως αυτή παρατίθεται στο τεύχος αυτό, αναγνωρίζει επισήμως την εξειδίκευση της Χειρουργική Ογκολογίας στην Ελλάδα.

Ευτυχής συγκυρία θέλει η αναγνώριση αυτή να συμπίπτει με την αντίστοιχη αναγνώριση της εξειδίκευσης στις Η.Π.Α., όπως πρόσφατα ανακοινώθηκε από την Αμερικάνικη Εταιρεία Χειρουργικής Ογκολογίας (SSO). Ωστόσο, σήμερα η Ελλάδα, είναι η πρώτη Ευρωπαϊκή χώρα που αναγνωρίζει επισήμως την εξειδίκευση της Χειρουργικής Ογκολογίας.

Θεωρώ καθήκον και υποχρέωσή μου να ευχαριστήσω όλους όσους συνέβαλαν στην επιτυχία αυτή. Όλα τα προηγούμενα Διοικητικά Συμβούλια που «λείαναν» το έδαφος επάνω στο οποίο κινήθηκε το παρόν Διοικητικό Συμβούλιο, τα μέλη του οποίου, Διονύσης Βώρος, Γιάννης Σπηλιώτης, Γιάννης Καραϊτιανός, Γιάννης Κακλαμάνος, Δημήτρης Ρούκος και Κώστας Ρωμανίδης έδωσαν τον καλύτερο εαυτό τους στην προσπάθεια για την καθιέρωση της εξειδίκευσης. Όλες οι προσπάθειες θα έπεφταν στο κενό αν δεν υπήρχαν τα «ευήκοα ώτα» του Ανδρέα Σερέτη, Προέδρου του ΚΕΣΥ, του Γιάννη Δατσέρη, Αντιπροέδρου του ΚΕΣΥ και Προέδρου της Επιτροπής Εκπαίδευσης και του Παναγιώτη Μέγα, Καθηγητή Ορθοπαιδικής του Πανεπιστημίου Πατρών και Εισηγητή στην Επιτροπή Εκπαίδευσης. Σημαντικό ρόλο έπαιξαν, οι Πρόεδροι των «αδελφών» Ογκολογικών Εταιρειών, Βασίλης Γεωργούλιας, Πρόεδρος της Εταιρείας Ογκολόγων Παθολόγων Ελλάδας, και Παναγιώτης Παντελάκος, πρώην Πρόεδρος της Ελληνικής Εταιρείας Ακτινοθεραπευτικής Ογκολογίας, οι οποίοι ως έμπειροι και καλοί γνώστες της πολυπαραγοντικής αντιμετώπισης των νεοπλασματικών ασθενειών, υποστήριξαν σθεναρά το ρόλο της Χειρουργικής Ογκολογίας ως αυτόνομης χειρουργικής οντότητας.

Η ΕΕΧΟ παρά τη δύσκολη εποχή που διανύουμε αναπτύσσεται ραγδαία. Ήδη το περιοδικό έχει μετατραπεί εξολοκλήρου σε αγγλόφωνο αναμένοντας έτσι να κατηγοριοποιηθεί, σύντομα πιστεύω, στους διεθνείς βιβλιομετρικούς δείκτες, ενώ το 12ο Πανελλήνιο Συνέδριό μας προγραμματίζεται να γίνει τον Οκτώβριο – Νοέμβριο 2013 στην Αθήνα. Θα ήταν παράλειψη στο σημείο αυτό, αν δεν ευχαριστούσα την κυρία Τζένη Σωτηροπούλου για τη διοικητική της υποστήριξη. Τέλος, η συνεργασία της ΕΕΧΟ με τις αντίστοιχες μεγάλες Εταιρείες Ευρώπης και Αμερικής, καθιερώνεται και ενισχύεται όλο και περισσότερο.

Ωστόσο είναι προφανές, ότι η σημαντική δύναμη της Εταιρείας είναι τα μέλη της. Ο ξεχωριστός ρόλος του καθενός είναι σημαντικός και ιδιαίτερος και γι' αυτό από τη θέση αυτή εκφράζω προς όλους σας απέραντη ευγνωμοσύνη.

Εκ μέρους του Διοικητικού Συμβουλίου
Καθηγητής Οδυσσέας Ζώρας

Διευθυντής Κλινικής Χειρουργικής Ογκολογίας
Πανεπιστημιακού Νοσοκομείου Ηρακλείου
Πρόεδρος ΕΕΧΟ

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ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ
ΚΕΝΤΡΙΚΟ ΣΥΜΒΟΥΛΙΟ ΥΓΕΙΑΣ

Αθήνα 29.1.2013
Αριθμ. Απόφ. 13 της 238ης
Ολομ./6.12.2012

Α Π Ο Φ Α Σ Η

«Εξειδίκευση στη Χειρουργική Ογκολογία»

Η Ολομέλεια του Κεντρικού Συμβουλίου Υγείας στην 238η Συνεδρίασή της (6.12.2012), αφού έλαβε υπ᾽ όψη:

- την υπ᾽ αριθμ. 29 απόφαση της 221ης/25.6.2009 Συνεδρίασης της «Σχετικά με την καθιέρωση – θεσμοθέτηση ιατρικών εξειδικεύσεων στην Ελλάδα» στην οποία σχετικώς με την ειδικότητα της Χειρουργικής, αναγνωρίζεται ως εξειδίκευσή της, η Χειρουργική Ογκολογία, κατόπιν λήψεως της ειδικότητας της Γενικής Χειρουργικής
  Επιπλέον, εξουσιοδοτείται η Εκτελεστική Επιτροπή του ΚΕ.Σ.Υ. προκειμένου: 1) να διαμορφώσει το πρόγραμμα εκπαίδευσης για την ανωτέρω εξειδίκευση και τα εκπαιδευτικά κέντρα, 2) να ορίσει τους εκπαιδευτές, 3) να καθορίσει τους όρους και τις προϋποθέσεις που θα διέπουν τη λήψη της ανωτέρω εξειδίκευσης και 4) να καθορίσει τις σχετικές μεταβατικές διατάξεις
- την υπ᾽ αριθμ. 5146/5.7.2010 απόφαση της Εκτελεστικής Επιτροπής σύμφωνα με την οποία συγκροτήθηκε Ομάδα Εργασίας στο ΚΕ.Σ.Υ. για την Εξειδίκευση στη Χειρουργική Ογκολογία και με έργο την γνωμοδότησή της προς την Εκτελεστική Επιτροπή του ΚΕ.Σ.Υ. σχετικώς με: 1) την διαμόρφωση του προγράμματος εκπαίδευσης για την ανωτέρω εξειδίκευση και τα εκπαιδευτικά κέντρα, 2) τον ορισμό των εκπαιδευτών, 3) τον καθορισμό των όρων και των προϋποθέσεων που θα διέπουν τη λήψη της ανωτέρω εξειδίκευσης και 4) τον καθορισμό των σχετικών μεταβατικών διατάξεων
- την με ημερομηνία 28/3/2011 εισήγηση της ανωτέρω Ομάδας Εργασίας του ΚΕ.Σ.Υ. προτείνοντας ομόφωνα:
  την θεσμοθέτηση της εξειδίκευσης «Χειρουργική Ογκολογία»
  το εκπαιδευτικό πρόγραμμα
  τα κέντρα εκπαίδευσης
- τις κατηγορίες Χειρουργών στους οποίους προτείνεται να απονεμηθεί ο τίτλος της εξειδίκευσης της Χειρουργικής Ογκολογίας
- την εισήγηση περί της εξειδίκευσης στη Χειρουργική Ογκολογία που ανέπτυξε στα μέλη του ΚΕ.Σ.Υ. κατά τη διάρκεια της 230ης/16.5.2011 συνεδρίασης της Ολομέλειας του ΚΕ.Σ.Υ. – Θέμα 6ο - ο Καθηγητής Χειρουργικής του Παν/μίου Κρήτης κ. Οδυσσέας Ζώρας, μέλος της Ολομέλειας του ΚΕ.Σ.Υ., μέλος της Επιτροπής Ογκολογίας του ΚΕ.Σ.Υ. στην οποία μετέχει θεσμικά ως Πρόεδρος της Ελληνικής Εταιρείας Χειρουργικής Ογκολογίας και μέλος της ανωτέρω Ομάδας Εργασίας του ΚΕ.Σ.Υ.,
- την υπ᾽ αριθμ. 6 απόφαση της 230ης/16.5.2011 Συνεδρίασής της σύμφωνα με την οποία μετά την υπ᾽ αριθμ. 29/221ης/25.6.2009 απόφαση της Ολομέλειας του ΚΕ.Σ.Υ. με την οποία κατ᾽ αρχήν αναγνωρίστηκε η Χειρουργική Ογκολογία ως εξειδίκευση της ειδικότητας της Γενικής Χειρουργικής και κατόπιν εισήγησης της Ομάδας Εργασίας που συστήθηκε για τον προσδιορισμό των παραμέτρων που θα διέπουν αυτή, η Ολομέλεια του ΚΕ.Σ.Υ. αποφάσισε να υποβάλει το θέμα στην Επιτροπή Εκπαίδευσης του ΚΕ.Σ.Υ. ώστε να διαμορφω-

θούν τόσο το πλαίσιο και το περιεχόμενο του οικείου εκπαιδευτικού προγράμματος όσο και να ορισθούν τα εκπαιδευτικά κέντρα για την εν λόγω εξειδίκευση

- το με ημερομηνία 16/11/2012 έγγραφο του Προέδρου της Επιτροπής Εκπαίδευσης – Μετεκπαίδευσης του ΚΕ.Σ.Υ. και Αντιπροέδρου του ΚΕ.Σ.Υ. κ. Ιωάννου Δατσέρη, γνωστοποιώντας ότι η Επιτροπή Εκπαίδευσης – Μετεκπαίδευσης κατά τη συνεδρίασή της στις 16/11/2012 εξέτασε το θέμα της εξειδίκευσης στη Χειρουργική Ογκολογία και μετά από διαλογική συζήτηση ομόφωνα αποφάσισε ότι αποδέχεται την εξειδίκευση στη Χειρουργική Ογκολογία υποβάλλοντας σχετικό σχέδιο Προεδρικού Διατάγματος, κατόπιν λεπτομερούς διαλογικής συζήτησης και ενδελεχούς και εμπεριστατωμένης μελέτης ομόφωνα **αποφάσισε** να υποβάλλει στην αρμόδια Υπηρεσία του Υπουργείου Υγείας σχέδιο Προεδρικού Διατάγματος για την εξειδίκευση στη Χειρουργική Ογκολογία, ως ακολούθως:

ΣΧΕΔΙΟ ΠΡΟΕΔΡΙΚΟΥ ΔΙΑΤΑΓΜΑΤΟΣ ΓΙΑ ΤΗΝ ΕΞΕΙΔΙΚΕΥΣΗ ΣΤΗ ΧΕΙΡΟΥΡΓΙΚΗ ΟΓΚΟΛΟΓΙΑ

Άρθρο 1
Καθορισμός εξειδίκευσης

Καθορίζεται, ως ειδικότερος τομέας εξειδίκευσης της Γενικής Χειρουργικής, η Χειρουργική Ογκολογία, με σκοπό την εκπαίδευση του σύγχρονου χειρουργού, στην εξειδικευμένη χειρουργική αντιμετώπιση των νεοπλασμάτων και στην πολυδιάστατη αντιμετώπιση τους.

Ο τίτλος της εξειδίκευσης διαφοροποιείται ως προς εκείνον της Γενικής Χειρουργικής, σε επίπεδο ειδικότερης εκπαίδευσης.

Άρθρο 2
Εκπαιδευτικό αντικείμενο

1. Το εκπαιδευτικό αντικείμενο της εξειδίκευσης στη χειρουργική ογκολογία, στο οποίο θα εξειδικεύονται οι γιατροί, είναι το ακόλουθο:

Το πρόγραμμα εξειδίκευσης θα πρέπει να εξασφαλίσει ώστε ο κάθε υποψήφιος κατά την διάρκεια των δύο (2) χρόνων να μετάσχει ως πρώτος χειρουργός ή ως πρώτος βοηθός σε τουλάχιστον 120 επεμβάσεις. Ο ελάχιστος αριθμός επεμβάσεων κατά κατηγορία αναφέρεται στον παρακάτω πίνακα:

• Χειρουργική μελανώματος	10
• Χειρουργική σαρκώματος	5
• Χειρουργική κεφαλής τραχήλου	5
• Χειρουργική ανώτερου πεπτικού	5
• Χειρουργική ήπατος και παγκρέατος	10
• Χειρουργική κατώτερου πεπτικού	10
• Χειρουργική ενδοκρινών αδένων	5
• Χειρουργική μαστού	20
• Αγγειακοί καθετήρες	10
• Κατευθυνόμενες ογκοθεραπείες	10
• Ανίχνευση λεμφαδένα φρουρού	20

Άρθρο 3
Χρόνος και τόπος εξειδίκευσης

1.1. Ο χρόνος άσκησης για την απόκτηση εξειδίκευσης στη Χειρουργική Ογκολογία είναι δύο (2) χρόνια.

1.2. Δικαίωμα στην εξειδίκευση έχουν ειδικευμένοι ιατροί, κάτοχοι τίτλου ειδικότητας Γενικής Χειρουργικής.

1.3. Η εξειδίκευση στη Χειρουργική Ογκολογία γίνεται στα κέντρα εκπαίδευσης που ορίζονται κατωτέρω.

1.4. Κέντρα Εκπαίδευσης

Λόγω του σκοπού της εξειδίκευσης, όπως αυτός εξηγήθηκε παραπάνω, θεωρούμε ότι ως ελάχιστη προϋπόθεση, τα Νοσοκομεία στα οποία θα γίνεται η εκπαίδευση, θα πρέπει να διαθέτουν:

α) Χειρουργική Κλινική

β) Ογκολογική Κλινική ή Μονάδα
γ) Ακτινοθεραπευτικό Τμήμα του ιδίου ή διασυνδεδεμένων Νοσοκομείων που μπορεί να αποδέχεται τους εξειδικευόμενους.
δ) Να λειτουργεί Ογκολογικό Συμβούλιο, στο οποίο να συμμετέχουν ιατροί των παραπάνω ειδικοτήτων.

Ο αριθμός των θέσεων που προτείνεται, αρχικά τουλάχιστον, είναι μία (1) θέση ανά Χειρουργική Κλινική και τουλάχιστον δύο (2) θέσεις ανά Νοσοκομείο.

Προτείνεται, επίσης, να δύναται να ενταχθούν στη διαδικασία εκπαίδευσης, κατόπιν αξιολόγησης από την ειδική επιτροπή του άρθρου 1.6, όσα Νοσοκομεία αποκτήσουν τις προϋποθέσεις που αναφέρονται παραπάνω.

1.5. Κατά τη διάρκεια των δύο (2) αυτών ετών, θα πραγματοποιείται εκπαίδευση (rotation) τριών (3) μηνών στις εξής Μονάδες:
- Παθολογική Ογκολογική Κλινική
- Ακτινοθεραπευτική Κλινική
- Παθολογοανατομικό Εργαστήριο

1.6. Για την αναγνώριση των κέντρων εξειδίκευσης, αλλά και των πιστοποιητικών εκπαίδευσης των ιατρών που εξειδικεύτηκαν, καθώς και των ιατρών στους οποίους θα αναγνωρισθεί ο τίτλος του Χειρουργού Ογκολόγου, κατά την εφαρμογή της παρούσας απόφασης ορίζεται επιτροπή με απόφαση του Υπουργού Υγείας, μετά από γνώμη του ΚΕΣΥ, που αποτελείται από επτά (7) μέλη, ως ακολούθως:
1. Καθηγητή Χειρουργικής Ογκολογίας, ως Πρόεδρο.
2. Καθηγητή ή Αναπληρωτή Καθηγητή Γενικής Χειρουργικής.
3. Συντονιστή Διευθυντή Γενικής Χειρουργικής Αντικαρκινικού Νοσοκομείου.
4. Καθηγητή ή Συντονιστή Διευθυντή Παθολ. Ογκολογίας.
5. Καθηγητή ή Συντονιστή Διευθυντή Ακτινοθεραπείας.
6. Εκπρόσωπο της Ελληνικής Χειρουργικής Εταιρείας.
7. Εκπρόσωπο του Υπουργείου Υγείας.

Άρθρο 4
Βεβαίωση ολοκλήρωσης εξειδίκευσης

1. Για την απόκτηση της εξειδίκευσης στη Χειρουργική Ογκολογία, χορηγείται βεβαίωση από το Κέντρο Εξειδίκευσης, στην οποία φαίνεται ότι ο γιατρός συμπλήρωσε τον απαιτούμενο χρόνο εξειδίκευσης.

2. Η βεβαίωση αυτή, μαζί με τα δικαιολογητικά υποβάλλονται στην επιτροπή του άρθρου 3, που εισηγείται την έγκριση **για την εξέταση** του εξειδικευόμενου.

3. Οι εξετάσεις για την εξειδίκευση είναι προφορικές και γραπτές, κατά τα ευρωπαϊκά πρότυπα.

4. Η επιτροπή εξετάσεων είναι τριμελής και αποτελείται από:
α) Καθηγητή Χειρουργικής Ογκολογίας, ως Πρόεδρο.
β) Συντονιστή Διευθυντή Γενικής Χειρουργικής από Αντικαρκινικό Νοσοκομείο.
γ) Συντονιστή Διευθυντή ΕΣΥ Γενικής Χειρουργικής.

Άρθρο 5
Δραστηριότητες εξειδικευμένων Ιατρών

1. Ο κάτοχος πιστοποιητικού εξειδίκευσης στη Χειρουργική Ογκολογία, είναι ειδικά εκπαιδευμένος Γενικός Χειρουργός για την διαγνωστική και θεραπευτική αντιμετώπιση χειρουργικά αντιμετωπίσιμων νεοπλασμάτων.

Άρθρο 6
Μεταβατικές Διατάξεις

1. Κατά την παρούσα (μεταβατική) φάση προτείνεται να απονεμηθεί ο τίτλος της εξειδίκευσης σε Γενικούς Χειρουργούς που πληρούν τα παρακάτω κριτήρια:
1) Γενικοί Χειρουργοί με πιστοποιημένη εκπαίδευση – εξειδίκευση από κέντρα του εξωτερικού.
2) Όσοι υπηρετούν τα τελευταία τρία (3) χρόνια ως ειδικευμένοι Γενικοί Χειρουργοί στα ειδικά Ογκολογικά Νοσοκομεία της χώρας (Ογκολογικό – Αντικαρκινικό Νοσοκομείο

Αθηνών «Άγιος Σάββας», Ειδικό Αντικαρκινικό Νοσοκομείο «Μεταξά», ΑΝΘ Θεαγένειο, Γενικό Ογκολογικό Νοσοκομείο Κηφισιάς «Άγ. Ανάργυροι»).

3) Γενικοί Χειρουργοί που πιστοποιημένα, κατά την τελευταία τριετία (3 έτη), εκτελούν σε ποσοστό πάνω από 50% της ετήσιας δραστηριότητάς τους ατομικά σε δημόσια Νοσοκομεία, ογκολογικές επεμβάσεις και ο συνολικός αριθμός της τριετίας είναι πάνω από 120. Η εμπειρία αυτή πρέπει να προκύπτει από πρακτικά χειρουργεία του υποψηφίου και να είναι επικυρωμένα από το Διευθυντή Ιατρικής υπηρεσίας και το Διοικητή του Νοσοκομείου.

4) Γενικοί Χειρουργοί που υπηρετούν στα Πανεπιστήμια, σε οποιαδήποτε βαθμίδα ή σε κρατικά Νοσοκομεία (Επιμελητές, Διευθυντές), με γνωστικό αντικείμενο με έμφαση στη Χειρουργική Ογκολογία όπως αυτό προσδιορίζεται από την προκήρυξη της θέσης και τον οργανισμό του Νοσοκομείου.

Για τις κατηγορίες 3 και 4, είναι αναγκαίο να διαθέτουν συγγραφικό έργο, με προσανατολισμό στη Χειρουργική Ογκολογία.

Τονίζεται, επίσης, ιδιαίτερα για τις παραπάνω ομάδες Γενικών Χειρουργών, ότι εργασιακά ή επαγγελματικά δικαιώματα δεν αναγνωρίζονται, ούτε περιορίζονται. Ο τίτλος της εξειδίκευσης αποτελεί επιστημονικό τίτλο.

2. Οι υποψήφιοι για την απονομή του τίτλου της Χειρουργικής Ογκολογίας υποβάλλουν τα ως άνω δικαιολογητικά στην επιτροπή του άρθρου 3, που συνεδριάζει τέσσερις (4) φορές τον χρόνο και αιτιολογημένα γνωμοδοτεί και εισηγείται για τη χορήγηση του πιστοποιητικού εξειδίκευσης. Η επιτροπή βαθμολογεί τους επιτυχόντες με την διάκριση: **1.** Καλώς **2.** Λίαν καλώς **3.** Άριστα

3. Για τον διορισμό ειδικευμένων ιατρών προς εξειδίκευση επί **διετή συνεχή υπηρεσία** και εκπαίδευση στα αναγνωρισμένα κέντρα εξειδίκευσης, οι υποψήφιοι ιατροί θα απευθύνονται:

α) **Διεύθυνση Προσωπικού του Υπουργείου** και να υποβάλλουν τα εξής δικαιολογητικά:

i) Αίτηση του ενδιαφερομένου.

ii) Αντίγραφο πτυχίου ή επικυρωμένη φωτοτυπία Ιατρικής Σχολής ημεδαπής ή αλλοδαπής, και άδειας ασκήσεως επαγγέλματος, σύννομα και επικυρωμένα.

iii) Τίτλο ιατρικής ειδικότητας Γενικής Χειρουργικής.

iv) Βεβαίωση εκπλήρωσης υπηρεσίας υπαίθρου ή νόμιμης απαλλαγής.

v) Φωτοαντίγραφο δελτίου ταυτότητας.

β) Στην αίτηση διορισμού οι ενδιαφερόμενοι ιατροί πρέπει να μνημονεύουν τη συγκεκριμένη Μονάδα και το Νοσοκομείο που επιθυμούν να ειδικευτούν.

γ) Αιτήσεις συμμετοχής μπορούν να υποβάλλουν ιατροί, κάτοχοι τίτλου ειδικότητας Γενικής Χειρουργικής.

δ) Τα εκπαιδευτικά κέντρα εξειδίκευσης οφείλουν να ενημερώνουν την Διεύθυνση Προσωπικού του Υπουργείου για τις κενές θέσεις εξειδίκευσης.

4. Η επιλογή των υποψηφίων προς εξειδίκευση θα γίνεται με προφορική συνέντευξη ενώπιον επιτροπής αποτελούμενης από τον οικείο Συντονιστή Διευθυντή του τμήματος, που έχει επιλεγεί για εξειδίκευση, που προεδρεύει της επιτροπής και από δύο άλλους Συντονιστές Διευθυντές άλλων Νοσοκομείων, που έχουν ορισθεί ως κέντρα εξειδίκευσης.

5. Οι επιτροπές αυτές συγκροτούνται με απόφαση του Υπουργού Υγείας, μετά από γνώμη του ΚΕΣΥ. Χρέη Γραμματέως εκτελεί υπάλληλος του ως άνω Υπουργείου, ενώ έδρα της επιτροπής ορίζεται η ΥΠΕ που εδράζεται το Εκπαιδευτικό Κέντρο.

6. Σε κάθε αναγνωρισμένο Κέντρο εξειδίκευσης της Χειρουργικής Ογκολογίας συνιστώνται τουλάχιστον δύο (2) θέσεις εξειδικευόμενων. Οι υπηρετούντες στο ΕΣΥ ή ΑΕΙ εξειδικευόμενοι Χειρουργοί Ογκολογίας διατηρούν τη μισθολογική κατάσταση της θέσης τους. Οι μη έχοντες θέση σε Δημόσιο Φορέα καταλαμβάνουν θέση επικουρικού ιατρού και αμείβονται αντιστοίχως. Οι εξειδικευόμενοι εφημερεύουν στις Πανεπιστημιακές Κλινικές ή Τμήματα του ΕΣΥ τα οποία

τους επιλέγουν.

7. Η ακριβής ημερομηνία της προφορικής συνέντευξης, θα γνωστοποιείται στους ενδιαφερόμενους ηλεκτρονικά και με ανάρτηση πίνακα σε κάθε Μονάδα Νοσοκομείου και στο κεντρικό κατάστημα του Υπουργείου.

8. Η επιτροπή συντάσσει πρακτικό επιλογής των υποψηφίων, επαρκώς αιτιολογημένο, το οποίο υποβάλλει στο Υπουργείο μέσα σε δέκα (10) ημέρες από την ημερομηνία συνεδρίασης.

9. Οι ιατροί, μετά το τέλος της εξειδίκευσης, προσέρχονται σε εξετάσεις στην επιτροπή του άρθρου 4 παρ. 4, σε ημερομηνία που καθορίζεται από την εξεταστική επιτροπή και γνωστοποιείται με ανακοίνωση στο Υπουργείο και στα κέντρα εξειδίκευσης.

10. Σε περίπτωση αποτυχίας, ο υποψήφιος έχει δικαίωμα να προσέλθει εκ νέου για εξέταση κατά την επόμενη εξεταστική περίοδο ή και σε προσεχείς περιόδους.

11. Ιατροί Γενικοί Χειρουργοί που έχουν εξειδικευθεί αθροιστικά επί διετία στην ημεδαπή ή στο εξωτερικό σε αναγνωρισμένο τμήμα Χειρουργικής Ογκολογίας δύνανται να αναγνωριστούν ως εξειδικευμένοι Χειρουργοί Ογκολόγοι αφού υποβάλλουν σχετικά δικαιολογητικά στην επιτροπή του άρθρου 3 και εφόσον εξασφαλίσουν την σχετική θετική εισήγηση, ακολούθως προσέρχονται στις εξετάσεις της επιτροπής του άρθρου 4 παρ. 4.

12. Η εξειδίκευση στην Χειρουργική Ογκολογία έχει καθαρά επιστημονική βάση και δεν συνδέεται με κανένα τρόπο με εργασιακά ή επαγγελματικά δικαιώματα της Γενικής Χειρουργικής.

13. Κατά τη διάρκεια του εκπαιδευτικού προγράμματος, οι εξειδικευμένοι θα πρέπει να δημοσιεύσουν δύο (2) άρθρα ως κύριοι συγγραφείς σε Ελληνικά περιοδικά αναγνωρισμένα από το Υπουργείο Υγείας ή σε ξενόγλωσσο περιοδικό με κριτές. Θα πρέπει, επίσης, να μετέχουν σε τρία (3) τουλάχιστον ογκολογικά συνέδρια – σεμινάρια ανά έτος, τα δύο εκ των οποίων διεθνή.

Για το ΚΕ.Σ.Υ.
Ο Πρόεδρος

Ανδρέας Σερέτης

Εσωτερική Διανομή
1) Γραφείο κ. Υπουργού Υγείας
2) Γραφείο κ. Αναπλ. Υπουργού Υγείας
3) Γραφείο κας Υφυπουργού Υγείας
4) Γραφείο κ. Γεν. Γραμματέα Υγείας
5) Δ/νση Γραμματείας ΚΕ.Σ.Υ. Τμήμα Α' (2)

Αποδέκτης προς ενέργεια
Δ/νση Επαγγελμάτων Υγείας & Πρόνοιας Τμήμα Α'

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REVIEW

Adjuvant hormonal therapy in breast cancer
The assessment of menopausal status

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ABSTRACT

Breast cancer, is the most common malignancy in women. Patients with hormone sensitive breast cancer are categorized as either clearly premenopausal, clearly postmenopausal or of uncertain menopausal status. The choice for a specific adjuvant hormonal treatment depends on the menopausal status of an individual woman.

KEY WORDS: breast cancer treatment, menopause, breast cancer hormone therapy

INTRODUCTION

Over the years, breast cancer mortality has declined partly due to implementation of surveillance programs leading to early detection, and partly due to improved treatment modalities, one of which is the adjuvant endocrine therapy for hormone – sensitive breast cancer patients. Still, breast cancer is the most common malignancy in women and the second leading cause of death among them, after colorectal cancer[1].

For patients with hormone sensitive breast cancer, knowledge of the precise point by which the ovarian reserve is depleted is of great importance for the decision regarding the optimal adjuvant hormonal treatment[2].

DEFINING MENOPAUSAL STATUS: THE DILEMMA

Natural reproductive aging in healthy women includes clinical definitions such as menopausal transition, perimenopause, final menstrual period, menopause and post-menopause.

Folliculogenesis refers to the process during which primordial follicles are continuously recruited out of the primordial follicle pool and develop to antral follicles via the primary secondary and tertiary stages. Dominant follicles measuring between 8 – 10 mm are follicle stimulating hormone (FSH) dependent. The final maturation steps preceding ovulation are driven by FSH and luteinizing hormone (LH)[3].

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At menopause there is a nearly complete depletion of primordial follicles. With advanced age decreasing number of oocytes and declining oocyte quality cause eventually the termination of estradiol production of the ovaries. The final menstrual period can only be defined in retrospect, after 12 months of amenorrhea.

The average age of menopause in women ranges from 40 up to 60 years of age[4].

Generally, we consider postmenopausal, women >60 years of age, women who underwent bilateral oophorectomy and women with an intact uterus and ovaries younger than 60 years of age, not using OCP's (Oral Contraceptive Pills) or HRT (Hormone Replacement Therapy) and being amenorrheic for at least one year prior to the diagnosis of breast cancer. We consider premenopausal, women having regular menses, without using OCP's or HRT[5].

Adjuvant chemotherapy for breast cancer may have a direct destructive effect on remnant functional follicles, induce ovarian fibrosis, or primary / hypergonadotropic hypogonadism (low levels of estradiol and high levels of FSH and LH), leading to CIA (Chemotherapy Induced Amenorrhea)[6].

CIA depends on the age and type of chemotherapy administered. Women >40 years have a grater propensity to develop CIA compared with women <40 years irrespective whether alkylating or anthracycline containing chemotherapy has been used[6,7].

An amenorrheic period after chemotherapy even more than a year in a patient with and intact uterus and ovaries could be transient. CIA can cause secondary amenorrhea (over 6 months) in a woman being pre – or peri – menopausal before the start of chemotherapy[7,8].

Tamoxifen can be safely given to premenopausal women, while AIs (Aromatose Inhibitors, block the conversion of androgens to estrogens by blocking aromatase and resulting in low estrogen and high FSH).

Categorizing premenopausal women inaccurately as postmenopausal and treating them with AIs without co-treatment with GRH agonist (Gonadotropin – Releasing Hormone) may be ineffective. In CIA treatment with AIs may induce ovarian function recovery, which would lead to inefficient therapy or even pregnancy[9].

MENOPAUSE BIOMARKERS

Elevated blood FSH levels reflect an age – dependent decrease in the follicle pool, with a subsequent decrease in estradiol levels, which are produced by the functioning granulosa cells. As a consequence, FSH levels will rise. The latest hormonal event preceding menopause is a monotropic rise in FSH[10].

However, the elevation of FSH may already occur approximately 3 – 8 years before menopause at least in the presence of an ovulatory cycle. In the late perimenopausal phase, FSH levels rise above 20 IU/L and this has been used by many physicians as the cut-off number to determine depletion of the ovarian reserve[11].

Treatment with tamoxifen in truly postmenopausal women, may induce a decrease in FSH levels even into the premonopausal range. Chemotherapy induced amenorrhea in premenopausal women, may result in highly increased FSH levels, which can be temporary or not.

Finally, no absolute cut-off level of FSH can be given, above which folliculogenesis does not occur anymore in any case[12,13].

As far as it concerns estradiol levels, research has reached the same conclusion, meaning that there is no cut-off estradiol level to measure, in order to confirm the menopausal status of women[14].

That is explained by the observation, that estradiol levels are higher in obese postmenopausal women, due to an increased number of adipose cells and therefore more aromatase activity.

Moreover, nicotine and its metabolite cotinine are strong inhibitors of aromatase leading to lower levels of estradiol among smokers.

Finally, hormone replacement theray (HRT) might lower FSH and increase estradiol levels up

to one year after cessation of therapy[15,16].

Another issue is the accuracy of the estradiol level reports due to the fact that the available methods for determination are largely variable. Routine use of direct estrogen assays for control of AI treatment compliance is not generally recommended, as increased pre-aromatization steroid concentrations by inhibition of the enzyme may bias the results. Accuracy of measuring lower estradiol levels would be improved largely by immunoassays including an extraction step or tandem gas chromatography and mass spectrometry assays[17].

In order to assess menopausal status more accurately two possible new biomarkers have been proposed for the purpose: inhibin B and anti-Müllerian hormone (AMH).

Inhibin B is produced by early antral follicles. With a dwindling number of antral follicles in the late perimenopause, inhibin B levels begin to drop and therefore might be a good marker of ovarian reserve[16]. However, inhibin B levels are not constant during the menstrual cycle.

Furthermore, they are already undetectable about 4 years prior to the final menstrual period[18]. Inhibin B has been investigated in a single study in 127 premenopausal early breast cancer patients who were treated with chemotherapy. Inhibin B was significantly associated with a risk of CIA even after controlling for FSH[19]. These levels could possibly predict whether the ovarian reserve before the start of chemotherapy is sufficient to survive the chemotherapy induced loss of follicles.

Anti-Müllerian Hormone (AMH), produced by primary, secondary and early antral follicles, rises sharply during puberty when folliculogenesis starts and remains relatively unchanged throughout the menstrual cycle.

This is due to the fact that AMH does not exert any feedback on the hypothalamic – pituitary – ovarian axis[20,21]. AMH inhibits the recruitment of primordial follicles and the FSH sensitivity of the late antral follicles. Lower levels of AMH will increase the rate of recruitment of primordial follicles and as a consequence result in an acceleration of the depletion of the primordial follicle pool toward the end of the reproductive period.

In a recently published long-term follow up study of normo-ovulatory women, age – specific AMH levels were highly predictive for timing the menopause[20].

However, despite the potential of AMH as a biomarker of menopause, several challenges remain. Moreover, the effect of chemotherapy and the interpretation of the AMH levels are still unclear. A declined AMH level after start of chemotherapy is not always permanent and as such cannot predict whether folliculogenesis will or will not recover within the following year[22].

Antral follicle count (AFC) by ultrasound is a transvaginal method to measure the ovarian reserve repeatedly during the first two years after breast cancer survivors have finished chemotherapy. The number of small antral follicles in both ovaries as measured by UlS is related to reproductive age and could be a reflection of the size of the remaining primordial follicle pool. AFC is highly positively correlated with AMH levels in breast cancer survivors[23].

INDICATIONS FOR ADJUVANT HORMONAL TREATMENT

Patients with hormone sensitive breast cancer are categorized as either clearly premenopausal, clearly postmenopausal or of uncertain menopausal status.

Clearly premenopausal women have a regular ovarian ciclicity prior to breast cancer diagnosis, without using oral contraceptives / HRT. For these women, the treatment indication is tamoxifen for 5 years with or without ovarian suppression.

Clearly postmenopausal women are women either older than 60 years or who have undergone bilateral ovariectomy or have amenorrhea >12 months prior to breast cancer diagnosis without using oral contraceptives / HRT.

Those women need to either switch therapy

from tamoxifen to AI or 5 years up front AI. Women of uncertain menopausal status are not falling within the definition of clearly pre – or clearly postmenopausal status. For these women, the current indication is to first of all discontinue the use of any oral contraceptive / HRT they may be on. Then they start tamoxifen without ovarian suppression and they are monitored for 2,5 – 3 years for their menstrual cyclicity, FSH, estradiol and if possible AMH levels.

If within 2,5 – 3 years they have irregular menstrual cycles or if either FSH ≤20 IU/L or estradiol ≥110 pmol/L or AMH >0.05 ng/mL, they are categorized as premenopausal. So, the indication is tamoxifen for 5 years with / without ovarian suppression.

If after 2,5 – 3 years no more than 1 menstrual cycle has been documented and FSH is >20 IU/L, estradiol <110 pmol/L or AMH (if determined) <0.05 ng/mL, these patients should be switched to AI[24].

The choice of adjuvant hormonal therapy in obese breast cancer patients is still a matter of debate[25,26]. An increase in BMI leads to an increase in total – body aromatization and as a consequence an increase in estradiol serum levels[26].

Several retrospective studies have suggested a non-significant trend in the efficacy of AIs versus tamoxifen in non-obese compared to obese postmenopausal patients. Also, the efficacy between the two treatment arms among normal weighted patients was not different[27-29].

CONCLUSION

For patients with hormone-sensitive breast cancer, the choice for a specific adjuvant hormonal treatment depends on the menopausal status of an individual woman. The currently available measures to determine the menopausal status are conflicting. Current treatment indications enable an optimal algorithmic choice of adjuvant hormonal therapy for women with hormone receptor positive breast cancer, taking into account uncertain ties about their menopausal status.

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REVIEW

Thymoma: diagnosis, treatment and prognosis
The role of postoperative radiotherapy

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ABSTRACT

Although thymomas are rare neoplasms, they are the most common tumor of the anterior mediastimum in adults. Preferred therapy for these neoplasms is complete surgical resection. If a thymoma cannot be completely resected, postoperative radiotherapy may produce satisfactory results in controlling the tumor. Significant 5-and 10-year survival rates have been treated by radiation therapy alone. Chemotherapy may be used in patients with unresectable thymomas as well, but the results are less promising than with radiotherapy and chemotherapy used on patients with unresectable thymomas have produced encouraging results. Whole mediastinal irradiation (WM) is effective in preventing mediastinal recurrences in patients with completely resected thymoma. Surveillance of patients with thymoma should be prolonged because late recurrence (more than 5 years after initial therapy) can be expected in a significant minority of patients. Additional treatment, such as prophylactic pleural and pulmonary irradiation or chemotherapy should be administered to prevent pleural based reccurence.

KEY WORDS: Chemotherapy, Radiotherapy, Surgery, Thymoma

INTRODUCTION

Thymomas are rare neoplasms that originate from the epithelial cells of the thymus and are the most common tumors of the anterosuperior mediastimum, representing 20-30% of all malignant mediastinal tumors[1-6]. These tumors occur with equal gender incidence, mainly in the group age 40-60 years[4]. Presentation is usually as an asymptomatic mass on chest radiograph or with associated symptoms, such as myasthenia gravis[7,8]. Clinical staging for patients with thymoma was introduced by Bergh et al in 1978[9], and subsequently was modified by Masaoka et al in 1981[10]. Currently, the Masaoka classsificasion has been the most widely used staging system. Malignancy generally is determined by invasiveness of tumor rather than by histologic type[11,12]. However, all thymomas potentially are invasive and should be considered malignant[11,13]. With respect to the

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prognosis for patients with thymoma, factors that clearly affect treatment out come are the invasiveness of the tumor[4,7,8,10,14-20], and the extent of surgical resection[10,11,14,18-25]. The importance of myasthemia gravis[7,8,11,16,17,19,20,26] and the histologic subclassification[3,4,7,12,17,19,20,27-29] as independent prognostic factors remains controversial.

Diagnostic and Staging Studies

Thymomas presents most commonly at age 40-60 years. Rare in children. Symptoms include ocular muscle weakness, ptosis, dysphagia, or fatigue. Impingement on mediastinal structures may cause chest pain, cough, dyspneia, hoarseness, and/or superior vena cava syndrome[51]. Because thymomas are anterior mediastinal tumors, they can be clearly seen on a lateral x-ray study. A CT scan allows precise definition of the extent of involvement of the suspected thymoma for staging. A cyst can be differentiated from solid tumors, and pleural and pericardial implants can be indentified. An MRI does not have a significant yield beyond that obtained with CT scan. In planning RT (either as sole treatment or postoperatively), the initial diagnostic CT scan is vital. It is important in a postoperative setting to treat the entire area from which the thymoma arose. It must be noted that often a thymoma may have abulted the posterior sternum or anterior chest wall, and this area may be at risk for reccurence if not included in the postoperative radiation fields. It is important to exclude the possibility that one is dealing with a mediastinal germ cell tumor. Consequently, appropriate serum markers should be obtained[50].

STAGING

There is no formal American Joint Committee on Cancer TNM system for staging thymic tumors. A system described by Masaoka and associates[52] is widely used. Of note, this system classifies pleural or pericardial metastases as stage IVA and lymphatic or hematogenous metastases as stage IVB. Approximately 40% of patients have the current stage I, 20% stage II, and the remainder stage III. 35-50% cases associated with myasthemia gravis (MG); 15% of MG patients have thymoma. Importance of histology a controversial. Of the 3 subtypes (cortical, medullary, mixed), cortical has a low but increased risk of late relapse even with minimal invasion. Prognosis is related to stage and completeness of resection[51].

CLINICAL STAGING

Clinical staging is based on the surgical and pathologic criteria described by Masaoka et al [10].

Stage I: macroscopically completely encapsulated and no microscopic capsular invasion; Stage II: 1) macroscopic invasion into surrounding fatty tissue or mediastinal pleura and 2) microscopic invasion into the capsule; Stage III: macroscopic invasion into neighboring organs (pericardium, great vessels, or lung); Stage Iva: pleural or pericardial dissemination of thymoma; and Stage IVb: lymphogenous or hematogenous metastases.

PATHOLOGIC CLASSIFICATION

All pathologic specimens and operative reports are reviewed, and the diagnosis of thymoma is based on the pathologic classification of Rosai and Levime, i.e., neoplasms of thymic epithelial cells regardless of the presence of a lymphoid component[1]. This definition is modified later by the same authors, such that thymic tumors containing cells with the cytologic aspect of malignancy are classified separately as thymic carcinoma[2].

TREATMENT

Although surgery remains the treatment of first choice for patients with thymoma, radiotherapy is used widely in patients with invasive thymoma and in some patients with noninvasive thymoma. The role of postoperative radiotherapy after incomplete resection or biopsy for invasive thymoma has been well established[7,15,24,29-31]. Conversely, there is no

clear consensus regarding the optimal adjuvant treatment of patients with thymoma after they undergo complete resection. In patients with completely resected, Masaoka stage I (noninvasive) tumors, routine postoperative irradiation has not been recommended because of the low incidence of recurrence even without postoperative irradiation[7,16,32]. In contrast, in patients with completely resected, stage II and III(invasive) tumors, postoperative mediastinal irradiation has been recommended routinely to prevent local recurrence[7,13,16,17,33-35]. However, a controversy exists concerning the optimal postoperative radiotherapy for tumors at these stages, especially with regard to the total dose and treatment field[32,36]. Some authors have reported low recurrence rates with the use of postoperative mediastinal irradiation alone in patients with Stage II and Stage III tumors and have pointed out the efficacy of this treatment method[7,15,17,36]. Others have found that postoperative mediastinal irradiation may be insufficient, because recurrences of pleural dissemination sometimes occurred remote from the initial tumor site even in patients with stage II tumors[32,37]. Furthermore, the optimal dose of postoperative radiotherapy in patients who undergo complete resection has remained unclear.

CHEMOTHERAPY

The use of chemoradiotherapy has not been well studied due to the rarity of this tumor and the fact that most patients are treated with surgical excision[53]. Some investigators have used combined etoposide and cisplatin therapy. These treatments result in responses in up to 70% of patients. A regimen of PAC demonstrated a 50% response rate[54]. Currently, the main indication for the use of chemotherapy is as preoperative therapy in an attempt to render a tumor resectable or amenable to radical RT. Chemotherapy is also used for palliation of metastatic disease[50].

RADIOTHERAPY

Radiotherapy is administered with a 6MV, or 10 MV linear accelerator with multileaf collimator, after the CT simulation. Patients lie supine with their arms above the head immobilized with a T bar or similar device. The mediastinal irradiation fields are classified into two patterns: 1) with involved field (IF) irradiation that covered the primary tumor bed with margins of about 1-2cm, and 2) with irradiation of the whole mediastinal field with or without boost (WM irradiation), including the primary tumor bed, with the upper margin at the thoracic inlet and the lower margin at the diaphragmatic crurae. Patients are treated with anteroposterior opposed fields with the spinal cord dose limited to 45 Gy. Two anterior wedged portals or off-cord, oblique, opposed portals are used to boost the anterior mediastinum to higher doses. The supraclavicular fossa is not usually included in the irradiated field (2% of patients). The total dose to the primary tumor is 45-60 Gy stage I-II: 45 Gy, stage III-IV 60 Gy (Mediam 50 Gy). Daily fraction sizes of 1,8-2,0 Gy, 5 days per week from Monday to Friday. Portal images should be taken on days 1-3 and weekly thereafter to ensure any day-to day set up variation is within tolerance.

POSTOPERATIVE RADIOTHERAPY

There is a general consensus that surgery is the treatment of first choice for patients with thymoma, and the extent of surgery is a significant factor for local control and survival[14,15,21]. Therefore, many authors have recommended complete resection for these patients whenever possible[5,18,22-24,40]. However, even in patients who undergo macroscopically complete resection, these tumors often recur in the thoracic region, such as the mediastinum or pleural cavity[7,10,13,24,36,37], and a poor prognosis has been observed in patients who experienced disease recurrence[7,18]. The incidence of intrathoracic recurrence for patients with stage II and III tumors

who do not receive adjuvant therapy has been approximately 28-40%[7,13,24,40]. Therefore, there is general agreement that postopetive radiotherapy should be used in the treatment of patients with stage II and stage III tumors[7,13,16,17,33-35].

Conversely, for patients with completely resected stage I tumors, the role of postoperative radiotherapy has been less clear for patients with stage I thymoma, most studies have reported no recurrences or very few recurrences after patients undergo surgery without receiving any adjuvant therapies[7,16,32]. Many authors have stated that there is no rationale for the use of postoperative radiotherapy for patients with stage I tumors[7,35].

In contrast, Regnard et al reported that, among 135 patients with stage I disease, 5 of 26 patients (19%) with peritumoral adherence experienced recurrences, whereas 0 of 109 patients without peritumoral adherence experienced recurrences [21]. The recurrence rate is significantly higher among patients with peritumoral adherence compared with patients who had no peritumoral adherence. Pollack et al. observed 2 recurrences in 11 patients with stage I tumors and advocated postoperative radiotherapy for patients who underwent complete resection for stage I thymoma when the tumor is large and adherent to pleura or pericardium[18]. Cowen et al. also found no failures among irradiated patients with stage I disease who had peritumoral adherence[22].

Although postoperative irradiation of invasive thymoma has been recommended commonly, the optimal radiation fields and doses remain uncertain[5,19,22,24,32,34-37,41]. The dose response in patients who receive irradiation for thymoma has not been established clearly. With regard to the total dose, most authors recommend a total dose of 40-50Gy in daily fractions of 1,8-2,0Gy after patients undergo complete resection[18,24,36,37,41,42] Jackson and Ball found that, in 14 patients who underwent macroscopic complete resection, there was no dose-response relation to local control within the range of 40-45 Gy[24].

Some authors have recommended the inclusion of supraclavicular fossa in the radiotherapy field[11,43]. Chahinian et al. found that 2 of 11 patients (17%) with invasive or metastatic thymoma experienced disease recurrence at the supraclavicular fossa[43]. In contrast, other authors have questioned the need of radiation therapy to the supraclavicular fossa[24,44]. Jackson and Ball found that 2 of 28 patients (7%) with invasive thymoma recurred at the supraclavicular fossa, and in neither patient was it the sole site of recurrence[24]. Prophylactic irradiation of the supraclavicular fossa does not appear to confer any therapeutic advantage to patients who undergo complete resection.

The most common pattern of failure in patients who undergo complete resection for invasive thymoma after they receive mediastinal irradiation reportedly is pleural dissemination[10,32,45,46]. However, it may be difficult to predict the risk of pleural-based recurrence by Masaoka stage alone, because recurrences sometimes occur even in patients with stage II tumors[32,37]. Several reports also have indicated that, with the use of mediastinal irradiation, no recurrences were observed in patients without pleural invasion[32,45]. These results suggest that invasive thymomas without pleural invasion may be localized disease with a lesser risk of pleural dissemination and that mediastinal irradiation would be effective in preventing recurrence.

Some patients with pathologic pleural invasion of the tumor already had latent microscopic pleural dissemination at the time they underwent surgery, even though they were classified with stage II disease. In such patients with pleural invasion, mediastinal irradiation may have only a limited effect. Not merely localized field irradiation but even whole mediastinal irradiation may be insufficient to prevent pleural-based recurrence, because it can cover only a part of the pleura.

To reduce the risk of pleural-based recurrence, some authors have advocated the use of prophylactic pleural and pulmonary irradiation[19,21,37]. Uematsu et al. compared irradiation of the entire hemithorax plus the mediastinum (Group 1) with

mediastinal irradiation only (Group 2) in patients with Masaoka stage II and III disease[37]. In both treatment groups, the median dose applied was 40 Gy. That study found local control rates of 60% in Group 2 (12 of 20 patients) and 96% in Group 1(22 of 23 patients). The authors concluded that, except in elderly patients, entire hemithorax irradiation after patients undergo complete resection appears to be safe and feasible and can reduce intrathoracic recurrence rates. Because systemic chemotherapy reportedly is capable of producing durable remissions in patients with advanced or metastatic thymoma[46,47] several authors have concluded that chemotherapy may deserve evaluation as adjuvant therapy for patients with invasive thymoma who undergo complete resection[14,32,36].

Conversely, several authors have indicated that the incidence of pleural-based recurrence seemed too low to recommend routine extensive treatment of the pleura[7,17,19,36]. Nakahara et al. noted a 95% 15-year survival rate in 35 patients with stage III thymoma who underwent complete tumor resection and who were given routine mediastinal irradiation[17]. Curran et al. reported that, among 43 patients with stage II and III tumors, the intrathoracic recurrence rate after they underwent complete resection and postoperative mediastinal irradiation was only 5%[7]. Urgesi et al. indicated that, among patients with stage III thymoma, only 5 of 59 patients (8,5%) experienced tumor recurrences outside the irradiated field[19]. These results are conflicting and are likely a function of selection bias, a common problem when comparing retrospective data sets[35]. To clarify the need of prophylactic treatment for patients with pleural-based recurrences, properly randomized trials are highly warranted. Additional treatment should be given to patients with pathologic pleural invasion of the tumor. A correlation of computed tomography scanning and magnetic resonance imaging with the surgical and pathologic findings also may provide additional data and may merit further investigation[48].

Several reports also indicated that some patients developed radiation pneumonitis or pericarditis[15,18,36,37]. Cowen et al. indicated that 7 of 149 patients (5%) developed Grade 3 or 4 (World Health Organization grading) pericarditis (3 patients) or lung fibrosis (4 patients), although no patient died due to side effects of complications resulting from treatment[22]. These results indicate that postoperative mediastinal irradiation may carry some risk of side effects; however, it can be administered without fatal complications.

CONCLUSION

Thymomas are rare neoplasms and are the most common tumors of the anterosuperior mediastinum, representing 20-30% of all malignant mediastinal tumors. Although surgery remains the treatment of first choice for patients with thymoma, radiotherapy is used widely in patients with invasive thymoma and in some patients with noninvasive thymoma. The role of postoperative radiotherapy after incomplete resection or biopsy for invasive thymoma has been well established. Whole mediastinal (WM) irradiation with a total dose of 40-45 Gy is effective in preventing mediastinal recurrences in patients with completely resected thymoma, although involved field(IF) irradiation carried some risk of mediastinal recurrence. Analysis of the mode of recurrence revealed that pathologic pleural invasion of the tumor is predictive of pleural based recurrence for patients with completely resected thymoma. Combinations of radiotherapy and chemotherapy used on patients with unresectable thymomas have produced encouraging results. In patients without pleural invasion, the tumor may be localized disease with a lesser risk of pleural dissemination, and postoperative mediastinal irradiation would be sufficient to prevent recurrence. Conversely, in patients with pathologic pleural invasion of the tumor, there is some possibility of microscopic pleural dissemination at or before the time of surgery. Therefore, additional treatment, such as prophylactic pleural and pulmonary irradiation or chemotherapy, should be administered to prevent pleural-based recurrence.

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REVIEW

Cancer Cachexia
Mechanisms and clinical management

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ABSTRACT

A consensus definition incorporating clinical, functional and biochemical parameters is necessary in order to adequately identify and treat patients with cancer cachexia. The process which drives cachexia is controversial and many mechanisms participated in the expression of this clinal condition. A number of issues remain to be resolved and the treatment or the management of cancer anorexia / cachexia which remains multifactorial depending on the tumor and the patient.

KEY WORDS: Cancer metabolism, cancer anorexia

1. INTRODUCTION

Cachexia is a multifactorial condition which comprises skeletal muscle and adipose tissue loss which may be compounded by anorexia, a dysregulated metabolic state with increased basal energy expenditure and is resistant to conventional nutritronal support. Cachexia correlates with poor performance status, poor quality of life and a high mortality rate in cancer patients.[1,2]

Loss of greater than 5-10% of body weight is usually taken as a defining point for cachexia, and a 2.5 Kgr weight change over 6-8 weeks is sufficient to produce significant changes in performance status and death usually occurs when there is 30% weight loss.[3,4]

Anorexia, inflammation, insulin resistance and increased muscle proteinolysis are frequently associated with cachexia. In adults the weight loss combined with water retention and edema.[5]

In cancer patients it is very controversial to define exactly the term cachexia and its reasons. More recent definitions describe cachexia as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat "mass"[5].

This highlights the unique consequences of muscle wasting – the hallmark of cachexia and downplays the importance of fat loss.

The prevalence of cachexia is up to 90% for upper gastrointestinal cancer with pancreatic, and oesophageal the most frequent types and 60% for lung cancer patients at the time of diagnosis[6]. The most important factor is the decreased muscle

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strength in order to distinguish cachexia from other causes of anorexia and fatigue in cancer patients such as the treatment effects (chemotherapy or radiotherapy) and this factor could be used as a diagnostic criterion with greater sensitivity and specificity for cancer patients[7].

2. CLINICAL AND PHYSIOLOGIC CONSEQUENCES OF CANCER CACHEXIA

There are many factors implicated in cancer cachexia models such as tumor factors, host-tumor interactions, host-response factor and finally metabolic and neuroendocrine factors[9].

2.1. Tumor factors

Cancer cells produce factors that stimulate a host inflammatory response, which are called inflammatory and procachectic factors.

Procachectic factors include proteolytic and lipid mobilizing factors[8,9] and these factors have been identified in the urine of patients with pancreatic, colon, ovarian, liver and lung cancers, with associated weight loss.

Stimulation of these pathways induce proteolysis in muscle and in hepatocytes via the ubiquitin proteosome pathway which results in the production of interleukins (IL-6, IL-8) and CRP[10].

Lipid mobilizing factor has been found in cancer patients losing weight but not in stable weight patients. This lipid mobilizing factor plays a lipolytic role in the increase of cyclic AMP or the increase of b-adrenergic receptors[11,12].

2.2. Host-tumor interactions

In the tumor microenvironment, the kytokines production and an interplay between IL-1β and IL-6 within the tumor, may drive the cachexia process[13].

It is not certain whether the cytokine production is primarily from the tumor or host inflammatory cells, and this question remains a hypothesis.

Some studies demonstrate tumor tissues with significantly elevated cytokines and others in which the production of cytokines is elevated from the peripheral blood mononuclear cells[14,15].

Tumor necrosis factor-a (TNFa) and tumor factor proteolysis induced factor are the major contenders for skeletal muscle atrophy in cachectic cancer patients.

There are controversial opinions about the correlation of TNF-and weight loss as a unique factor to weight loss, but on the other hand the use of antagonists of TNFa as a treatment, prevents muscle loss in cancer patients and suggests that tumor factors are the most important in the cancer cachexia process.[16]

2.3. Host responses

Up to 50-60% of patients with solid tumors may have an elevated acute phase associated response. This response has been associated with hypermetabolism, elevated resting energy expenditure and reduced energy intake in cancer patients[17].

C-Reactive protein (CRP) is the most valuable tool used to assess the magnitude of the systemic inflammatory response. The combination of CRP and the plasma albumine concentrations create a scoring system which is a prognostic factor that predicts the survival, independent of stage and treatment[18,19] (table 1).

It is unknown the linking mechanisms between acute phase protein and cachexia. The most attractive hypothesis is that "this systemic alterations in protein metabolism drives the proteolysis of skeletal muscle to fuel the switch to acute phase reactant production"[20].

Table 1. Modified Glasgow prognostic score: An inflammation – based score[18]

Biochemical measure	Score
CRP ≤10 mgr/L + Albumin ≥35 g/L	0
CRP ≤10 mgr/L + Albumin <35 g/L	0
CRP >10	1
CRP >10 + Albumin <35 g/L	2

2.4. Neuroendocrine and metabolic factors

In cancer patients, a number of metabolic and neuroendocrine factors appear to be dysregulated such as insulin resistance, elevated cortisol, reduced anabolic activity and metabolic changes resemble those of infection rather than starvation[1].

The cytokines have been implicated in insulin resistance. The ATPubiquitin dependent proteolytic pathway is the major contribution to proteolysis in cancer cachexia[21,22]. Activation of proteolysis is an early event during tumor growth and it may be present for a long time period prior to its clinical manifestation. The role of testosterone or derivates have been shown to be implicated in protein synthesis in cancer patients.

In conclusion metabolic and endocrine changes in cancer cachexia are a result of the interactions of host and tumor factors.

3. ANOREXIA AND CACHEXIA: THE TWO FACES OF THE SAME COIN?

There is a controversial process to explain the two different and similar phenomenos of Cachexia and Anorexia in cancer patients.

Anorexia itself may have a number of axis, nausea, altered taste sensation, swalling difficulties or depression. It is essential that the lack of appetite is secondary to factor which include tumor and host immune system, as a response to the tumor. Cytokines inhibits neuropeptide Y or mimics negative feedback action of leptin in the hypothalamus leading to anorexia[23].

On the other hand in cancer patients the failure to replace nutritional regimens in order to reserve weight loss, leads primarily to the cachexia disease process[4].

The physiological mechanisms of appetite regulation have been studied.

There are two main mechanisms in the hypothalamus identified to be involved, the melanocortin system and the neuropeptide Y system. The neuropeptide Y stimulates appetite and melanocortin system decreases in food-seeking behavior, increased basal metabolic rate and decreased lean body mass.

4. CACHEXIA RESULTS

Cachexia results in a catabolic state due to acute inflammation process which implicates tumor factors and host (patient) response.

This state is the ultimate cause of death in some cancer patients, and cachexia directly impacts in quality of life, physical activity and finally in overall survival[6].

4.1. Quality of life

Cachexia is associated with symptoms, such as fatique, weakness, poor physical performance in cancer patients. Thus leads to a lower self-rated quality of life.

Patients who continue to lose weight while receiving palliative chemotherapy have reduced quality of life and performance status scores when compared with same patients whose weight loss stabilizes[24].

4.2. Physical activity

Activity levels are influenced by several quality of life domains. Measurement of physical activity are controversial and very difficult due to different reasons[25]. The most important factor is that the dearease of activity leads to the decrease of performance status and a decreased ability of mobilization daily, and also decreases social interactions.

4.3. Survival

The weight loss and malnutrion has been indicated as an important prognostic factor for cancer patients, and plays and important role in the final survival. The mechanism to explain why patients with weight loss or malnutrition have a poorer survival is the increased incidence of complications from surgical, chemotherapeutic or radiotherapeutic treatments[26]. The question

which rises in cancer cachexia patients, is whether reduced survival is due to more aggressive tumor behavior or due to suboptimal treatment related to weight loss. The answer remains unknown.

5. THERAPEUTIC APPROACHES TO CANCER CACHEXIA

The goal of treatment starts with the hypothesis that effective management of cancer cachexia will improve performance status, by inhibiting the process, and this way cachexia survival may be improved.

Current therapeutic interventions in CC are of limited benefit, and despite the fact that nutritional intake is frequently reduced, the treatment with hypercoloric feeding has not been shown to promote weight gain[27].

5.1. Nutritional counseling

Important factor in cancer treatment of patients requiring nutritional support, must be determined at the beginning of anticancer treatment. The European Society of Parenteral and Enteral Nutrition (ESPEN) reports in a consensus statement that there is a Grade A evidence for intensive dietary counseling with food plus or minus oral nutritional supplements in preventing therapy – associated weight loss, preventing treatment interruptions and increasing dietary intake in gastrointestinal or head and neck cancer patients undergoing radio – or chemotherapy[28].

The poor results observed with conventional nutritional support, in cancer cachectic patients, with tube entereral or parenteral nutrition led to the emergence of so-called nutraceuticals or immunonutrition supplements in an attempt to nutritionally modify the metabolic milieu by providing anti-inflamatory substances such as eicosapentaenoic acid (EPA) at levels much higher than typically found in the diet.

5.2. Eicosapentaenoic Acid (EPA)

EPA is a long chain polyunsaturated fatty acid of the ω-3 family (n-3 family).

It is of interest in the context of cancer cachexia, that it has the potential to impact on both, the underlying metabolic abnormalities of tumor – induced weight loss, as well as modulation of immune function. When EPA is consumed at levels higher that normally found in the diet it replaces Arachidonic Acid (A.A), an n-6 polyunsaturated fatty acid, in cell membrane phospholipids. It then, acts as a substrate for the production of the 3 series prostaglandins and the 5 series leukotriens.

Eicosanoids, synthesized from the n-3 as EPA rather than n-6 as AA have lower potential in promoting inflammation. Modulation of dietary fatty acids can therefore have an impact on many immune processes such as proliferation phagocytocis, cytotoxicity and cytokine production[29].

Another attractive method may be the use of nutritional supplements containing agents proven to effectively prevent treatment related toxicities. Glutamine, melatonin and octreotide are such agents.

Glutamine decreases the esophagitis and related complications of radiotherapy in lung cancer. Melatonin decrease the severity and incidence of chemotherapy induced enteritis and octreotide has been shown to effectively prevent the cancer treatment induced diarrhea[27]. What is the effect of this agents in cancer cachexia?

Theoretically their preventive properties on treatment related toxicities suggest their important role in the management of cancer cachexia. It can be assumed that any decrease in mucositis, diarrhea and malabsorption will theoretically result in improved nutrition, quality of life and decreased loss of weight.

5.3. Pharmacological agents

i) Conticosteroids may be a good choice as orexigenic agents, megestrol acetate is by far the most widely prescribed and at least most investigated agent which significantly improves appetite[30]. A recent meta-analysis has reported this effect, of weight gain in cancer patients[31].

ii) Non-steroid anti-inflammatory drugs (NS AIDs), can reduce weight loss and aid maintenance of performance status in advanced cancer patients.
These drugs showed activity against PIF-induced proteolysis, reduced resting energy expenditure and acute phase response[32].

iii) Thalidomide, is a unique drug with multiple immunomodulatory properties and potent inhibitory effects on TNFa production.
Gordon et al[33] showed that thalidomide administration significantly attenuated both the total body weight and lean body mass loss.

5.4. Combination therapy

1. Most recently[34] a study which randomised 332 patients with cancer – related cachexia / anorexia in 5 arms of treatment
2. Megestrol acetate 320 mgr/d or medroxyproge sterone 500 mgr/d
3. Oral supplementation with eicosapentaenoic
4. L-carnitine 4gr/d
5. Thalidomide 200 mgr/d
6. A combination of the above 4 arms for a total of 4 months.

Results showed the superiority of arm 5 over the others for all primary end points. Toxicity was negligible and comparable between treatment arms[34].

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REVIEW

The current role of radiotherapy in vertebral hemangiomas without neurological signs
A case report and a review of literature

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ABSTRACT

Vertebral hemangiomas are benign vascular lesions occurring in spine. They are slowly growing tumors, sometimes causing local pain in the spine and/or neurologic disorders. Though vertebral hemangiomas are frequently seen, they are rarely symptomatic. Pain is the commonest symptom. Radiotherapy has been shown effective in many studies in terms of pain relief and at times in cord compression, too. We report a case with vertebral hemangioma without neurological signs, which has been treated in the Radiation Oncology Department of AHEPA University Hospital.

KEY WORDS: Vertebral Hemangioma, radiotherapy, symptomatic vertebral hemangioma

INTRODUCTION

Hemangiomas are benign slow growing vascular tumors that may occur anywhere in the body including bone. Vertebral hemangioma was first described by Virchow in 1867 and characteristic radiological appearances were first noted by Perman in 1926.[1] Is the most commonly encountered tumor of the vertebral column.[2] This benign vascular lesion has an estimated incidence of 10-12% in the population, based on large autopsy series (in about 11% at general autopsy) and a large review of plain spine films.[3-6] The true incidence of vertebral hemangioma is unknown as the majority of them are asymptomatic and remain undiagnosed throughout the life. They may be detected as incidental roentgenographic findings or when they produce local pain and/or swelling and/or symptoms or signs of spinal cord compression. Only 0,9-1,2% of all vertebral hemangiomas are symptomatic.[7,8] Women are affected more often than men and young adults more commonly symptomatic than the elderly.[9] Involvement of more than five vertebral bodies is extremely rare.[2] Hemangiomas may occur in the posterior elements, the vertebral body, or even

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in a circumferential pattern involving all three columns. Significant paraspinal tumor masses are occasionally seen.[9] Treatment of vertebral hemangioma is usually done to relieve symtoms. Treatment methods include radiotherapy, surgery, embolization, intralesional injection of ethanol, and vertebroplasty with methyl methacrylate. In this report the result of a patient who received radiotherapy is analysed.

CASE REPORT

A 50-year old man with hemangioma in the 8th Thoracic vertebra was refered to our Department for irradiation, in June 2011. MRI showed a paravertebral mass (Figure 1), the differential diagnosis of which could not exclude neoplastic or tubercular nature of the lesion. Ultimate diagnosis was confirmed by open biopsy. Routine blood examination, abdominal ultrasonography, chest and whole spine X-ray, were conducted in the patient and did not reveal any disorder. The clinical features evaluated included back pain, radiculopathy(±), myelopathy(±). There were no neurological signs, sensory deficits and the patient was with normal bladder/bowel function and normal reflexes. The patient was treated with embolization initially, then with surgery and perioperative alcohol injection. Because of the failure of the treatments received he was referred to our department for radiotherapy. He received 3D-conformal radiation therapy to the involved vertebra(Thoracic 8) with one vertebra above (Thoracic 7) and one below (Thoracic 9) (Figures 2, 3, 4). The dose given to the planning target volume (PTV) was 40 Gy I 20 fractions (2Gy/Fr), over 4 weeks. Radiation was delivered

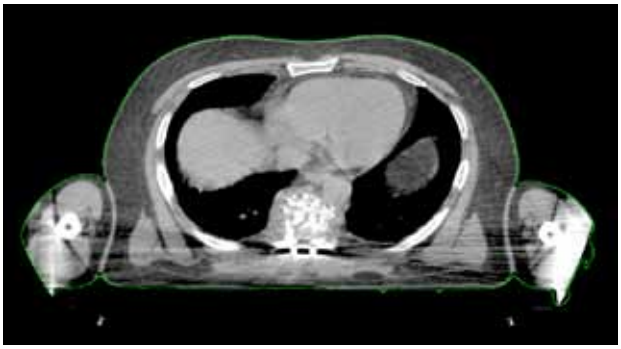

Figure 1. Paravertebral mass in Th8 (MRI before radiotherapy).

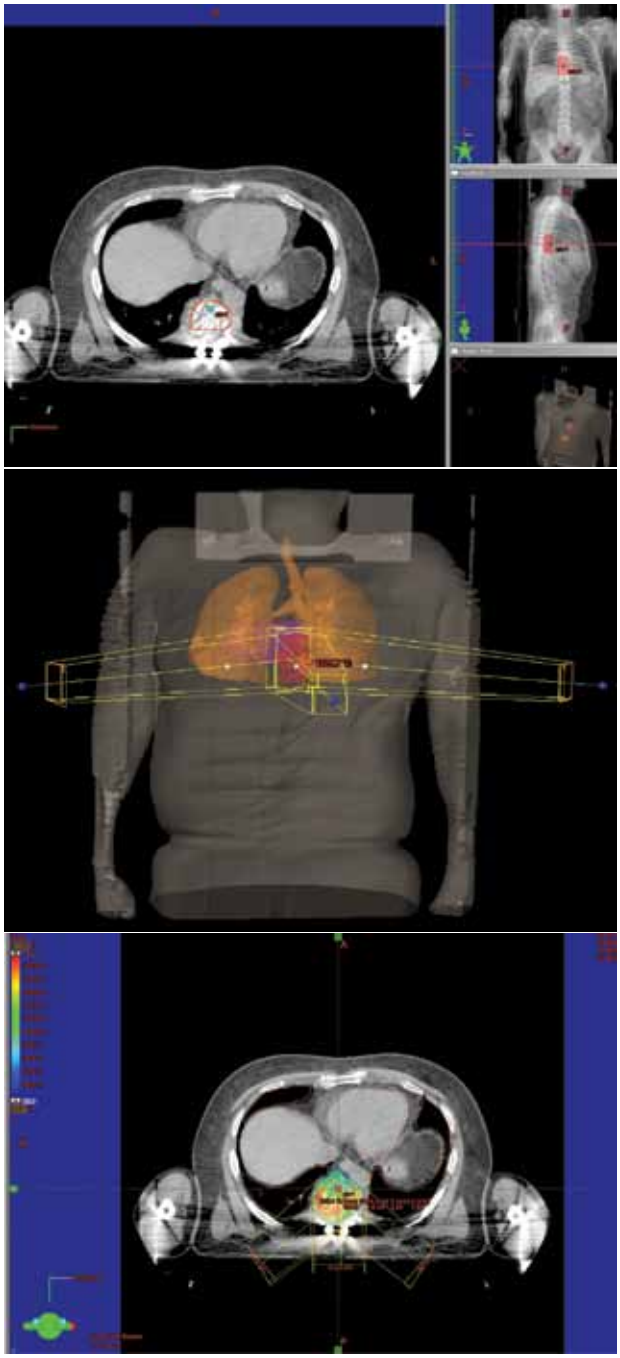

Figure 2,3,4. CTV-clinical target volume(red)Treatment planning-fields.For 2D,3D conformal radiotherapy.

by three fields. Oral Dexamethasone at a dose of 12mg daily in divided doses was started along with radiotherapy to minimize radiation induced edema and gradually tailored off at the end of radiation. Analgesics were given as required; physiotherapy was started at soon as patient's condition permitted and continued even after completion of radiation. Muscle power was assessed at the beginning of radiation, 4 weeks after completion and thereafter at three months interval during follow-up. The patient at the end of therapy had decreased pain and much better improvement of his performance status. The MRI 3 months after the end of irradiation therapy, showed reduction of the paravertebral mass at the level of the 8th thoracic vertebra (Figure 5). The patient did not develop backache and myelopathy. Analgesics were no more required to the patient two months after the completion of radiotherapy.

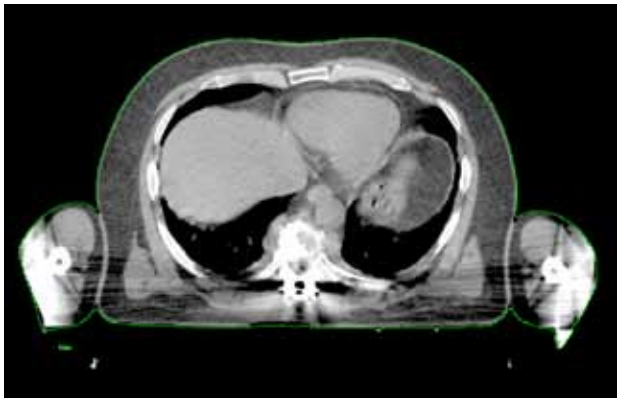

Figure 5. Reduction of paravertebral mass in Th8(MRI after 3 months at the end of radiotherapy)follow-up.

DISCUSSION

Hemangiomas are benign slow growing vascular tumors composed of newly formed capillary, cavernous or venous blood vessels. Among skeletal locations, vertebrae are the second commonest site and thoracic spine is affected most frequently.[10] In the present case, the vertebral hemangioma was of thoracic origin.

Vertebral hemangiomas are benign vascular lesions[11]. They can be of cavernous, capillary or mixed type[2,9]. In the cavernous form, dilated blood vessels get clustered without the intervention of bone stroma. In the capillary form, the walled blood vessels are separated by normal bone tissue. Arteriovenous shunting is not typically present[9].

Several options are available for the management of symptomatic vertebral hemangiomas and multiple modalities may have to be used for a single patient. Among the treatment modalities, the non-surgical ones (such as endovascular embolization, injection of alcohol or methyl methacrylate into the vertebral body and radiation therapy) are preferred due to the highly vascular nature of the tumor, because of the threat of mortality due to exsanguinations, the difficulty in approaching and the complete excision of the tumor with its associated morbidity during surgery. The goals of surgery include bony decompression by laminectomy or vertebrectomy and excision of soft tissue components of the tumor compressing the neural elements. Surgery can be correlated with embolization or injection of absolute alcohol.

Endovascular embolization with particulate agents such as polyvinyl alcohol foam is reported to produce dramatic but usually transient remissions of the lesion[12-14]. Recently, percutaneous injection of methyl methacrylate into the vertebral body has generated considerable interest.[21] Methyl methacrylate is an ideal agent to stabilize the vertebral bodies which are at risk of collapse. Leakage of the agent into the draining veins or posteriorly into the spinal canal may be hazardous.

Even in a paraparetic patients, due to extension of the hemangioma into the spinal canal, methacrylate may fill the intra spinal compartment and may exacerbate the already existing cord compression, requiring immediate laminectomy. In addition, when laminae and pedicles are also involved by the hemangioma (which is a frequent feature in cord compression), the surgeon is in front of considerable intra operative bleeding during laminectomy. The injection of methyl methacrylate

into the vertebral body and N-butyl cyanocrylate into the laminae and pedicles are recommended, in order to overcome this complication. Methyl methacrylate strengthens the vertebral body to prevent pathological fracture and cyanocrylate reduces the intra operative bleeding during subsequent laminectomy[22].

Vertebral hemangiomas are radiosensitive lesions that respond to administration of 30 to 40 Gy[15]. Radiation therapy has been used most often to treat lesions associated with pain. Different reports suggest that radiotherapy alone or in combination can give good symptomatic relief of pain[16,17]. The radiation therapy is also used in some patients, after decompression to avoid further deterioration. In cases of acute spinal compression, radiation offers satisfying results of relief[18,19]. Young et al reported that five out of seven paraplegic patients recovered sufficiently to walk again, after external radiotherapy alone. Recovery was complete in three of them. They also concluded that radiation can be used as a primary treatment in patients with severe cord compression. Operative decompression can be employed in cases of failure of radiation therapy[17].

The exact mechanism of action of radiotherapy on vertebral hemangiomas is not clearly known. On the other hand pain relief is seen in almost all patients treated with radiation. It may be supposed that response to radiotherapy is similar to that seen in pain relief due to radiation in the management of vertebral metastasis. Radiotherapy can result in loss of segments of capillaries causing deficit of micro vascular network, with subsequent ischaemic changes. Anti-inflammatory effect of radiation has also been attributed for the relief of pain observed with radiotherapy.[20] In our case, the patient presented therapeutic response (pain relief and regression of hemangioma) after receiving a dose of 40Gy (2GyX20fraction in 4 wks). The radiation dose received in the target volume and fractionation schedule was similar to the schemes used by several investigators that suggest a total dose of 30 to 40 Gy (1,8 to 2Gy/fraction)[16-18,24]. Rades et al (2003) pooled and studied (LQ model-statistical analysis) the data to understand the impact of total dose on complete pain relief by using equivalent dose to 2Gy fractions[25]. It was concluded that 40Gy with 2Gy/fraction gives sufficient pain relief.

Malignant transformation of vertebral hemangiomas is virtually unknown.[26]

Malignant component was reported in a patient in whom repeated irradiation was given for recurrent hemangioma. The lesion was aggressively behaving with repeated recurrences, which is not characteristic of benign hemangiomas. It was concluded that malignancy is unlikely to be due to irradiation[27]. Up to date there is not much evidence of malignant transformation of the lesions, because of radiation therapy.

CONCLUSION

The aim of radiotherapy in hemangiomas is to eliminate the abnormal veins and capillaries and to reduce the size of the lesion. A known long term effect of radiotherapy is impairment of circulation by causing vascular endothelial damage. Radiotherapy is an effective and acceptable mode of treatment for symptomatic hemangiomas of vertebra, where pain is the main symptom. Other options exist, like intralessional injection of ethanol, vertebroplasty with methacrylate, surgical decompression etc. These options are invasive techniques involving risks, where as radiotherapy in non-invasive and safe.

It is considered that 40Gy delivered by conventional fractionation (2Gy/fraction) is the best dose at present, at this is the accepted standard dose to achieve compensatory pain relief and at the same time is close to the tolerance level (TD5/5) of the spinal cord. However, in the present era of Intensity Modulated Radiation Therapy (IMRT), higher doses of radiation may be delivered to the involved parts of the vertebrae and may yield improved results without any substantially increased risk of spinal cord damage. But this needs further

evaluation by new clinical studies.

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REVIEW

What's new is Gynecologic Oncology clinical practice 2012

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ABSTRACT

Comprehensive genomic analysis and a tumor-specific new intraoperative finore scence imaging technique using a folate receptor – a targeted agent, seems to improve intraoperative staging and a more radical cytoreduction in the management of ovarian cancer. We discuss information on bevacizumab and poly (ADP-ribose) polymerase inhibitors, risk-reducing salpino-oophorectomy, and risk evulation of a pelvic mass. We reviewed new findings on human papillomavirus vaccines and tests and clinical trials on locally advanced cervical cancer. The value of sentinel lymph node biopsy in the management of early stage endometrial cancer was followed by the research on exemestane for the prevention of breast cancer and eribulin for the treatment of metastatic breast cancer. Lastly, we discuss the effect of GRH analogue on the occurrence of chemotherapy – induced early menopause, in premenopausal women with breast cancer.

KEY WORDS: Gynecologic oncology, breast cancer, HPV – Vaccine, poly (ADP – ribose) polymerase inhibitors, genomic analysis.

INTRODUCTION

We have summarized the latest noteworthy clinical research achievements in breast, cervical, endometrial and ovarian cancer, with the hope that more, potentially practice – changing researches and trials, will be performed in the near future, in the field of gynecologic oncology.

BREAST CANCER

Concerning the latest achievements on breast cancer (B.C.) research, a study was conducted on the efficacy of an aromatase inhibitor, "exemestane", in the prevention of B.C. in postmenopausal woman.[1] The eligibility criteria included postmenopausal women 35 years of age or older with at least one of the following risk factors: 60 years or older; Gail 5-year risk score greater than 1.66% (chances in 100 of invasive breast cancer developing within 5 years); prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ; ductal carcinoma in situ with mastectomy. A total of 4560 women were randomized to exemestane (2.285 patients) or placebo (2.275 patients). The primary outcome was the incidence of invasive breast cancer. At a median follow-up of 35 months,

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11 and 32 invasive breast cancers were diagnosed in the exemestane group and the placebo group, respectively (annual incidence, 0.19% vs. 0.55%; HR, 0.35; 95% CI, 0.18 to 0.70; p=0.002). Adverse events occurred in 5% or more of subjects, 88% in the exemestane group versus 85% in the placebo group (p=0.003). Arthritis (p=0.01) and hot flushes (p<0.001) were more common in the exemestane group. The major reason for early discontinuation of the protocol treatments were toxic effects (15.4% vs. 10.8%, p>0.001). However, the researchers concluded that, with its excellent safety profile, exemestane significantly reduced invasive breast cancers in postmenopausal women were at modelately increased risk for breast cancer, based on the similarity between the two groups in terms of skeletal fractures, cardiovascular events, other cancers, or treatment related deaths.

Another clinical phase III, open-label randomized study named "EMBRACE" has been conducted, testing the efficacy of "eribulLin", a non-taxane inhibitor of microtubule dynamics in the improvement of overall survival (OS) in patients with heavily pretreated metastatic B.C.[3] A total of 762 women were randomized either in the eribulin or the treatment of physicians choice (TPC) group. Overall Survival was 13.1 and 10.6 months for the eribulin and the TPC group respectively. Peripheral neuropathy (5%) on the eribulin group was the only noteworthy adverse event. Authors concluded that eribulin is a potential standard drug with a manageable toxicity profile for the treatment of women with heavily pretreated metastatic B.C.[3]

Finally, a randomized, phase III study evaluated a patient sample of 281 premenopausal women with stage I-II breast cancer randomly allocated to receive either chemotherapy alone, or chemotherapy plus "triptorelin", a GnRH analogue in order to detect the role of GnRH analogue in preserving ovarian function during chemotherapy for B.C.[4]

The study was named "PROMISE – GIMG". Symptoms of early menopause were detected in a percentage of 52.9% in the chemotherapy - alone group, and in a 8.9% in the chemotherapy plus triptorelin group. The PROMISE – GIM6 study is the largest study that shed some light in the use of hormonal protection for chemotherapy – induced gonadotoxicity in premenopausal women, with early – stage B.C.

CERVICAL CANCER

Concerning the latest achievements on cervical cancer (C.C.) research, a recent study evaluated the overall efficacy of HPV – 16/18 ASO4 – adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia it was a 4 year end – of – study analysis on a randomized, double-blind patient population, named "PATRICIA" trial.[5] Strong evidence for near 100% prophylactic vaccine efficacy was reported in HPV – naive women at any age and cross – protective efficacy of the HPV 16/18 vaccine. Vaccine efficacy was reported for a 6 month persistent infection, CIN II or greater, associated with 12 non-vaccine HPV types, and CIN III associated with the composite of 12 non-vaccine HPV types. Consistent cross – protective efficacy of the HPV 16/18 vaccine against 4 oncogenic non-vaccine HPV types (33, 31, 45, 51) was documented.[6]

Another study, named "The Costa Rica vaccine trial" evaluated the efficacy of fewer than 3 doses of the HPV 16/18 vaccine.[7]

They found that the incidence of HPV 16 or HPV 18 infections that persisted for 1 year were not related to dosage of the control vaccine. Two doses of the HPV 16/18 vaccine, and maybe even one dose, was as protective as three doses against persistent HPV 16/18 infections.

In an ecological study on the early effect of the HPV vaccination programme on cervical abnormalities, the authors compared the incidence of high-grade cervical abnormalities (HGAs) and low-grade cytological abnormalities (LGAs), before and after the vaccination program begins.[8]

A decrease in the incidence of HGAs in girls younger than 18 years was documented, after the

implementation of the vaccine program, however, no similar results were recorded for LGAs or in older age groups. This study was the first to report the effect of a national HPV vaccination program at a population level, supporting the high cost-effectiveness of the HPV vaccine coverage especially in preventing cervical cancer, in the young age group of women.

Co-screening with HPV and a Pap test, every three years, women with normal cytology and a nerative HPV test was recommended by the American Cancer Society and the American College of Obstetricians and Gynecologists guidelines.[9] However, since then, clinicians have been concerned about the cancer risk accrued over three years.

A recent population – based study in routine clinical practice was conducted, in order to evaluate cancer risk for women undergoing concurrent testing for HPV and cervical cytology.[10]

A higher percentage of disease outcomes was shown in HPV – positive / Pap-negative women, than in HPV-negative / Pap – positive women for CIN III or adenocarcinoma in situ. They suggested that incorporating HPV testing with cytology, could earlier detect women at high risk of cervical cancer, especially adenocarcinoma, which was poorly identified by Pap test.

A phase III, open – label, randomized study, compared concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. Treatment – related hematologic toxicities and deaths in this study made the adjuvant gemcitabine and cisplatin regimen difficult to accept as a standard - of - care without a more careful study regading late loxicily.[12]

Three GCIG (Gynecologic Cancer Intergroup) clinical trials for locally advanced cervical cancer are open to recruitment and still running, with primary endpoint OS (Overall Survival).

First, the "OUTBACK" trial, led by the Australia and New Zeland Gynecological Oncology Group (ANZGOG), is a phase III trial of adjuvant chemotherapy following chemoradiation as the primary treatment for patients with stage IB1 and positive LNs, IB2, II, IIIB or IVA cervical cancer, compared with chemoradiation alone.

Second, the "INTERLACE" trial, led by the Medical Research Council National Cancer Research Institute (NCRI), is a phase III multicenter trial of weekly induction chemotherapy (paclitaxel plus carboplatin) followed by standard chemoradiation, versus standard chemoradiation alone in patients with locally advanced cervical cancer.

Lastly, the "TACO" trial, led by the Korean Gynecologic Oncology Group (KGOG) and by the Thai Gynecologic Cancer Society (TGCS) is a phase III multicenter international randomized trial, comparing six cycles of weekly cispatin (40 mg/m^2) with three cycles of tri-weekly cisplatin (75 mg/m^2) for chemoradiation in locally advanced cervical cancer.[13]

ENDOMETRIAL CANCER

In a recent research study concerning endometrial cancer (E.C.). The main interest was the sentinel-node concept for patients with early stage endometrial cancer in order to reduce the morbidity of extensive surgical staging by lymphadenectomy, while accurately identifying patients who will benefit from adjuvant therapy.

A total of 133 patients in a prospective multicenter study SENTI – ENDO, with stage I-II endometrial cancer, had pelvic sentinel LN assessment via cervical dual injection with technetium and patent blue. The extent of lymphadenectomy was determined according to preoperative pathologic results[14]. All patients belonged to one of the free risk groups defined by FIGO in 2009: low risk – type 1 E.C. stage IA grade 1 or 2; intermediate risk – type 1 E.C. stage IA grade 3 or stage IB grade 1 or 2; and high risk type 1 E.C. stage IB grade 3 or type 2 E.C. or any stage and grade. Notably, no LN metastasis other than positive sentinel LN occurred in patients with low or intermediate risk E.C. The study suggested that sentinel LN biopsy alone

was enough to justify adjuvant therapy without the need for complete pelvic lymphadenectomy in these patients. However, the high incidence of metastasis in both sentinel and non-sentinel LNs in pts with high risk endometrial cancer, led to the performance of pelvic lymphadenectomy in high risk patients.

OVARIAN CANCER

Two large studies, published in 2011 were heralded by many researches as laying the foundation for paradigm shift in the management of ovarian cancer.

In the first study conducted by The Cancer Genome Atlas (TCGA) Research Network, genomic and epigenomic abnormalities were measured on clinically annotated high-grade serous ovarian cancer (HGS-OvCa). The TCGA project analyzed m-RNA expression, micro RNA expression, promoter methylation and DNA copy number in 489 HGS – OvCa. The project reported 96% of a TP53 mutation rate while BRCA1 and BRCA2 were mutated in 22% of tumors. In 2-6% of HGS – OvCa six other statistically recurrently genes were identified: RB1, NF1, FATB, CSMD3, GABRA6 and CDK12. This study found 113 significant focal somatic copy number alterations (SCNA), the most common focal amplifications of which encoded CCNE1, MYC and MECOM as well as promoter methylation events involving 168 genes. Finally, different mutation spectrums between ovarian cancer histological subtypes were suggested as a rationale of subtype – specific care.[15]

The second study was conducted by Van Dam et al[16] and concerned a new intraoperative imaging technique using a folate receptor-a (FR-a) targeted fluorescent agent. The researchers tried to develop a real-time tumor – specific surgical visualization system with a detection power up to the submillimeter level because the degree of cytoreduction is one of the most important prognostic factors in ovarian cancer. Using fluorescein thiocyanate conjugated folate which was overexpressed in 90-95% of malignant tumors, fluorescence was detectable intraoperatively in all patients with a malignant tumor and FR-a expression, but not in those with benign tumors. The real – time image guided excision of fluorescent tumor deposits of size <1 mm was feasible. Van Dam et al[16] suggested several advantages of the intraoperative fluorescence imaging system avoiding needless extensive surgical procedures and associated morbidity thanks to a large field of view for inspection and staging; contributing to more efficient cytoreduction and ultimately improving the effect of adjuvant chemotherapy, particularly when combined with hyperthemic intraperitoneal chemotherapy (HIPEC).[17] The promising value of an intraoperative imaging system appeared valid even in a laparoscopic setting and interval debulking surgery after chemotherapy because FR-a expression was not significantly altered after chemotherapy.

Three important updates of previously reported phase III studies concerning antiangiogenic agents in ovarian cancer were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2011. Updates of two front-line bevacizumab studies were presented. First the addition of 15 mg/m^2 of bevacizumab every 3 weeks during both 6 cycles of paclitaxel (175 mg/m^2) / carboplatin (AUC 6) and 16 cycles of maintenance drug alone (16 months of total duration (arm 111) were found to prolong progression-free survival (PFS/ of paclitaxel / carboplatin alone (arm I) by 6 morths (hazard ratio [HR], 0.63; p<0.0001.[18]

The second updated study was a subgroup analysis of poor prognosis patients by International Collaborative Ovarian Neoplasm (ICON) 7.[19]

According to Gaitskell et al meta-analysis of two trials,[20] women who received bevacizumab in addition to chemotherapy had lower risk of disease progression compared with women who received placebo, but meta-analysis found no statistically significant difference in OS.

Aghajanian et al[21] reported the preliminary results of the OCEANS trial, the first phase III trial

of antiangiogenic agent to demonstrate a clinical benefit to platimum sensitive recurrent epithelial ovarian cancer (EOC), primary peritoneal (PPC), and fallopian tube cancer (FTC).

484 patients were randomized to arm A who received 6 cycles of gemcitabine, carboplatin and placebo and arm B who received 6 cycles of gemcitabine / carboplatin with bevacizumab. Arm B significantly increased PFS (progression free survival) compared to arm A during the median follow up of 24 months.[21]

In AURELIA trial, an angoing phase III trial of bevasizumab in platinum – resistant settings, all patients received chemotherapy with either paclitaxel or topotecan or liposomal doxorubicin. Bevacizumab was injected concominantly only in the patients of arm 2. The primary endpoint is PFS and preliminary data is expected soon.

In 2005 two studies demonstrated pre-clinical efficacy of PARP (poly-ADP-ribose polymerase) inhibitors in tumors with homologous DNA repair detects such as in BRCA1 and BRCA2 mutation carries with ovarian cancer.[22,23] The studies confirmed the activity of the PARP (olaparib) with response of 33% in patients with ovarian cancer,[24,25] which accounted about 10% of epithelial ovarian cancer.[26]

In 2011 two phase II studies showed the activity of olaparib in women with high grade serous ovarian cancer without BRCA1 and BRCA2 mutation. In the first study (91 patients, 65 ovarian – 26 breast cancer)[27] with objective response in 41% and 24% in patients with and without BRCA1 and BRCA2 mutations.

The second study by Leudermann[28] with 265 patients with platinum – sensitive relapsed serous ovarian cancer were randomized regardless of BRCA1 and BRCA2 mutation PFS by RECIST was longer in the olaparib than the placebo group. PARP inhibitor therapy can effectively be used in patients with common sporadic tumours.[26]

RRSO (Risk-reducing Salpingo-oophorectomy) is currently recommended for BRCA1 / BRCA2 between 35-40 or younger with familial cancer history of early onset.[29-31] The MD Anderson Cancer Institute demonstrated that most women at high risk for breast and ovarian cancer were satisfied with their choice of a risk – reduction strategy.[32] The practice of RRSO increased the number of post-RRSO survivors at risk of peritoneal cancer, bone loss and menopausal symptoms.[33]

Several studies in 2011 focused on post-RRSO care with Hormone replacement therapy (HRT) following RRSO was not associated with a higher risk of breast cancer compared with those with no RRSO. In BRCA1 mutation carriers, HRT used with and without RRSO was associated with a decreased risk of breast cancer. Women currently on HRT presented with less hot flushes, night sweats and vaginal dryness than those who had never used HRT or previous HRT users.

Women undergoing RRSO 50 years ago should be counseled because the risks of breast cancer from estrogen – only HRT appeared to be relatively small. Cohen et al[34] reported high rates of osteopenia and osteoporosis in BRCA 1/2 mutation carriers with breast cancer undergoing RRSO prior to 50. Based on this result, Chapman et al[33] concluded that the inconsistent post – RRSO case was due to the lack of post – RRSO health care guidelines and proposed the development of standardized guidelines.

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screen trial, was conducted in 2011 and reported that the screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality.[35] Final results are though expected from the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).[36] Risk evaluation for epithelial ovarian cancer in women with pelvic mass is another important issue that reactions to be established. Moore et al[36] demonstrated the importance of the dual marker combination of human epididymis protein 4 (HE4) and CA-125 for risk prediction of ovarian malignancies in 2009. Furthermore, combination of HE4 and CA-125 values has been investigated for effective triage

of women with a pelvic mass: risk of ovarian malignancy algorithm (ROMA),

A ROMA study of patients with a pelvic mass failed to demonstrate a better performance of ROMA than CA-125 alone. Ovarian cancer will cause a raised CA-125 and HE4, whereas endometriosis will only cause a raised CA-125.

Another study on ROMA by Bandiera et al[37] analyzed the performance of HE4 and ROMA with preoperative serum samples from a diverse patient pool of women who were healthy controls and others that had ovarian benign cysts, endometriosis or epithelial ovarian cancers. Multivariate analysis demonstrated that elevated HE4 and ROMA were independept prognostic factors for shorter OS and PFS and that there is a need for multicenter studies in order to reach final conclusions.

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ORIGINAL PAPER

Expression of p53, bcl-2, EGFR and survivin, in pancreatic ductal adenocarcinomas
A clinicopathological study

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ABSTRACT

Aim: To examine the expression of the anti-apoptotic factors p53, bcl-2, EGFR and survivin in pancreatic ductal adenocarcinomas. **Material and Methods:** 115 cases of resected pancreatic adenocarcinomas examined at the Pathology Department of Aretaieion University Hospital during a decade (2001-2010) were studied. Additional sections from the archived specimens were obtained and further studied by a Ventana automatic immunohistochemistry method for the expression of p53, bcl-2, EGFR and survivin. The findings were correlated with clinical and pathological data available in all cases. **Results:** *Clinico-Pathological Data:* 70 patients were male and 45 were female, with age ranging between 38-83 years (mean age was 60). Tumors were located mainly in the head of the pancreas (84.3%) and measured 0.5-6.5cm in diameter. *Immunohistochemistry:* In **stage I** tumors, out of 22 cases (19.1%), positive immunoreaction was observed in 6 cases for p53, in 15 cases for bcl-2, in 5 cases for EGFR and in 3 cases for survivin. In **stage II** tumors, out of 44 cases (38.2%), there were 21 positive cases for p53, 13 cases for bcl-2, 16 cases for EGFR and 13 cases for survivin. In **stage III** tumors, out of 36 cases (31.3%), positive were 24 cases for p53, 6 cases for bcl-2, 25 cases for EGFR and 23 cases for survivin. Finally, in **stage IV** tumors, out of 13 cases (11.3%), positive were 11 cases for p53, 3 cases for bcl-2, 10 cases for EGFR and 10 cases for survivin. **Conclusions:** Higher p53, EGFR and survivin expression was noted at higher stages of disease and poorly differentiated tumors and may constitute, and the aforementioned molecules might be markers of poor prognosis while bcl-2 immunoreaction was observed mainly in stage I, well differentiated tumors, and may imply better prognosis.

KEY WORDS: Pancreas, Adenocarcinoma, p53, bcl-2, EGFR, Survivin, Prognosis

INTRODUCTION

Ductal adenocarcinoma of the pancreas represent 85-90% of all pancreatic tumors. In the Western world the annual incidence rates range

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from 3.1-20/100.000 in male patients and 2.0-11.0/100000 in female patients. Pancreatic cancer is the fifth cause of cancer death, with a mean survival time of the surgically treated patients 10-20 months and an overall 5-year survival rate about 5%[1]. The dismal long term results of this disease following even R0 resections are partially due to the relative chemo and radioresistance of pancreatic neoplasms.

Current investigation of pancreatic carcinogenesis focuses on identifying molecular markers with possible prognostic significance. The apoptotic mechanisms expressed by neoplastic cells and the regulators of the cell cycle and various growth factors, are targets of intense research[2-6]

It has been postulated that chemo- and radiotherapy act primarily by inducing neoplastic cell apoptosis therefore, preferential expression of various inhibitors of apoptosis (IAP) may be responsible for the resistance of pancreatic ductal adenocancercinomas to these therapies[7].

The aim of our study was to examine the expression of the antiapoptotic gene bcl-2, the tumor suppressor gene p53, the Epidermal Growth Factor Receptor (EGFR-1, HER-1), and survivin, an inhibitor of apoptosis, on ductal pancreatic cancer cells with immunohistochemical methods. Finally we correlated the immunoexpression of these markers with clinical and pathological data, in order to identify any prognostic significance.

MATERIALS AND METHODS

During a decade, from January 2000 to December 2009, 224 specimens of surgically treated pancreatic ductal carcinoma were examined at the Pathology Department of Aretaieion University Hospital. Clinical data (gender, age, tumor stage, type of therapy) and pathological characteristics (tumor size, tumor grade, location, extend of disease, lymph node and adjacent organ infiltration) were retrieved form patient records. The stage of the disease was based on the TNM classification of the exocrine pancreas tumors, according to UIC. Additional sections from the archived paraffin-embedded tumor tissues were obtained and examined by Ventana automatic immunostain method, using anti-human bcl-2 protein (DAKO M0887,clone 124), p53 antibody (DAKO, M7001, DO-7), EGFR (Zymed Lab. Inc, San Francisco, CA), and survivin (A-Diagnostics Intern. San Antonio TX), according to manufacturer's instructions, with appropriate positive and negative controls.

The immunoreaction was evaluated semi-quantitatively, depending on the percentage of positively stained cells to the total number of cells examined (at least a 100 cells per case). The score was considered negative (-) where no positive cells were found, or the percentage of immunostained cells was <10% of total cells examined, and positive (+) where >10% of cells were stained. Positive immunoreaction was observed in the nuclei (p53), the cytoplasm (bcl-2 and survivin) and on the cellular membrane and the cytoplasm (EGFR).

RESULTS

Clinical findings

Overall 115 cases of pancreatic ductal adenocarcinoma met the criteria of our study and were reviewed. Of these, 70 /115 were men and 45 /115 were women. The age range was 38-83 (mean age was 60 years), with equal gender distribution. The youngest patient was a male 35 years of age, with a stage IV, high grade carcinoma and with a family history of intestinal polyposis syndrome.

The pancreatic tumors were located mainly at the head of the pancreas (84.3%) and measured 0.5-6.5cm in greatest diameter with mean diameter 3cm.

According to TNM classification of pancreatic carcinomas, 22 cases (19.1%) were stage I, 44 cases (38.2%) were stage II, 36 cases (31.3%) were stage III and 13 cases (11.3%) were classified as stage IV. According to the degree of differentiation 26 tumors (22.5%) were well differentiated (grade 1), 55 tumors (47.8%) were moderately differentiated

(grade 2), and 34 tumors (29.5%) were poorly differentiated (grade 3).

All cases were common ductal adenocarcinomas as no rare histological types were included in our study.

Immunohistochemistry

In **stage I** tumors, positive immunoreaction was observed in 6/22 cases for p53, in 15/22 cases for bcl-2, in 5/22 cases for EGFR and in 3/22 cases for survivin.

In **stage II** tumors, positive immunoreaction was observed in 21/44 cases for p53, in 13/44 cases for bcl-2, in 16/44 cases for EGFR and in 13/44 cases for survivin.

In **stage III** tumors, positive immunoreaction was observed in 24/36 cases for p53, 6/36 cases for bcl-2, in 25/36 cases for EGFR and in 23/36 cases for survivin

In **stage IV** tumors, positive immunoreaction was observed in 11/13 cases for p53, in 3/13 cases for bcl-2, in 10/13 cases for EGFR and in 10/13 cases for survivin (Table 1, Figure 1).

According to grade, in **grade I** tumors, positive immunoreaction was observed in 13/26 cases for p53, 15/26 cases for bcl-2, in 10/26 cases for EGFR and in 6/26 cases for survivin.

In **grade II** tumors, positive immunoreaction was observed in 29/55 cases for p53, 17/55 cases for bcl-2, 22/55 cases for EGFR, and 20/55 cases for survivin

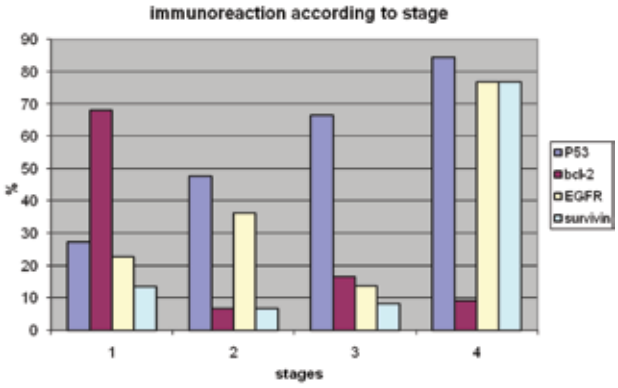

Figure 1. Immunoreaction accoeding to stage.

In **grade III** tumors a positive immunoreaction was observed in 20/34 cases for p53, in 5/34 for bcl-2, in 24/34 cases for EGFR and in 19/34 cases for surviving (Table 2).

DISCUSSION

The p53 pathway is the molecular connection between cell cycle and apoptosis and inhibits cell growth through cell cycle arrest and apoptotic death. Mutations of p53, observed in >50% of all kind of cancers are thought to promote tumor progression. Various therapeutic approaches have been studied to restore normal p53 function[5].

Table 1. Immunoreaction of p53, bcl-2, EGFR and survivin according to TNM stage

TNM classification	p53	bcl-2	EGFR	Survivin	Total No of pts
Stage I	6 (28%)	15 (68%)	5 (23%)	3 (14%)	22 (19%)
Stage II	21 (48%)	13 (30%)	16 (36%)	13 (30%)	44 (38%)
Stage III	24 (67%)	6 (17%)	25 (69%)	23 (64%)	36 (31%)
Stage IV	11 (85%)	3 (23%)	10 (77%)	10 (77%)	13 (11%)

Table 2. Immunoreaction results according to tumor grade

Tumor grade	p53	bcl-2	EGFR	Survivin	Total
Grade 1	13 (50%)	15 (58%)	10 (38%)	6 (23%)	26
Grade 2	29 (53%)	17 (31%)	22 (40%)	20 (36%)	55
Grade 3	20 (59%)	5 (15%)	24 (71%)	19 (56%)	34

In the recent literature, p53 immunoexpression varies from 47% to 64% of pancreatic cancers, in accordance with our results. The prognostic significance of p53 immunoexpression in pancreatic adenocarcinomas has been debated amongst investigators. Bold et al (1999) report a trend towards improved survival in patients whose tumors stained positive for p53[8] while other investigators reported no effect of p53 immunoreaction on survival or even a better prognosis. Some authors postulate that mutations of p53 gene enhance tumor development and progression[7,9]. In our study a higher expression of p53 in high grade and stage of pancreatic tumors was observed.

Bcl-2 family of apoptosis regulators is well studied in various types of human malignancy. In pancreatic cancer there is evidence that, in contrast to other human cancers where bcl-2 is highly expressed, its expression is normal or even decreased[6,7]. Bold et al and Makinen et al report that bcl-2 over-expression is associated with a statistically significant improvement in survival[2,8]. According to Seki et al the reduced expression of bcl-2 may be involved in the growth-inhibitory effect of cisplatin in pancreatic cancer[3].

In various experimental and clinical phase II studies using G3139, which is a bcl-2 antisense construct, in combination with other chemotherapeutics, a regression of neoplasms growth was observed. Current research is geared towards developing various peptidic agents that mimic the action of bcl-2 family proteins to promote apoptosis of neoplastic cells[4]. In our study, higher bcl-2 immunoexpression was observed in early stage and well differentiated tumors.

Epidermal Growth Factor (EGF) promotes the cellular proliferation and differentiation of many cell types, through its receptor EGFR, and is usually over-expressed in pancreatic cancer[10,11]. Treatment with cetuximab, an anti-EGFR antibody, in combination with gemcitabine and radiation therapy, resulted in complete regression of cancer cells in a pre-clinical setting[12,13]. Our study is in accordance with these reports, as higher EGFR expression was noted in higher grades and stages of the disease.

Survivin is a member of the inhibitor of apoptosis (IAP) family which is expressed at the G2/M phase of the cellular cycle. Survivin presents a distinct structure, different from the other inhibitors of apoptosis and there is evidence that it is implicated in the radio-resistance of pancreatic cancer[14]. In our study, higher survivin expression was found in high clinical stage and hign histological grade, therefore is considered an indicator of poor prognosis. Sarela et al report the expression of survivin in 88% of the cases of pancreatic carcinomas examined, but they conclude that no correlation exists with clinical or pathological tumor characteristics[14].

CONCLUSIONS

In the current study a higher expression p53, EGFR and survivin was observed in high stages of disease and poorly differentiated tumors and these may constitute markers of poor prognosis. On the other hand bcl-2 immunoreaction was mainly observed in well differentiated stage I tumors and may correlate with good prognosis.

These changes of apoptotic proteins, common in pancreatic cancer, constitute the basis of future targeted combined therapies specific for each one pancreas cancer patient[8,15,16].

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CASE REPORT

Microcystic adnexal carcinoma
Misdiagnosis after superficial biopsy of a long existing tumour

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ABSTRACT

Microcystic adnexal carcinoma (MAC) is a rare malignant tumor, which is locally aggressive with extensive microscopic invasion of surrounding tissue and requires heightened clinical acumen in order to evaluate and diagnose accurately, consequently allowing appropriate treatment. A case of MAC is presented in which a tumor has been present in the right nasolabial fold for decades before increasing in size. It was initially misdiagnosed after a superficial biopsy as basal cell carcinoma and accordingly excised with limited margins. MAC is usually a smooth-surfaced, non-ulcerated, ranging from flesh to yellowish colored, non-symptomatic tumor located on the face and characterized by gradual growth over time or stable size for a prolonged period, followed by more rapid growth. Despite its stable size or slow growth, such a lesion should not be dismissed as insignificant. When a lesion as described above is observed, MAC should be suspected and a deep biopsy should be taken to avoid preoperative misdiagnosis and consequently inadequate treatment. Its locally aggressive growth results in a high local recurrence rate after surgical excision, even when surgical margins are reported tumor free at histological examination. Treatment consists of Mohs micrographic surgery or conventional wide excision.

KEY WORDS: microcystic adnexal carcinoma, cutaneous oncology, dermatologic surgery

INTRODUCTION

Microcystic adnexal carcinoma (MAC) is a rare slow growing, but locally aggressive skin cancer that requires heightened clinical acumen for accurate diagnosis and consequently appropriate treatment.[1,2] Despite its stable size or slow growth, such a lesion should not be dismissed as insignificant. Superficial biopsy often leads to misdiagnosis and inadequate treatment.[1,2] Hence, when such a tumour is suspected a deep biopsy is indicated. An illustrative case is reported.

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CASE REPORT

A 67-year-old male, with an unremarkable medical history, presented with an asymptomatic skin tumour of the right nasolabial fold. Interestingly, the approximately 1cm lesion had been stable in size for more than 30 years. One year before presentation, the tumour started growing spontaneously. At presentation, a 3 cm in diameter, flesh to reddish coloured and locally darker pigmented, non-tender tumour of the right nasolabial fold was observed (Figure 1).

Regional lymph nodes were not palpable. Partial biopsy, removing the protruding portion of the tumour, revealed features of basal cell carcinoma (Figure 2a). Subsequently, the remaining tumour was excised with a macroscopic 0.5 cm peripheral margin and until the macroscopically uninvolved buccal mucosa. The defect was closed with a Z-plasty. The postoperative course was uneventful. Histological examination of the excised tumour demonstrated MAC with perineural invasion (figure 2b-d) and infiltration of surrounding subcutaneous fat and muscular tissue. The surgical margins were free of tumour.

Disease staging with whole body computed tomography showed no evidence of metastatic disease. Five months after definite excision, functional and cosmetic results were satisfactory (Figure 3). The patient remains without signs of recurrence 3 years after.

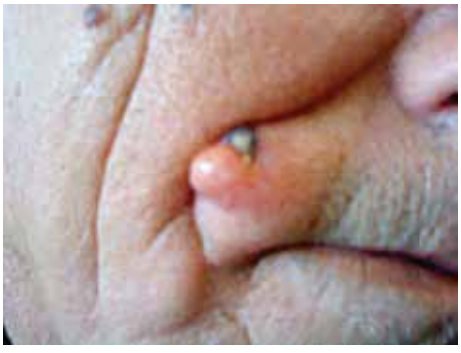

Figure 1. The skin tumor at presentation.

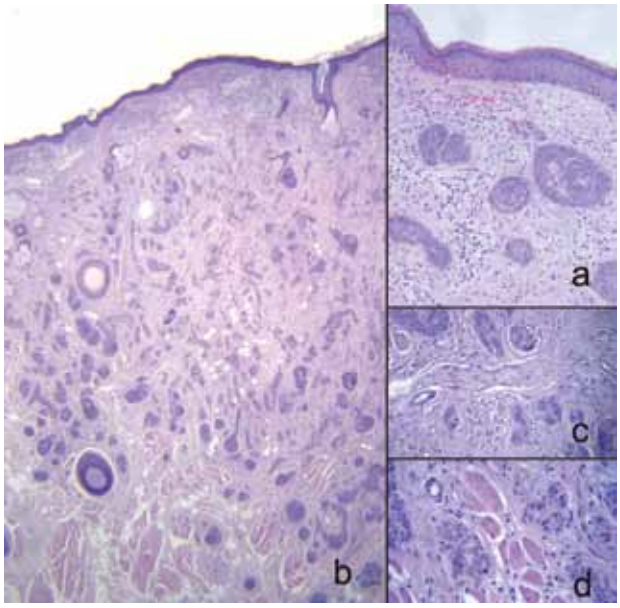

Figure 2. Histology of initial superficial biopsy and excision specimen of microcystic adnexal carcinoma. a: microscopic examination of superficial biopsy suggesting basal cell carcinoma. b: microscopic picture showing the tumour extending in the dermis and subcutis, the epidermis been uninvolved (×20, H&E). c: high power view, showing perineural invasion of the tumour (×200, H&E). d: high power view, showing the neoplastic cells with minimal atypia and occasional mitosis arranged in solid nests, cords and tubules and infiltrating striated muscles (×200, H&E).

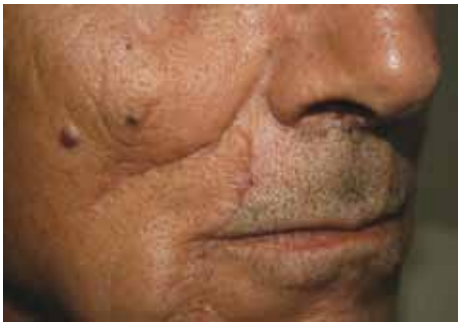

Figure 3. Satisfactory cosmetic and functional result, without signs of local recurrence, five months after excision and reconstructive surgery.

DISCUSSION

This cutaneous neoplasm was first described as a distinct clinicopathologic entity by Goldstein et al in 1982.[1] Several other names had been used

until then, including sweat gland carcinoma, aggressive trichofolliculoma, combined adnexal tumour of the skin, malignant syringoma and sclerosing sweat duct carcinoma. Just over 300 cases of MAC have been presented in literature worldwide.[2]

MAC characteristically presents as a smooth-surfaced, non-ulcerated, flesh coloured or yellowish, asymptomatic tumour, most frequently located in the central zone of the face.[2] However symptoms such as numbness, burning, paraesthesia or pruritus, when present may reflect perineural invasion.[2] The tumour either gradually grows over time or seems to have a stable size for a prolonged period followed by growth, as in our patient.[2-4,] Despite its locally aggressive behaviour, systemic and nodal metastases are rare, even in cases of tumours growing for decades.[2]

MAC is a tumour of pilar and eccrine differentiation that typically extends considerably beyond the clinically visible margins and deeply to the subcutaneous fat or deeper structures.[1, 2] The epidermis may be spared in some cases[1]. The tumour exhibits a stratified appearance with superficially larger keratin horn cysts and epithelial nests, while deeper smaller cysts and ductal structures exist. The cell of origin is probably a pluripotent adnexal keratinocyte[1, 2]. Perineural invasion is both common and a most helpful diagnostic feature.[2] Cytologic atypia is usually minimal and mitotic figures rare. Histologic differential diagnosis includes benign syringoma desmoplastic trichoepithilioma, pappilary eccrine adenoma, morpheaform BCC, SCC and metastatic breast carcinoma. Although many immunohistochemical markers such as positive CEA, pancytokeratin, cytokeratin 1, 14, 15, 19, AE1/AE3 and negative monoclonal antibody Ber-EP4 staining have been proposed to help the differential diagnosis, they are rarely needed. Notably, a superficial biopsy leads to misdiagnosis in about 30% of cases, as in our patient.[1,2,5] It is essential to have a clear estimation of the depth of invasion and perineural involvement in order to have an accurate diagnosis. This highlights the importance of obtaining an adequately deep biopsy specimen and clinical acumen upon receipt of a biopsy report from a superficial specimen.

Treatment consists of complete excision, which may be difficult due to its microscopic extension.[4-6] This is reflected by the high rate (30%) of positive surgical margins after initial conventional surgical excision, necessitating additional surgery.[2] That is why preoperative biopsy is important for appropriate treatment planning. Standard macroscopic excision margins have not been defined. Although Mohs micrographic surgery is much more time consuming and demanding, local recurrence rate is significantly lower than after conventional excision (0-12% versus 40-60%). Our patient is probably at risk for local recurrence, because erroneous preoperative diagnosis of basal cell carcinoma led to conventional surgical excision with limited margins. There is no evidence that adjuvant radiotherapy may be beneficial.[2]

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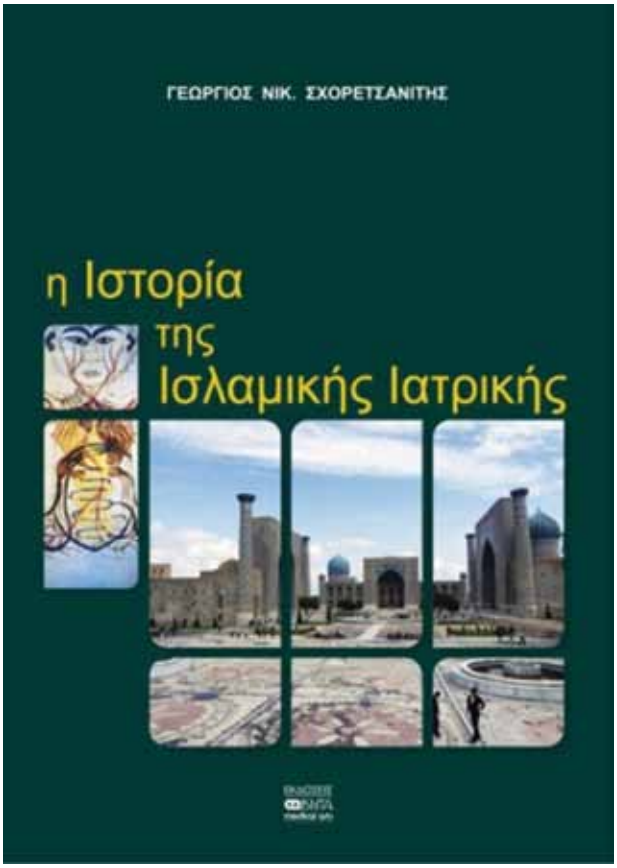
BOOK REVIEW

The History of Islamic Medicine
by George Schoretsanitis, MD., PhD.

How much do we know about Islamic medicine? To what extent are we aware of history of Islamic medicine? Those who are generally interested in the history of medicine, will no doubt find this work dealing with the history of Islamic medicine, extremely interesting.

The unique book is divided into three main sections with totally 31 chapters. The first section includes nine chapters, where the author deals with a short history of Islam as a new religion in various countries, the origins and the rise of Islamic medicine, and the role of mosques and madrasahs in the whole education process in the Islamic land. Chapter 9, "The Hospitals", deals with the hospitals and their function into Islamic society and chapter 10, with universities and specifically medical schools and the education of both, medical students and doctors. In the 14 chapters of the second section, the theoretical framework of the basic studies (anatomy, embryology, pharmacology, etc), as well as the medical specialties (internal medicine, ophthalmology, ENT, urinary tract stones disease, surgery, dermatology, dentistry, psychiatry, and nursing history are reviewed). In the last eight chapters which are included in the third section, medical biographies of the Arabian giants (Razes, Ibn Al Nafis, Ibn Sina, Al-Kindi, Bukhtishu, Ibn Zuhr, Al-Zahrawi) are written in details. Last chapter deals with Hunayn Ibn Ishaq (809-877) and the impact of the translation movement on the development of a medical terminology in Arabic with the eventual transmission of Islamic medicine to Europe.



Available only in Greek language. BETA Medical Publishers Ltd. Nov. 2011. Athens. Greece.
ISBN 978-960-452-144-9

Most of chapters deal with medicine and the

holistic theory that constituted medical reality in those days, including paragraphs on the structure and function of the human body, regimen, diet and drug therapy, diagnosis and prognosis, classification of diseases, clinical specialties and finally prophetic medicine. The role of physicians and their social status, is also stressed. Each chapter is followed by a useful paragraph of references for further reading. The book consists of 405 pages and also contains more than a hundred illustrations. This volume makes the history and principles of medieval Islamic medicine accessible to our medical community and provides the reader with deep insight into Islamic medicine. The author has travelled excessively in many Islamic countries and visited a large number of Islamic museums and places of great interest to Islamic medicine.

The History of Islamic Medicine is a work that anyone with an interest in the history of medicine ought to read. In other words, in order to comprehend the history of Western medicine, one must understand what happened in Arabic lands between the seventh and the fifteenth centuries, the time period covered in the text.

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Επικήδειος στο Γιώργο Βλαστό

Καθηγητή Ιατρικής Σχολής Πανεπιστημίου Γενεύης που απεβίωσε στις 8/2/13

Ευαίσθητος και καλλιεπής – γλυκός – μειλίχιος και προσηνής – ελεύθερο δημοκρατικό πνεύμα.

Βαθύς γνώστης της επιστήμης του σε όλο το εύρος και την διαχρονικότητά της. Εκφράζει τις ιδέες και τα επιχειρήματά του με απαράμιλλη ενάργεια και πειθώ.

Δεν είχε κακίες δεν είχε εμπάθειες. Πέρα από τη σχέση φιλίας υπήρχε μία σχέση αγάπης μεταξύ μας. Η μοίρα ήθελε να σου αφιερώσω σήμερα τούτα τα λόγια…

Αλησμόνητε συνάδελφε, φίλε! Αλησμόνητε Γιώργο. Εκ μέρους της Ευρωπαϊκής Εταιρείας Χειρουργικής Ογκολογίας και της Educational and Training Committee που τόσο υπερήφανα υπηρέτησες και ελάμπρυνες με την παρουσία σου, σου απευθύνω το ύστατο χαίρε.

Νιώθω ειλικρινά αμηχανία γιατί τα λόγια δύσκολα θα αποδώσουν στην ολότητά της τη χαρισματική σου προσωπικότητα.

Στη ζωή σου έδωσες εντυπωσιακά δείγματα επιστημονικής και κοινωνικής παρουσίας αφήνοντας λαμπρό παράδειγμα Ακαδημαϊκής δραστηριότητας.

Εμπνευσμένος δάσκαλος αλλά και αφοσιωμένος γιατρός ο Γιώργος Βλαστός υπηρέτησε με σύνεση ευθυκρισία και ανιδιοτέλεια στο Πανεπιστημιακό Νοσοκομείο της Γενεύης. Με σημαντικές μεταπτυχιακές σπουδές στο MD Anderson του Texas αλλά και με ένα εντυπωσιακό συγγραφικό έργο θεωρείται πρωτοπόρος παγκοσμίως στην αντιμετώπιση των νεοπλασματικών παθήσεων του μαστού.

Πρόσφατα το Πανεπιστήμιο της Γενεύης τον τίμησε με την εξέλιξη σε Αναπληρωτή Καθηγητή και Διευθυντή της μονάδας μαστού του Πανεπιστημιακού Νοσοκομείου.

Σε αυτή την ωραία και ώριμη φάση της ζωής του ήλθε το χτύπημα της αρρώστιας. Την τελική αυτή σωματική, ψυχική και διανοητική δοκιμασία την αντιμετώπισε με θλίψη βέβαια όπως κάθε άνθρωπος που έχει συνείδηση του κοινού τέλους, αλλά κυρίως με αξιοπρέπεια και αισιοδοξία, και με τεράστια αποθέματα αγάπης για την Anne-Therese του δικούς του αλλά και για όλους τους γύρω του.

Στη σκιαγράφηση της προσωπικότητάς του επικρατούν τρία αδρά χαρακτηριστικά: Ήθος κοινωνικό – Ήθος επιστημονικό – Ήθος Ακαδημαϊκό.

Ο Βλαστός δεν δίδαξε μόνο Γυναικολογία και Χειρουργική δίδαξε ήθος και σεβασμό και τα δίδαξε όχι μόνο στους φοιτητές του αλλά και σε όλη την Ακαδημαϊκή κοινότητα.

Τα δίδαξε σε όλους μας.

Όσοι εργάστηκαν μαζί του είναι τυχεροί.

Όσοι μπορούν ας του μοιάσουν.

Ας αγαπούν τον άρρωστο, τον αδύναμο, τον

φοιτητή, τον συνάδελφο. Ας αγαπούν στον άνθρωπο.

Η διάχυτη αίσθηση της αδικίας της πικρίας και του κενού που αφήνει ο θάνατός σου και που κυριαρχεί στον Ευρωπαϊκό επιστημονικό κόσμο και σε όσους είχαν την τύχη να σε γνωρίσουν είναι μία πρώτη αυθόρμητη μαρτυρία της σπάνιας ποιότητας του έργου και της προσωπικότητάς σου.

Γιώργο γνωριζόμαστε πολλά χρόνια.

Η συζήτηση μαζί σου και η αφήγησή σου ήταν απολαυστικές.

Η σημαντική κοινωνική παρουσία σου θα είναι σίγουρα δυσαναπλήρωτη.

Σύντομη η ζωή σου!

Ο απρόσμενος θάνατός σου επισφράγισε το τέλος μιας πορείας ακατάβλητης εργατικότητας και ευσυνειδησίας.

Σήμερα τι ειρωνεία!

Με τον θάνατο σου έδωσες σ' εμένα την ESSO και την Education and Training Committee την δυσάρεστη δυνατότητα να σου εκφράσουμε όλα αυτά που θέλαμε πάντα να σου πούμε.

Ας αποδώσουμε τιμή στο Γιώργο.

ΟΙ ΤΙΜΕΣ ΤΩΝ ΝΕΚΡΩΝ ΕΙΝΑΙ ΤΑ ΣΤΟΛΙΔΙΑ ΤΩΝ ΖΩΝΤΑΝΩΝ ΦΙΛΩΝ ΠΟΥ ΜΕΝΟΥΝ ΠΙΣΩ.

Αντίο Φίλε!

Οδυσσέας Ζώρας