ABSTRACT BOOK

XXV CONGRESSO NAZIONALE IMI

BOLOGNA, 10-12 NOVEMBRE 2019

ROYAL HOTEL CARLTON

Via Montebello, 8

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ABSTRACT AREA EPIDEMIOLOGIA GENETICA E PATOGENESI

Two pathways of nevus associated melanoma: clinical and dermoscopic characteristics

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Background: The "traditional" model of melanoma progression suggests that this tumor develops through a stepwise malignant transformation process (1), from a common nevus to a dysplastic nevus and, finally, to melanoma in situ, which eventually becomes invasive with the potential to metastasize. The aim of this retrospective morphological study was to gain insights into the morphological spectrum of nevi associated with melanomas and vice versa.
Methods: This retrospective, morphological study involved skin lesions collected in Austria (Graz, Vienna) and Italy (Napoli, Reggio Emilia, Trieste). Each participating center searched its database for clinical and dermoscopic images of histopathologically diagnosed nevus associated melanoma (N+MM). The evaluation was based on 3 questions (Q1,Q2,Q3): Q1 was related if a nevus component was clinically visible; Q2 which referred to the question whether dermoscopically a nevus component was recognizable; Q3 which aimed to assess melanoma-specific patterns.
Results: A total of 165 patients with 165 NAM were included in the study. Clinically, a nevus component was not recognized in 85 cases and recognizable in 80. Of note, the melanoma component arose adjacent (peripheral/eccentric) to the associated nevus in 45 cases (56.25%), while being located central within the nevus in 35 (43.75%) cases. Dermoscopically, the melanoma was located eccentric/peripheral in 59 cases (53.15%), and central in 52 (46.85%) cases. The melanoma component of any NAM, independent from the subgroup, tended to be more frequently central in patients aged < 40 years and eccentric/peripheral in those > 40 years.
Conclusion: Our study reveals two types of NAMs, namely melanomas arising within/overlying congenital nevi, characterized by a clod/globular or structureless brown pattern and those arising adjacent to acquired nevi appearing as hypopigmented nodules or plaques. Furthermore, persons developing the former type are generally younger compared to the latter subtype; all these data support the thesis of two different pathways of N+MM.. Our results confirm current data with regard to the epidemiology of NAMs but opens also novel insights into their morphologic variability which suggest different pathways leading to melanoma formation in nevi.

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Vitamin D and disease free survival in stage II melanoma

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Background: Since sun exposure is a recognized risk factor for melanoma, the commonly given advice to melanoma patients to reduce their sun exposure after diagnosis could further exacerbate their vitamin D insufficiency. Observational cohort of melanoma patients suggest that the variation of 25-hydroxyvitamin D (25OHD) from baseline is associated with risk of relapse.
Study design: One hundred and 4 stage II melanoma patients were randomised to vitamin D_3 (2000 IU per day) or placebo and follow-up to investigate the effect of vitamin D on relapse (median follow-up 3 years).
Results: Fifty-seven percent were in stage IIa, 54% had ulceration, 43% were female and median age at diagnosis was 50. Median 25OHD at diagnosis was 18 ng/mL and the lowest quartile was 13 and the highest 24: 80% of patients were found with insufficient vitamin D at diagnosis.
VDR BsmI BB was found to be significantly associated with pT and it remained significantly associated with stage in multivariable model, adjusting for 25OHD.
Changes in 25OHD during trial showed a big increase after 4 months of supplementation in the vitamin D arm. 24OHD was found to be associated with Breslow thickness and the change in 25OHD was also associated with Breslow thickness: patients with Breslow at baseline (<3mm) had a double increase from baseline whereas patients with greater thickness had a significantly lower increase in time.
No differences by treatments arms were observed in disease free survival but the statistical power was drastically reduced given the low accrual. However patients which have still low 25OHD at 12 months of trial and thick Breslow (>3mm), presented significantly greater relapse (P=0.02), compared with patients with thick Breslow but high 25OHD or thin melanoma but low 25OHD. The association is confirmed in the multivariate Cox proportional hazard models, adjusting for age and treatment arms: (HR=4.81, 95%CI 1.44-16.09: P=0.011).

Conclusions: Vitamin D supplementation was not found to be associated with a reduced risk of relapse. Patients with thicker melanoma have lower increase in 25OHD in the vitamin D arms and at 1 year of trial, if vitamin D is still low, they have a greater risk of relapse. Further randomized clinical trials on patients with low 25OHD and thicker melanoma should be conducted to confirm these results.

Progetto IMI Tele-consulenza genetica (TG): utilizzo di strumenti di telemedicina per consulenza genetica e test molecolare di predisposizione al melanoma. Risultati preliminari.

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Introduzione: La Telemedicina, come in molti paesi europei, è possibile anche in Italia (Accordo Stato-Regioni, seduta 22 gennaio 2015, reti di eccellenza per le malattie rare). Scopo generale dell'attività di Telemedicina è consentire ai pazienti l'accesso a distanza ad assistenza specialistica con condivisione dell'informazione clinica tra i centri di riferimento, riduzione della mobilità dei pazienti e disponibilità delle competenze dei centri di riferimento nella sede del paziente.
Materiali e metodi: In questo progetto IMI la TG fornisce a pazienti selezionati da specialista IMI la verifica dei criteri di accesso al test molecolare per predisposizione genetica al melanoma o per condizione sindromica(CS) in cui il melanoma può essere segno clinico oncologico associato di cui può essere fatta diagnosi.
La TG pretest infatti prevede: ricostruzione del pedigree, revisione degli esami istologici, informazione sulla possibilità di indagine molecolare, scopo, limiti, vantaggi personali e familiari del test con redazione di relazione scritta.
Il test è condotto su campione di sangue inviato al centro Genetica dei Tumori Rari (Genova) che per primo ha introdotto in Italia, in un contesto clinico, il test genetico su predisposizione al melanoma e recentemente in pannello multigenico in Next Generation Sequencing (NGS). I risultati sono comunicati in TG post-test con successiva spedizione di referto e relazione clinica con commento al test e consigli di follow-up. In caso di positività si propone l'indagine molecolare ad altri familiari invitati a partecipare con medesima modalità.
Risultati: Dal 01/06 al 31/08: 30 richieste di TG da sei diversi specialisti IMI da diverse regioni (Lombardia-Lazio-Marche-Sicilia); 29 TG pretest concluse (una esclusa per mancato consenso alla TG); 26 test molecolari proposti: 15 melanoma multiplo, 4 melanoma familiare-3 melanoma multiplo e familiare, 4 CS (es. melanoma+ACA pancreas); 10 referti: 9 wild-type, 1 POT1 variante di significato sconosciuto.
Conclusioni: In soli tre mesi di attività si sono già raggiunti alcuni scopi del progetto come l'ampliamento della platea di soggetti inseribili nel percorso di consulenza genetica e analisi molecolare, tramite pannelli genetici in NGS, consentendo appoggio a centri di riferimento nazionale, diminuzione della mobilità, assenza di tempi di attesa per TG, mantenimento del rapporto con il clinico di riferimento, inclusione di numerosi pazienti afferenti a centri che non eseguono consulenza e test.

Mutation screening at germline and somatic levels in patients with multiple primary melanomas

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Background: Multiple primary melanomas (MPM) occur up to 8% of patients with cutaneous malignant melanoma (CMM). They are often sporadic harbouring several somatic mutations, but also familial cases harbouring a *CDKN2A* germline mutation has been describe in Caucasian populations. The aim of this study was to investigate the incidence, the distribution patterns and the impact of known and unknown germline and somatic mutations in patients with MPM from Italy.
Materials and Methods: One-hundred and two MPM patients were enrolled for germline mutation analysis, and five patients with at least four MPMs were identified for somatic mutation analysis. The demographic, pathologic and clinical features were retrieved from medical records. Molecular analysis for both germline and somatic mutations was performed in genomic DNA from peripheral blood and tissue samples, respectively, through a next generation sequencing approach, using a specific multiple-gene panel constructed by the Italian Melanoma Intergroup for somatic analysis and a commercial cancer hotspot panel for somatic analysis.
Results: *CDKN2A* mutations were detected in 6/16 (37.5%) and 3/86 (3.5%) MPM cases with and without family history for melanoma, respectively. Furthermore, multiple *MC1R* and, to a lesser extent, *ATM* variants have been identified. *BAP1* variants were found only in MPM patients from southern Italy. The most frequent somatic variants were the pathogenic $BRAF^{V600E}$ and *TP53*, followed by *KIT, PIK3CA*, *KDR*, and *NRAS*. Single *APC, ERBB4, MET, JAK3* and other variants with unknown function were also detected.
Conclusions: *CDNK2A* mutation is the most relevant susceptibility mutation in Italian patients with MPM, especially those with a family history for CMM. The prevalence of this mutation and other sequence variants identified in this study varies among specific sub-populations. Furthermore, some heterogeneity in driver somatic mutations between sporadic MPMs has been observed, as well as in a number of associated sequence variants the clinical impact of which needs to be further elucidated.

The Melanoma Unit of Sassari (MUS) includes the following members who participated as investigators in this study: Maria Filomena Dedola, Maria Antonietta Fedeli, Maria Antonietta Montesu, Stefano Profili, Corrado Rubino, Rosanna Satta, Tiziana Scotto, Germana Sini (Sassari, Italy). The Italian Melanoma Intergroup (IMI) includes the following additional members who participated as investigators in this study: Anna Maria Di Giacomo (Siena, Italy); Paola Ghiorzo (Genova, Italy), Paola Queirolo (Milan, Italy); Mario Mandalà (Bergamo, Italy); Pietro Quaglino (Torino, Italy), Vanna Chiarion Sileni (Padova, Italy); Ignazio Stanganelli (Meldola, Italy).

Caratterizzazione genomica del melanoma acrale

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Introduzione: Il melanoma acrale (MA) è un sottotipo raro di melanoma (2 casi per milione di persone all'anno) con caratteristiche cliniche, patologiche e molecolari peculiari (1). Insorge in zone glabre non particolarmente esposte alle radiazioni solari, protette da uno strato corneo o da una lamina ungueale, in genere ha una morfologia lentigginosa e presenta alterazioni genetiche non correlate alle radiazioni UV e diverse rispetto a quelle associate all'insorgenza del melanoma cutaneo comune. Inoltre, il MA è caratterizzato, fin dagli stadi iniziali, da una maggiore frequenza di aberrazioni cromosomiche ed amplificazioni geniche (2). Scopo di questo studio è identificare le aberrazioni genomiche del MA in una popolazione caucasica italiana.
Materiali e metodi: su una casistica di 34 campioni istologici FFPE di MA (di cui 6 casi dell'apparato ungueale e 4 casi nodulari) è stato analizzato il profilo di copy number variation mediante analisi di genome-wide SNP-array (Affymetrix) e il profilo mutazionale mediante next generation sequencing utilizzando un pannello custom comprendente 43 geni considerati "drivers" della melanomagenesi su piattaforma Illumina MiSeq. Le mutazioni individuate sono state poi confermate con tecnica Sanger.
Risultati: nel MA sono stati riscontrati gains nei cromosomi 1p, 5p, 6p, 8q, 13, 22, X e losses nei cromosomi 9 e 10. Caratteristiche dei MA sono la presenza di interi bracci cromosomici frammentati, principalmente nel cromosoma 5, 11 e 22, e di isocromosomi, a carico del 4, 6 e 8. Inoltre, le aberrazioni sono per lo più focali, interessano, cioè, regioni genomiche di lunghezza <1 Mb; tra queste troviamo l'amplificazione dei geni *MITF, NOTCH1, TERT, CCND1*. Sia i MA dell'apparato ungueale che i MA nodulari sembrano avere più frequentemente delezioni in omozigosi della regione cromosomica 4q12 comprendente i geni *KIT, PDGFRA* e *KDR*. Il gene più frequentemente mutato è *KDR* (40%), seguito da *TP53* (26%), *NRAS* e *NOTCH2* (23%), *BRAF* (20%), *KIT*, *ARID1A*, *TERT* e *GRIN2A* (10%) e *NF1* (6%). Nei MA dell'apparato ungueale non sono state riscontrate mutazioni di *BRAF* e *NRAS*, mentre nei MA nodulari non sono state trovate mutazioni di *BRAF* e *TP53*.
Conclusioni: questi risultati evidenziano le regioni da indagare con ulteriori analisi molecolari per comprendere i diversi meccanismi patogenetici alla base del MA. Le frequenze delle varie mutazioni riscontrate nella presente casistica sono comparabili con quelle riportate in letteratura (3). Il ruolo di KDR nel MA deve essere approfondito.

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Proposta di management per pazienti affetti da Melanoma Familiare e Multiplo

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In circa il 10% dei casi il melanoma cutaneo si presenta in un ambito familiare. Inoltre la ricorrenza di piu' casi di melanoma nello stesso soggetto (melanoma primitivo o multiplo) è di frequente riscontro in queste famiglie.
Negli ultimi venti anni, il Servizio di Dermatologia Oncologica dell'Istituto San Gallicano I.R.C.C.S di Roma ha selezionato, circa 10.000 pazienti affetti da melanoma cutaneo. Di questi, circa 900 sono affetti da melanoma familiare e/o melanoma primitivo multiplo.
Questi pazienti hanno seguito negli anni programmi di follow up personalizzati in relazione ai fattori di rischio clinico-biologici individuali.
Infatti per tutti coloro affetti da melanoma familiare e multiplo, oltre alle normali visite dermatologiche ed alle indagini strumentali relative alla stadiazione del melanoma, è stata effettuata anche la consulenza genetica con albero genealogico su tre generazioni e test di biologia molecolare finalizzati all'identificazione di eventuali mutazioni dei geni ad oggi conosciuti che inducono suscettibilità al melanoma familiare e multiplo.
Per i test molecolari, sono stati utilizzati metodi di sequenziamento di nuova generazione, con particolare riferimento ai 5 geni principali (CDKN2A, CDK4, BAP1, MITF e POT1).
Gli Autori, alla luce della loro esperienza, propongono un modello di management per la gestione del paziente affetto da melanoma familiare e multiplo.
Tale proposta si avvale di un percorso multidisciplinare che tenga conto dei fattori di rischio clinici e biologici del paziente e della sua esposizione ai fattori ambientali.
L'obiettivo finale è quello di promuovere un programma di follow-up personalizzato che consenta una diagnosi precoce e un miglioramento della prognosi con una conseguente riduzione della spesa sanitaria.

The association between pesticide use and cutaneous melanoma: a systematic review and meta-analysis.

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Background: Pesticides directly endanger agricultural workers, neighbouring populations, wildlife, and consumers with a short and long term impact on health biological systems. Ecological wisdom demands to monitor methods of pesticide exposure and to improve the current knowledge based on epidemiological and biological data such as risk assessment indicators. The United States Environmental Protection Agency (USEPA) and the European Environment Agency (EEA) should investigate violations in biocide use, with appropriate public oversight provisions to diminish bias from government and industry. Moreover, USEPA, EEA and all scientific community should improve standards used to determine the safety and relative risk of chemicals allowed on the market.
Epidemiological studies suggested that agricultural workers are at an increased risk of CM because they were exposed to pesticides. However, little is known about the relationship between pesticides and cutaneous melanoma. We performed a systematic review and meta-analysis to investigate the possible association between pesticide exposure and CM. Moreover, we tried to determine the categories of pesticides mainly involved in CM development.
Methods: Our analysis was performed up to September 2018 using Medline, Embase and Web of Science. Studies assessing CM risk in licensed pesticide applicators were considered. Priory criteria were established to select independent studies and risk estimates; random effect models, taking into account heterogeneity, were applied. A pooled risk estimate for CM was calculated for the use of each type of pesticide and type of exposure. Between-study and estimates heterogeneity was assessed and publication bias investigated.
Results: A total of 9 studies comprising 184389 unique subjects were included (1-9). The summary relative risks for the categories “herbicides - ever exposure”, “insecticides - ever exposure”, “any pesticide - ever exposure” and “any pesticide - high exposure” resulted 1.85 (95% CI: 1.01, 3.36), 1.57 (95% CI: 0.58, 4.25), 1.31 (95% CI: 0.85, 2.04) and 2.17 (95% CI: 0.45, 10.36), respectively. Herbicides and insecticides had no between-study heterogeneity (I^2=0%), while a significant heterogeneity (I^2>50%) was detected for the high exposure to any pesticide. No indication for publication bias was found.
Conclusions: Individuals exposed to herbicides are at an increased risk of CM. Future properly designed observational studies are required to confirm this finding.

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Progetto per la ricerca dei determinanti genetici alla base dello sviluppo e della risposta al trattamento.

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Nel contesto di un progetto di ricerca multicentrico volto allo studio dei determinanti dello sviluppo del melanoma e la risposta ai trattamenti, sono stati raccolti **420** casi indice affetti da melanoma cutaneo giovanile (diagnosi ≤ ai 40 anni) e/o multiplo (almeno 2 tumori indipendenti) e/o familiare (almeno due parenti di primo grado e/o almeno tre parenti di secondo grado affetti) per lo più residenti in Regione Piemonte.
Una prima analisi genetica volta all'identificazione di mutazioni germinali del principale gene di suscettibilità al melanoma CDKN2A (analisi in sequenza e ricerca di delezioni/duplicazioni) nonché del gene CDK4, TERT (promotore) e MITF (variante p.Glu318Lys) ha dimostrato la presenza di mutazioni deleterie di CDKN2A nel **13,5%** dei casi. Tale percentuale sale nei casi familiari **al 42%-37% (diagnosi prima o dopo i 40 anni)**, e nei soggetti affetti da melanoma multiplo (**60%-25%, diagnosi prima o dopo i 40 anni)**. In nessun caso sono state identificate varianti patogenetiche del gene CDK4 (p.Arg24His e p.Asg24Cys) né del promotore del gene TERT. Solo in **7** casi **(2%)** è stata identificata la variante di suscettibilità allo sviluppo del melanoma p.Glu318Lys del gene MITF, **5 affetti da melanomi multipli e 2 da melanoma e basalioma**.
In 15 casi di melanoma cutaneo con storia personale e/o familiare positiva per tumori renali (a cellule chiare, papilliferi e/o sarcomatoidi) senza mutazioni dei geni di cui sopra e del gene BAP1, è stata eseguita l'analisi del gene CDKN2B riportato in letteratura come gene di suscettibilità allo sviluppo di tumori renali, senza identificare alcuna mutazione.
In un paziente affetto da melanoma e astrocitoma è stata identificata la mutazione patogenetica del gene TP53 p.Arg158Cys mentre in **10 pazienti affetti da melanoma cutaneo** e familiarità positiva per tumori della mammella e/o dell'ovaio era presente una mutazione **dei geni BRCA2 (6 casi), CHEK2 (2 casi), BRCA1 (1 caso) e ATM (1 caso)**.
I dati riportati rafforzano il concetto dell'elevata eterogeneità genetica del melanoma e l'importanza di un approccio diagnostico con analisi multi-gene: i casi raccolti verranno sottoposti **ad analisi di 21 geni** di suscettibilità / determinanti della pigmentazione cutanea nonché ad analisi di 500 cancer genes.
Nell'ambito di tale progetto, le caratteristiche genetiche dei pazienti saranno valutate in associazione con i parametri clinici, fototipo/fenotipo, numero di nevi, eventuali altre neoplasie, con particolare attenzione a pazienti con familiarità per melanoma e/o melanomi multipli.

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ABSTRACT AREA PREVENZIONE E DIAGNOSI

CT and FDG PET/CT imaging in Melanoma Patients: rationale, strengths and weaknesses, radiation exposure and relative risks

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Background: During the last ten years medical imaging made a big leap forward thanks to hybrid imaging, i.e. the fusion of anatomical and molecular images (the best of two worlds). Malignant melanoma is one of the most beneficial clinical settings, especially after availability of new target therapies with a definite improvement in patients survival. We focus on *FDG PET/CT*(PET) and *contrast-enhanced CT*(CeCT) complementary role in staging and follow-up and the related radiation burden (1).
Methods: We checked the Guidelines of the NCCN and AIOM, and performed a literature search using as keywords *PET-malignant melanoma-CT*. We focused on the accuracy In evaluating specific lesion sites. Then we analyzed the dose reduction due to the technical evolution and the age-related risk estimate
Results: Either guidelines agree in recommending PET and/or CeCT for staging patients with disease stage III or more but do not give criteria for performing the former or the latter. Literature shows a better accuracy for CeCT in identifying brain, liver or lung lesions whilst PET is better for nodal or bone/bone marrow involvement (2,3). Modern LSO crystal-based PET scanners allows to half the FDG administered activity (and then the radiation burden). CT protocols are also evolving towards a reduction in doses, preserving image quality (4,5).
Conclusions: The combined accuracy of CeCT and PET is higher than that each one singled out. Technical evolution allows to maintain/improve diagnostic yield without an increase in radiation burden. Concerns about detrimental effects of irradiation due to diagnostic imaging in teenager/young adults (the most worrysome age range), seems not justified.

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A case of a pigmented epithelioid melanocytoma of mucosal site

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Background
Pigmented epithelioid melanocytoma (PEM) (1) is a melanocytic tumour showing overlapping features between an atypical epithelioid blue nevus (2,3), and a low-grade "animal-type melanoma" (4,5). PEM occurs over a broad age range, with a predilection for children and young adults (1,6,7) and clinically appear as macular, papular and nodular lesions. Dermoscopically, PEM appear to present as polymorphic lesions dermoscopically, characterized by homogeneous blue pigmentation and a variable combination of black, brown and white colour. Histopathologically, it is characterized by a dermal proliferation of heavily pigmented, both dendritic and spindle/epithelioid melanocytes, admixed with slightly larger, plumper and less pigmented epithelioid cells (1). Involvement of the regional nodes has been reported, but usually with no further spread of the disease (1,6-8). No histological criteria are predictive of metastatic behaviour. Thus, the tumour could be a low-grade, lymphotropic variant of melanoma with frequent lymph node metastases but an indolent clinical course (1,6-8).
Methods
We describe a case of mucosal PEM, occurred on the right vulvar small lip of a 50-years old woman. This is as far as we know the first case of mucosal PEM ever reported in the English literature. Clinically it appeared as an oval papule, brown-black in colour, intensely pigmented, about 1 centimeter in size. On dermoscopy we observed many irregular, black globular structures surrounded by a whitish-blue veil. No atypical vascular feature was detected. The lesion was of course suspicious due to the clinical aspect and the recent appearing. An excisional biopsy was performed.
Results
The histological examination showed an intraepidermal pigmented epithelioid melanocytoma with focal aspects of blue nevus.
Conclusions
Usually melanomas in mucosal site arise de novo (not on a pre-existing lesion) and in elderly. Dermoscopically they usually show lines, dots, clods, and structureless areas characterized by a various degree of colour variegation (eg, a combination of brown, gray, black, red, purple, or white) (9).

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Reazioni avverse cutanee indotte dai nuovi farmaci antitumorali

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Negli ultimi decenni, i progressi scientifici legati all'introduzione di nuovi farmaci antitumorali, le cosidette target therapy, hanno portato ad una drastica riduzione della mortalità e ad un miglioramento della sopravvivenza, aprendo nuove prospettive nella gestione di molte neoplasie.
Come è noto, in corso di tali trattamenti, la comparsa di effetti collaterali a livello di cute e annessi è di frequente osservazione; inoltre, a volte, questi sono di gravità tale da incidere nel proseguo della terapia oncologica e possono indurre modifiche nel protocollo terapeutico.
In altri casi, il coinvolgimento cutaneo, pur non avendo rilevanza clinica, modificando comunque l'immagine corporea, può interferire con la qualità di vita dei pazienti. Risulta fondamentale il ruolo del Dermatologo nel team multidisciplinare.
A tutt'oggi mancano linee guida largamente condivise nella gestione degli effetti collaterali del paziente in corso di trattamento oncologico e la mancanza di approfondite conoscenze dei meccanismi alla base di tali eventi avversi ne rende difficile la gestione.
L'approccio specialistico dermatologico al paziente oncologico non può prescindere dalla conoscenza delle differenti classi di farmaci chemioterapici e dai loro meccanismi di azione da cui spesso dipendono gli effetti collaterali a livello sistemico e cutaneo.
I principali farmaci antitumorali possono essere suddivisi, in base al meccanismo d'azione, in: chemioterapici citotossici, target therapy, ormonoterapia e farmaci non classificabili.
Gli effetti collaterali delle diverse categorie di farmaci presentano, in alcuni casi, caratteristiche simili anche se non sovrapponibili, in altri casi, tali quadri sono peculiari dell'uno o dell'altra classe.
Infine, bisogna anche tener conto che spesso si utilizzano protocolli polichemioterapici con farmaci appartenenti alle diverse classi, rendendo più difficile e complessa l'individuazione dei patomeccanismi.
Le manifestazioni dermatologiche di più frequente riscontro sono: xerosi, prurito, rash, manifestazioni bollose, eritema acrale, reazioni fotoallergiche, alterazioni della pigmentazione, reazioni da stravaso e alterazioni degli annessi.
In corso di oncoterapia, sono molto comuni anche le mucositi e spesso di gravità tale da imporre la riduzione del dosaggio dei farmaci o addirittura la sospensione degli stessi; pertanto, la gestione di tali quadri necessita spesso di un corretto approccio preventivo, oltre che terapeutico per evitarne, ove possibile, l'insorgenza.
Gli Autori presentano l'esperienza di un team multidisciplinare composto da Oncologi e Dermatologi istituito da circa 3 anni nell'ambito dell'Istituto Regina Elena-San Gallicano che si fa carico del percorso diagnostico-terapeutico dei pazienti oncologici affetti in particolare da Melanoma ma anche da Carcinoma mammario, intestinale e delle vie urinarie.

Multidisciplinary management of patients with malignant melanoma: the experience of the Melanoma Unit of Sassari (MUS).

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Background: The clinical management of malignant melanoma MM is complex, especially in advanced stages. In particular, the advent of targeted therapies and immunotherapy treatments, dictate a careful selection of the patients and an integrated approach for implementing optimal therapeutic strategies. For this reason, the institution of multidisciplinary melanoma management units is currently widely recommended. In this study we report the experience of the Melanoma Unit of Sassari (MUS) in the clinical management of patients with MM.
Methods: Consecutive patients with a clinical suspect or a diagnosis of MM managed by the MUS from January 2018 through August 2019 were included. Demographic, clinical and pathological data were retrieved from clinical visits and records, and were statistically analyzed.
Results: 144 patients were managed by the MUS in the period under investigation. Among them 81 (56.2%) were males; the mean age of the patients was 63.9 (±15.2) years. The crude incidence of MM was 13.8/100.000. 2 (1.4%) patients had a family history for MM, while 2 further patients (1.4%) had a family history for pancreatic cancer. 22 (15.3%) were referred to the MUS by other Sardinian institutions and hospitals. Most patients performed the first clinical visit in the units of Dermatology (41, 28.5%) and Plastic and Reconstructive Surgery (40, 27.8%), while 17 (11.8%) were visited by private practitioners. The most common pathological T stage was T1 (53, 36.8%), followed by T3 (26, 18.1%) and T4 (19, 13.2%); 13 (9%) were in situ melanomas. The most common histological types were: superficial spreading melanoma (63, 43.7%), nodular melanoma (27, 18.7%) and lentigo maligna (13, 9%). The mean time between the biopsy and the final diagnosis was 9.7 (±5) days, while time between diagnosis and surgery was 28.7 (±12.6) days. 55 (38.2%) patients underwent sentinel lymph node dissection, while 3 (2.1%) patients had a second stage axillary lymph node dissection.
Conclusions: The crude incidence of MM and the mean age of the patients at diagnosis in the period under investigation were higher than those reported in previous epidemiological studies performed in the region. A satisfactory mean time between first biopsy, diagnosis and surgery was registered. The availability of data regarding the clinical activities of MUS is essential for the monitoring of the epidemiological aspects of the disease and for improving the clinical management of patients with MM.

Melanoma indotto da farmaci oncologici?

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Introduzione/Background: Lo sviluppo di melanoma può essere favorito da diversi gruppi di farmaci tra cui diuretici tiazidici (1), idroclorotiazide (2), sildenafil (3). In letteratura è descritta una maggiore incidenza di nuovi melanomi primari (NPM) nei pazienti oncologici trattati con inibitori BRAF e recentemente è stato riportato tale evento anche per un paziente in tripla terapia con vemurafenib, cobimetinib e atezolizumab per il melanoma metastatico (4). Noi presentiamo la nostra casistica di NPM nei pazienti giunti alla nostra osservazione per tossicità cutanea in corso di trattamento oncologico.
Materiali e metodi/Methods: Noi abbiamo cercato nel nostro archivio 2018-2019 quanti casi di NPM sono stati diagnosticati in 1520 pazienti giunti alla nostra osservazione per tossicità cutanea da terapie oncologiche.
Risultati/Results: In 19 mesi abbiamo diagnosticato 6 melanomi in 4 donne e 2 uomini in terapia oncologica. I melanomi si trovavano prevalentemente in zone fotoesposte: 2 tronco, 2 arto superiore, 2 viso. Il loro spessore in media è stato di 0.5mm: 1 pTis, 4 pT1a, 1 pT1b. I pazienti erano affetti da differenti tumori per i quali erano in terapia oncologica: 1 linfoma non Hodgkin B diffuso a grandi cellule, 1 melanoma, 1 carcinoide tipico polmonare, 1 adenocarcinoma polmonare, 1 carcinoma squamocellulare polmonare, 1 carcinoma mammario duttale infiltrante. Tre pazienti presentavano localizzazione primitiva al polmone ma con diversi istotipi. Tre pazienti (2F e 1 M) presentavano in anamnesi remota problematiche tiroidee: 2 carcinoma papillifero della tiroide e 1 adenoma di Plummer. Un'altra paziente era stata operata anche per carcinoma mammario, carcinoma renale e leiomioma intestinale. Tutti i pazienti erano in corso di terapia oncologica: 1 lenalidomide, 1 trilogy study (vemurafeniv e cobimetinib + atezolizumab/placebo), 1 temozolide, 2 afatinib, 1 epirubicina e ciclofosfamide Due pazienti sono deceduti.
Conclusioni/Conclusions: Il melanoma indotto da farmaci si sta rivelando essere un problema di importanza significativa. Per indagare tale fenomeno è importante spogliare completamente i pazienti in corso di visita dermatologica anche se richiesta per la sola tossicità cutanea per effettuare un controllo nevi.

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L'ecografia dei tessuti molli nel melanoma

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Lo studio ecografico dei tessuti molli cutanei ha acquisito un importante ruolo di supporto nella stadiazione dei pazienti affetti da melanoma perché consente, in maniera non invasiva, di riprodurre in una scala di grigi le strutture anatomiche delle sedi esaminate definendone la forma, la dimensione, il tipo di vascolarizzazione, la densità dei tessuti e i rapporti anatomici con le strutture circostanti.
***Materiali e metodi*:** Abbiamo valutato i dati acquisiti in maniera prospettica nel periodo compreso dal gennaio 2008 al dicembre 2018 relativamente alle ecografie dei tessuti molli eseguite in una coorte di 579 pazienti affetti da melanoma e seguiti in follow up nel nostro Centro. Ogni paziente è stato sottoposto all'esame obiettivo dermatologico dell'intera superficie cutanea, all'esame palpatorio delle stazioni nodali superficiali e della cute pericicatriziale. L'esame clinico è stato completato dallo studio ultrasonografico delle sedi nodali tributarie con un ecografo Esaote MyLab 25 munito di sonda lineare 5-12 MHz.
Risultati: Durante il periodo in esame 58 pazienti, pari al 10% dei casi, hanno avuto una progressione a carico dei tessuti molli cutanei o muscolari. Quattordici pazienti (27%) hanno individuato con l'autoesame periodico la recidiva della neoplasia; per 25 pazienti (47%), il sospetto diagnostico è sorto in occasione della visita mentre nei restanti 9 pazienti (25%) l'esame ultrasonografico ha permesso di rilevare una metastasi altrimenti clinicamente occulta.
Discussione: Le recidive da melanoma a localizzazione dermica, sottocutanea o muscolare possono sfuggire all'esame clinico quando di piccole dimensioni, se insorgono in pazienti con abbondante pannicolo adiposo, in pazienti con lipomatosi diffusa o qualora siano localizzate negli strati più profondi del derma o nei tessuti muscolari (1,2).
Integrare nell'ambito della visita dermatologica lo studio ultrasonografico dei tessuti molli cutanei ha molti vantaggi: consente l'immediata interpretazione del nodulo, evita lo stress legato alla esecuzione differita della prestazione, permette un rilevante risparmio di tempo per distacco dal lavoro o dalla famiglia e riduce sensibilmente le liste di attesa per tali prestazioni.
L'ecografia dei tessuti molli completa l'esame semeiotico (1). Non è di per se un esame diagnostico ma seleziona con discreta precisione le lesioni dichiaratamente benigne da quelle che meritano un supplemento di indagine citologico o istologico (2).

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La Prevenzione "Social" nella lotta al melanoma: nuove strategie di informazione e comunicazione su Facebook

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Introduzione: L'esposizione ai raggi ultravioletti rappresenta ancora oggi il principale fattore di rischio per il melanoma in particolare tra i più giovani. Negli ultimi anni il notevole incremento nell'utilizzo dei social network ha portato associazioni dei pazienti e organizzazioni dedicate ad una maggiore diffusione on line di informazioni e campagne di prevenzione soprattutto nel periodo estivo.
Materiali e Metodi: Lo studio è stato condotto attraverso una ricerca iniziale per individuare le pagine delle principali associazioni italiane impegnate in questo setting, utilizzando i seguenti parametri: "Associazioni Melanoma Italia", "Melanoma", "Melanoma prevenzione" per poi esaminare i messaggi (post) divulgati sulla prevenzione e una corretta esposizione al sole nel periodo compreso tra il 15 Maggio e il 15 Agosto 2019. L'obiettivo principale di questo studio è analizzare il ruolo di Facebook, il più popolare sito di social networking, come strumento di sensibilizzazione alla prevenzione del melanoma.
Risultati: Sono state identificate n. 10 pagine, che presentano globalmente 57.347 like, riguardanti l'Intergruppo Melanoma Italiano (IMI), la Fondazione Melanoma Onlus e la Fondazione AIOM, le principali associazioni italiane pazienti melanoma (ACM onlus, Aimame, Ailmag, Apaim, Melanoma Italia Onlus (MIO), Melavivo) e l'Associazione Italiana di Oncologia Medica (AIOM). I post pubblicati (221) caratterizzati per il 38,4% da immagini, 16,7% da link, 9,9% da video, hanno ricevuto n. 5898 like e n. 7344 condivisioni e 255 commenti, in prevalenza positivi, sviluppando principalmente informazioni inerenti la corretta esposizione al sole (41%) in particolare per i bambini (7,2%), l'uso delle creme solari (18%) e i rischi correlati alle lampade solari (4%). Sono altresì stati pubblicati post inerenti specifiche campagne di prevenzione (35%) promosse dalle varie associazioni, divise in itineranti (Sole con Amore, Il Sole non è un gioco, La Piazza della Salute, Salviamoci la pelle in vacanza), di screening (Preveniamo il Melanoma), mediante affissioni pubbliche (Campagna prevenzione contro melanoma) e progettuali (Safe Sun Coast, Mi Salvo la pelle).
Gli hashtag utilizzati sono stati: #SoleConAmore, #MiSalvolapelle, #Ailmag#Sentinellaattiva, #proteggilatuapelle #latuapellehamemoria.
Conclusione: I risultati dell'indagine evidenziano che l'utilizzo dei social network rappresenta uno strumento valido ed economico di informazione e comunicazione, per una maggiore sensibilizzazione sul tema prevenzione in grado di raggiungere un'utenza più ampia e diversificata.

Rapid On-Site Evaluation (ROSE) without EBUS in the diagnosis of polypoid melanoma metastasis: a case report

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Abstract
Some authors had already assumed that cytology is comparable to histology in the diagnosis of lung lesions. Whenever an adequate diagnostic material is available, Rapid On-Site Evaluation (ROSE) has proved to be an important, easy and cost effective adjunct in the diagnosis of lung lesions, so that cytology may even outperform biopsy in lung tumor diagnosis (1). Our team experienced a ROSE on a sample from a trans-bronchial needle aspirate (TBNA), which has been proved to be diagnostic for metastasis. The primitive tumor was a polypoid melanoma, which had been excised in 2013.
The most malignant form of melanoma is the polypoid variant of nodular pattern. The polypoid nodular variant differs from the nonpolypoid nodular variant because melanoma cells are dislodged and carried to superficial lymphatic vessels without invading the reticular dermis, after accumulating in large, pressing volumes above the skin's surface. We performed a ROSE on FNAB without EBUS support, succeeding in confirming the diagnosis of polypoid melanoma metastasis suspected by the history collection. ROSE is a diagnostic procedure, that allows considerable time and cost savings, when the sample is collected, prepared and read by expert operators. Indeed, we could notice a perfect morphological reproducibility between primitive lesion's cells in the histological preparation and our sample's metastatic cells, aspirated from the mediastinal lymph node.

Background
Polypoid melanoma, which is considered the most malignant form of melanoma, is a variant of nodular pattern. Melanoma cells accumulate in large volume above the skin's surface, encouraging dislodgment of tumor cells that are carried to superficial lymphatic vessels without invading the reticular dermis; this feature differentiates polypoid melanoma from the nonpolypoid nodular variant (2). Polypoid melanoma is associated with an increased thickness, more frequent ulceration than the nodular variant of melanoma, younger patient age, and higher probability of occult metastasis. Polypoid melanomas were most frequently located on the trunk, but also unusual sites (nasal mucosa, hard palate, anorectal junction) are known. The five-year survival rate for patients with the polypoid variant was 42%, in contrast to 57% for the nonpolypoid nodular and 77% for the superficial spreading melanomas: maybe this poor prognosis is due to the deepest penetration of polypoid melanoma at the time of surgical excision (3).

Case presentation
The patient was a 57-year-old white man, never smoker, currently presenting irritated cough, without sputum. Remote pathological history was positive for polypoid melanoma excised in 2013 from the trunk, staged I B. During the last annual CT scan follow up (April 2019) emerged on the left and mediastinal hilar sites the evidence of inhomogeneous density tissue of likely adenopathic nature, sized 9 cm, and extending up to the middle third of the esophagus from which it is not dissociable; the tissue is distributed in a sleeve until the arteries and the pulmonary veins emerge without infiltrating them. The size of the pulmonary trunk is reduced. Three nodular formations in the lingula. Splenic hypodense formations left adrenal pseudonodular formation sized 28 x 21mm. Three other diaphragmatic nodular formations.
The patient underwent bronchoscopy, which showed gross extrinsic compression of the left main lobe with congestion and hyperemia of the mucosa. For the rest, endoscopic picture of cronic bronchopathy. FNAB without EBUS (Endo-Bronchial Ultra-Sound) has been practised on the subcarinal lymph node station (VII) for

cytological examination. We got a sample stained by Diff Quick method. We saw epiteliomorphic, pigmented cells, mostly arranged individually, with voluminous and pronounced nucleoli and powdry cytoplasmic pigmentations.

Histopatologic findings

Through in-depth research in our histopathology archive, we obtained the histological preparation of polypoid melanoma excised in 2013 from the trunk. It was an atypical polypoid nodular melanocytic lesion, with no apparent vertical growth, and with a pagetoid, focally ulcerated growth pattern. The lesion was rich in melanin pigment. Mitotic figures between 1 and 6 were present. The intra-tumoral lymphoid infiltrate was absent. Excision margins were large and free from tumor invasion. The sentinel lymph node examination was negative. There was no evidence of vascular and perineural invasion in the sections under examination.

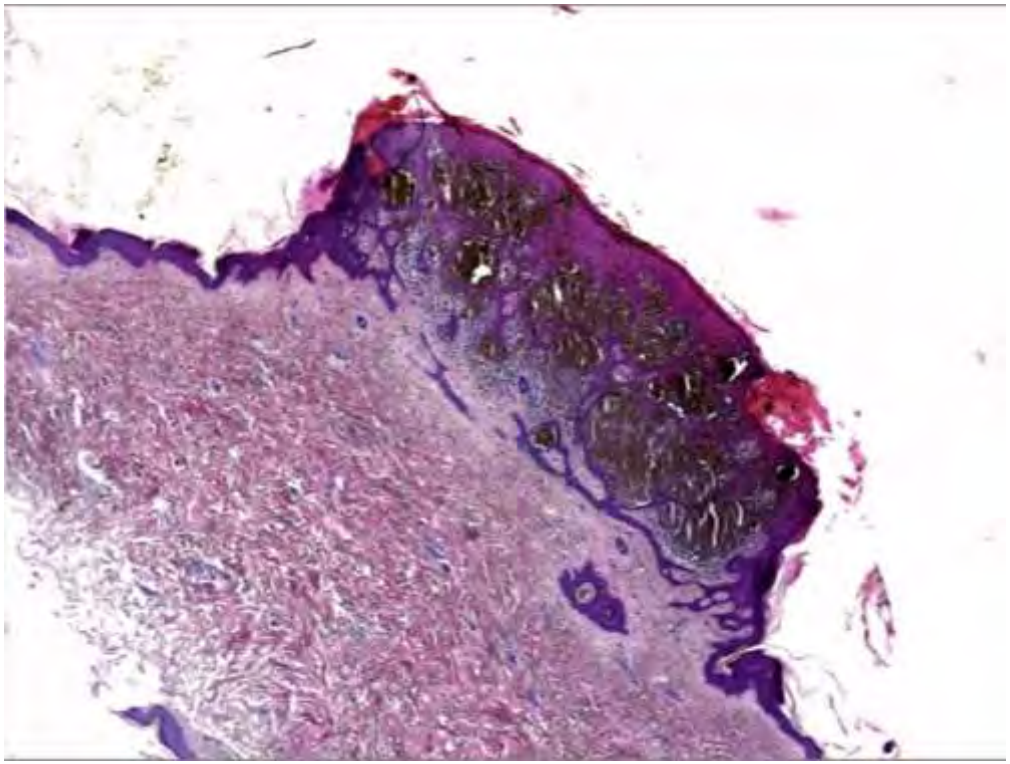

Figure 1: Nodular polypoid pigmented lesion taken from the trunk, consisting of atypical melanocytes, with pagetoid spreading. Wide and free excision margins. Absence of necrosis, focal ulceration. E. E. 2.5 X

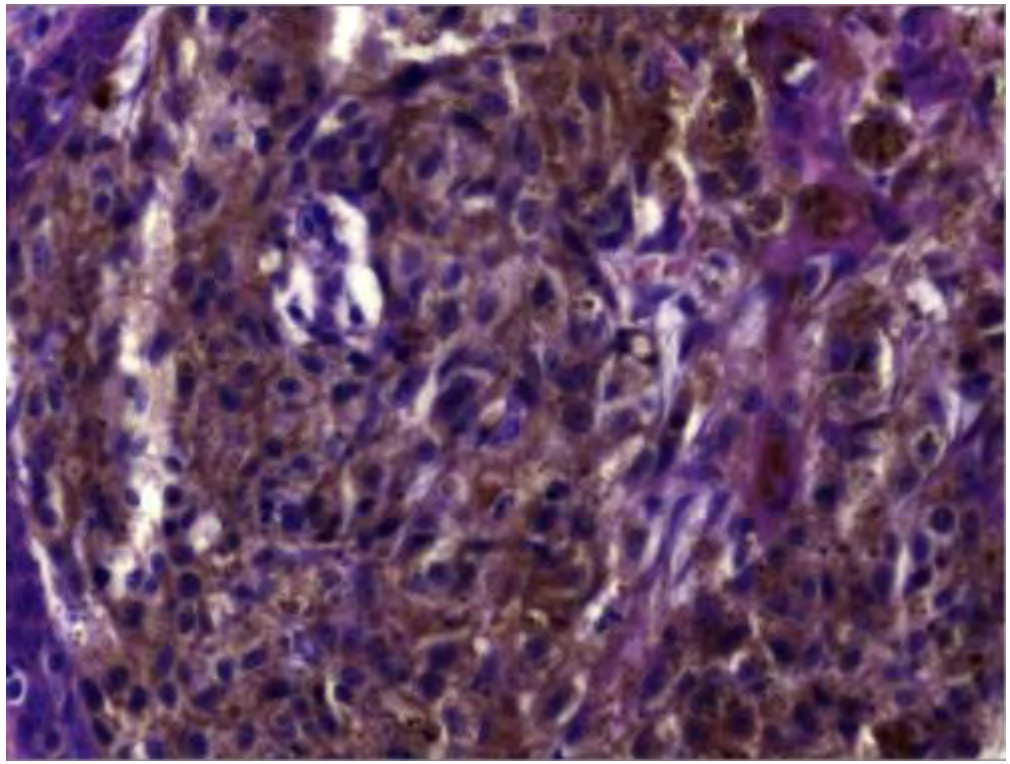

Figure 2: At higher magnification the prominent nucleoli and the abundant powdery melanin pigment are visible. E.E. 40X

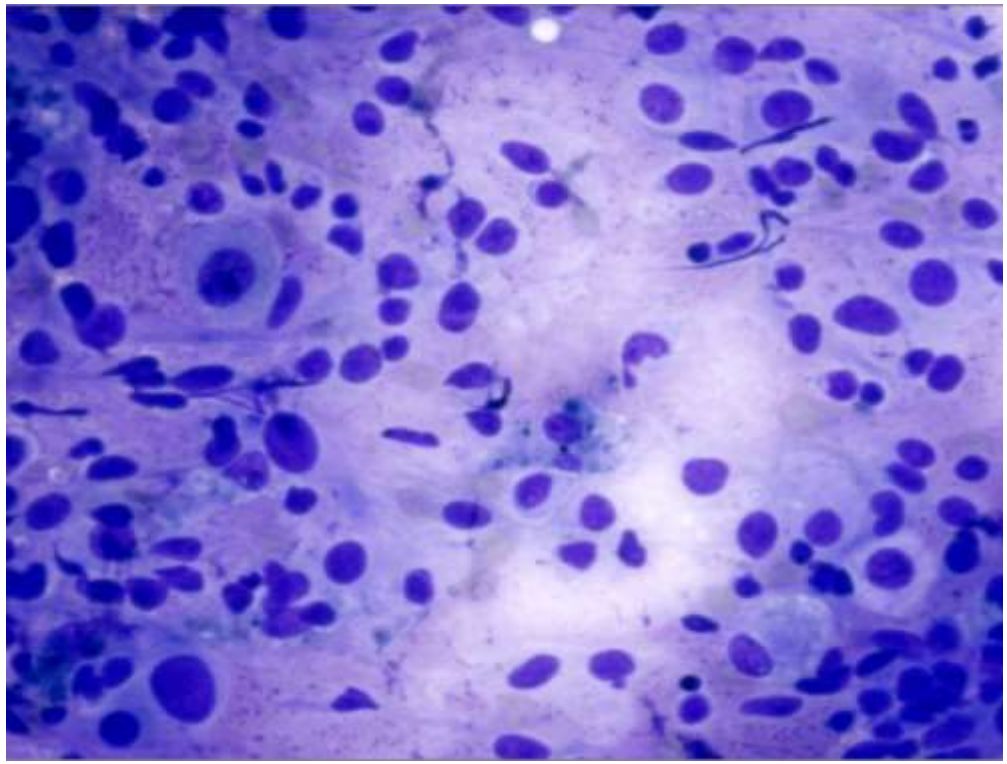

Figure 3: Cytological preparation prepared with ROSE technique and colored with Quick Stain. Pleomorphic epitheliomorphic cells are visible, with an inverted cytoplasmic nucleus ratio, a voluminous nucleolus, scattered cytoplasmic pigmented cells characterized by powdered melanin granules. These cells occur in non-cohesive clusters Q.S. 40 X

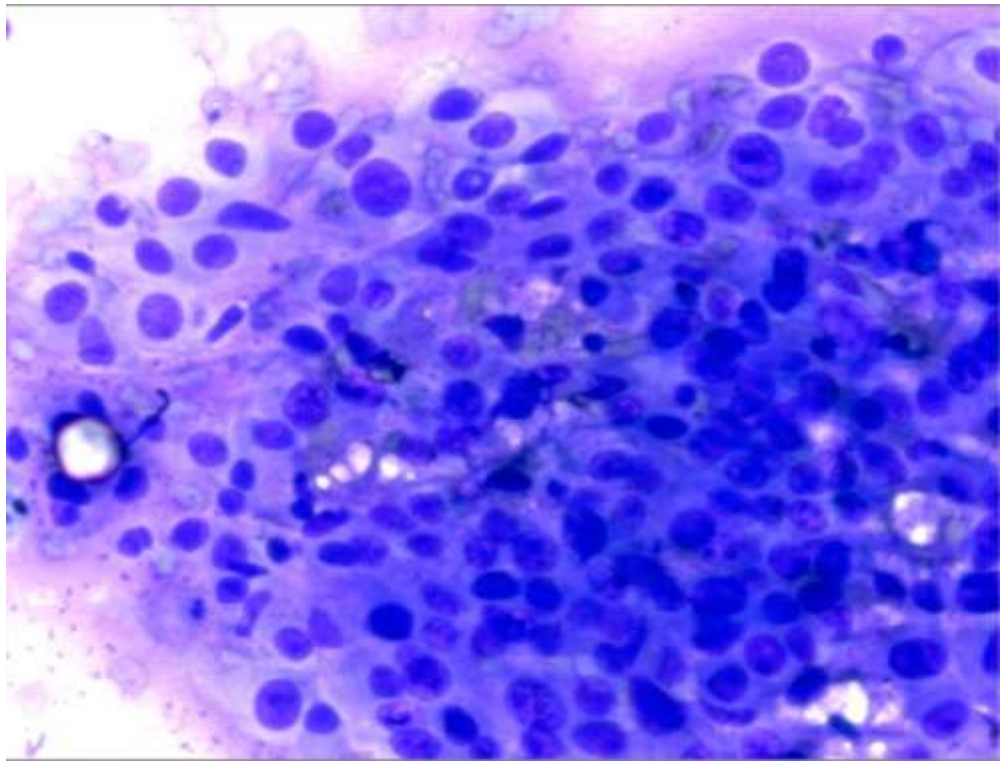

Figure 4: Note the perfect morphological reproducibility between the cells of the primitive lesion and those metastatic aspirated from the mediastinal lymph node. Q.S. 40 X

Discussion

CT scan surveillance has a high potential value in patients at high risk for systemic relapse in malignant melanoma. The thorax is the site of predilection for initial, that detection of early, surgically resectable metastases correlates with longer patient survival (4). For the early formation of pulmonary metastasis univariate predictors can be found, such as male sex, black race, increased primary thickness (millimeters), higher Clark's level, nodular or acral lentiginous histology, location on trunk or head and neck, and regional lymph nodes positive for metastasis (5). Our patient is a white male, but his primitive tumor, located on trunk, was a very aggressive histological type. Although the margins of excision were unscathed and the sentinel node was negative, the close follow-up was indicated and proved to be useful (6). Furthermore, we must consider that numerous molecular alterations associated with melanoma have been identified successfully (7). A recent whole-genome sequencing study conducted on 331 patients with primary and metastatic cutaneous melanoma has identified four distinct molecular subtypes

(based on as many mutational assets): cases with mutations activating the BRAF gene, cases with mutations activating RAS genes, cases with mutation inactivating the NF1 gene, cases without mutations in these three genes (triple wild-type) (8).
Rapid on-site evaluation can ensure that the targeted lesion is being sampled; ROSE can minimize repeat procedures for additional desired testing (ie, molecular studies), without adversely affecting the number of aspirations, total procedure time of TBNA, or the rate of post-procedure complications; it is also helpful in providing a preliminary diagnosis that can reduce the number of additional invasive procedures, such as mediastinoscopy (9). Despite the importance of the analysis of biomarkers and of the molecular profile, we have postponed this analysis because it had already been carried out on the primitive tumor from the trunk. ROSE during TBNA allows for deferring additional biopsy without loss in diagnostic yield, likely lowers procedural risk, and is cost-effective (10). In particular in the case of our patient, ROSE has allowed us to formulate the diagnosis completely excluding the biopsy.

Conclusions

We performed a ROSE on FNAB without EBUS support, succeeding in confirming the diagnosis of polypoid melanoma metastasis suspected by the history collection. The procedure is diagnostic when the sample is collected, prepared and read by expert operators, with considerable time and cost savings. The comparison between our sample and the histological preparation of notice the perfect morphological reproducibility between the cells of the primitive lesion and those metastatic aspirated from the mediastinal lymph node.

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LIGHT BROWN STRUCTURELESS AREAS AS PREDICTOR OF MELANOMA IN SITU

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Background: Dermoscopic criteria and algorithms have been developed in order to increase the sensitivity and specificity of melanoma diagnosis, although the detection of thin melanoma can still present some difficulties. The aim of our study is to assess the sensitivity of the three-point and seven-point checklist diagnostic algorithms, as well as the frequencies of each dermoscopic criteria and the frequency of the "light brown structureless areas", in 32 melanoma in situ (MIS) and 25 invasive superficial spreading melanoma (SSM).
Materials and methods: **We have retrospectively collected all consecutive cutaneous MIS and invasive SSM. The dermoscopic images were evaluated by three experienced dermatologists, blinded for histopathological diagnosis, who contemporarily assessed the presence or absence of some dermoscopic findings.**
Results: Our study suggests that the diagnostic sensitivity of both algorithms is lower for MIS lesions compared to invasive melanoma ones (16% lower for the three-point checklist and 14% lower for the seven-point one). Structureless light brown areas occurs mostly in the MIS group; in this group they occur with a 75% relative frequency compared to a 32% relative frequency in the invasive melanoma group, indicating a statistically significant difference between the two groups.
Conclusions: Structureless light brown areas should be considered a major dermoscopic finding while observing a suspected melanocytic lesion. In fact, by adding the presence of structureless light brown areas to both the seven- and three-point checklists instead of the blue-white veil and the blue-white structures, the diagnostic sensitivity in the subgroup of MIS could be higher of the 22%.

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AREA CLASSIFICAZIONE PATOLOGICA E MOLECOLARE

MELANOMA MALIGNO SARCOMATOIDE VS SARCOMA A CELLULE CHIARE: CASE REPORT

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INTRODUZIONE Il sarcoma a cellule chiare (CCS) è una forma rara e aggressiva di tumore dei tessuti molli che coinvolge giovani adulti ed origina dai tendini e dalle aponeurosi delle estremità (1). Sono descritti rari casi di localizzazioni inusuali di CCS che possono mimare un melanoma metastatico (2). Le similitudini morfologiche e immunoistochimiche tra il CCS e i tumori melanocitari rendono la diagnosi differenziale difficile e laboriosa (3). A nostra conoscenza, non ci sono casi di CCS originanti dalla cute del volto.
MATERIALI E METODI Presentiamo il caso di un paziente maschio di 26 aa con neoformazione nodulare sottocutanea in sede sottorbitaria sinistra presente da 3 mesi, a crescita rapidamente espansiva. Venivano eseguite TC, RMN, visita dermatoscopica e ORL prima di procedere a all' asportazione chirurgica ed esame immunoistochimico.
RISULTATI All'esame istologico la lesione risultava una neoplasia mesenchimale pleomorfa di alto grado, negativa ai principali marker immunoistochimici delle lesioni di origine mesenchimale ma positiva ai marker dei tumori melanocitari (S-100 e SOX-10). La TC risultava negativa per secondarismi. La visite dermatoscopica e ORL non evidenziavano lesioni melanocitarie sospette.
CONCLUSIONE Le diagnosi istologica e immunoistochimica non dirimenti aprono a differenti possibilità diagnostiche. La possibilità di una localizzazione ipodermica di melanoma cutaneo o delle mucose è da escludersi data la negatività della valutazione dermatologica e ORL e la bassa incidenza del melanoma delle mucose nelle popolazioni giovani (4).
L'età anagrafica, la localizzazione inusuale, la positività per i marker immunoistochimici della linea melanocitaria e la negatività per i marker della linea mesenchimale ha portato in prima battuta ad escludere il sarcoma come possibile diagnosi, giungendo alla diagnosi errata di localizzazione intradermica di melanoma metastatico particolarmente indifferenziato.
Alla luce dell'elevata indifferenziazione di queste lesioni, solo l'analisi genetica con l'individuazione della traslocazione t(12;22) che produce il gene di fusione EWS/ATF1 e l'assenza della mutazione BRAF/NRAS permette di escludere l'origine melanocitaria del tumore e concludere per la diagnosi di sarcoma a cellule chiare. Questo studio conferma che la presenza di tumori dermici maligni che mimano il melanoma dovrebbe far sospettare la presenza di un CCS e orientare la diagnosi sull'analisi genetica alla ricerca della traslocazione t (12;22).

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Prognostic utility of CAF1 (p60 and p150 subunits) expression in uveal melanoma.

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BACKGROUND: Uveal melanoma (UM) is the most common intraocular neoplasia in adults. Despite the recent advances in local therapy approaches, more than 50% of patients with uveal melanoma still develop distant metastases (1), with a very poor survival rates from the diagnosis of metastatic disease (2,3). There is an urgent need to identify new reliable biomarkers for the accurate prediction of clinical behaviour for each UM case. Molecular tests developed in recent years, including single-gene or multi-gene analysis and gene expression profiling, have yet displayed limits.
Chromatin Assembly Factor-1 (CAF-1), a trimeric protein complex required for chromatin assembly after replication, which assembles histone octamers onto newly-replicated DNA, is a very promising new prognostic factor for solid malignancies of various histogenesis (4,5).
METHODS: We tested the immunohistochemical expression of the two major subunits of CAF-1 (p60 and p150) on paraffin-embedded tissue sections from 4 tissue microarrays (TMAs) made by 2 mm cores, obtained from each of 68 uveal melanomas FFPE blocks, collected from 2005 to 2018, from the archives of the UOC of Surgical Pathology of the Federico II University of Naples.
RESULTS: CAF-1/p60 and CAF-1/ p150 proteins were found overexpressed in our series of uveal melanoma, with a significant correlation with an unfavorable outcome.
DISCUSSION: The results of this study demonstrate that CAF-1/p60 and CAF-1/p150 are able to identify UM patients with high risk of recurrence or metastasis, opening up the chance of adding CAF-1 immunohistochemistry to the routine tissue prognostic algorithm for uveal melanoma.

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P16 EXPRESSION IN UVEAL MELANOMA metastases: A DIGITAL APPROACH.

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Background: Metastases from unknown primary melanoma represent a diagnostic, clinical and therapeutic issue[1]. In particular, the derivation of liver metastases is often difficult to assign to a uveal or cutaneous primary melanoma, basing upon the current melanocytic markers[2]. $P16^{INK4a}$ is a tumor suppressor gene, located on chromosome 9p21, with a definite role in human malignancies. In familial cutaneous melanoma (CM), germline mutations of this gene are frequent and the loss of p16 tissue expression is thought to play a central role in melanocytes' malignant transformation. Immunohistochemical staining with anti-p16 antibody is routinely used to aid the discrimination between dysplastic nevi and cutaneous melanoma. Uveal melanoma (UM) relies on a quite different genetic background. In literature, the p16 immunohistochemical expression has been variously reported in UM, in contrast with the p16 absent expression in CM[2].
Methods: We tested the immunohistochemical $p16^{INK4a}$ expression on paraffin-embedded tissue sections from tissue microarrays (TMAs), made of 2 mm cores obtained from each of 54 uveal melanomas (primary tumors and liver metastases) collected from 2005 to 2018 at the UOC of Surgical Pathology of the Federico II University of Naples. A Digital Image Analysis (DIA) with QuPath[3] was performed on these sections, to calculate the percentage of p16 positive cells in whole slide images and, using QuPath algorithms, to compare the results obtained by digital and manual assessment.
Results: We observed a frequent and significative overexpression of p16 in our series of UM, by routine evaluation at optical microscope, in double observation by expert pathologists. This finding was detected and validated by DIA of the corresponding digital sections.
Conclusions: Our results suggest a role of p16 evaluation as a diagnostic biomarker in patients with melanoma metastases from unknown primary origin to discriminate between UM and CM.

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Intra-patient heterogeneity of *BRAF*, *NRAS*, and *c-KIT* molecular alterations during melanoma progression

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Background: Activating mutations in genes of the *MAPK* signaling are driver events in melanoma with therapeutic relevance in the metastatic and adjuvant setting [1]. Intra-patient molecular heterogeneity between primary melanoma and related metastases may exist, and changes of mutational status over time might occur. Data on somatic heterogeneity have been mainly reported for *BRAF* gene, while poor is known for *NRAS* and *c-KIT* [2]. Mutations of *BRAF, NRAS and c-KIT* are usually identified by molecular methods [3], but immunohistochemical analysis represents a useful option being widely available, less labor intensive and less expensive [3].
Objective: We investigated the mutational status of *BRAF*, *NRAS* and *c-KIT* in primary melanoma and related metastases and evaluated the intra-patient heterogeneity of mutational profiles during progression. Moreover, we compared the consistency of mutational findings obtained by molecular analysis and by immunohistochemistry.
Materials and Methods: Seventy-nine FFPE paired samples of primary melanomas and related nodal and/or visceral metastases (30 primary melanomas and 39 metastases) were analyzed by molecular methods using Real-Time PCR and Sanger Sequencing and by immunohistochemistry using the anti-human $BRAF^{V600E}$ VE1 and anti-$NRAS^{Q61R}$ SP174 and CD117/c-Kit polyclonal antibodies.
Results: *BRAF* mutations were identified in 46.7% of primary melanomas and in 48.7% of metastases and *NRAS* mutations in 20% and in 25.6%, respectively. c-*KIT* mutations were detected in one melanoma and c-KIT gene amplification in 4.3% of the cases. An intra-patient heterogeneity was detected in 13.3% of patients for both *BRAF* and *NRAS* genes and was not associated with clinico-pathological characteristics of either melanoma or metastases. We observed a high consistency between immunostaining and molecular methods for $BRAF^{V600E}$ mutation ($k = 0.90$; $p<0.001$) and for $NRAS^{Q61R}$ ($k = 0.87$; $p<0.001$).
Conclusions: Our findings demonstrate a clinically meaningful intra-patient heterogeneity between primary and metastatic lesions that is independent of clinical variables and methodological approach. Immunohistochemistry is useful as a screening test in clinical practice for the molecular diagnosis of melanoma.

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AREA CHIRURGIA

Multiple lymphatic-venous anastomoses in reducing the risk of lymphedema in melanoma patients undergoing complete lymph node dissection.

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BACKGROUND: Sentinel lymph node biopsy (SLNB) is an indispensable surgical procedure in staging and management of intermediate-to-thick melanomas. Although recent studies have demonstrated that complete lymph node dissection (CLND) does not improve 3-year specific survival, its utility in increasing the disease-free period and the control of local disease remains confirmed. The most frequent complication related to CLND is lymphedema, which may affect up to 20% of patients undergoing CLND. The preventive use of lymphatic-venous micro-anastomoses could avoid this complication.
MATERIALS AND METHODS: We performed a single-institution retrospective case-control study. CLND was proposed to all subjects with positive-SLNB; a preventive procedure involving multiple lymphaticovenular anastomoses (PMA) was performed in a cohort of subjects undergoing CLND. Frequency of lymphedema was compared among subjects undergoing and not-undergoing PMA during CLND.
RESULTS: We selected patients affected by melanoma of the trunk and with a minimum follow-up of 3 years, identifying 23 patients who underwent PMA during CLND (PMA group) and 120 subjects who underwent CLND without PMA (control group). The frequency of lymphedema was significantly lower in the PMA group than in the control group (4.3% vs. 24.2%, $p = 0.03$). Patients of the PMA group and the control group showed similar 3-year recurrence-free period (65.2% vs. 62.5%, log-rank test $p = 0.88$) and 3-year overall survival (73.9% vs. 72.5%, log-rank test $p = 0.97$) and frequency of nonsentinel-node metastases (26.7% vs. 30.4%, $p = 0.71$).
CONCLUSION: PMA appear to represent a useful and safe procedure in reducing the risk of lymphedema in patients with melanoma undergoing CLND.

Mancata visualizzazione di linfonodi sentinella alla linfoscintigrafia preoperatoria nel melanoma: studio retrospettivo della casistica della Chirurgia Plastica ISG dal 2004 al 2018.

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Introduzione: La linfoscintigrafia preoperatoria viene effettuata di protocollo in tutti i pazienti con melanoma a partire dallo stadio pT1b e risulta indispensabile nella stadiazione dei melanomi insorti in regioni cutanee che potrebbero avere siti multipli di drenaggio linfatico (1). In letteratura (2, 3) il distretto testa-collo presenta una maggiore probabilità di mancata impregnazione linfoscintigrafica.
Materiali e metodi: Questo studio retrospettivo, condotto su 2684 pazienti che, dal 2004 al 2018 sono stati sottoposti a linfoscintigrafia preoperatoria, analizza le caratteristiche ed il follow-up dei casi in cui non è stato possibile individuare un linfonodo sentinella. I pazienti di questo gruppo sono stati sottoposti, secondo i protocolli e le linee guida AIOM, alla sola radicalizzazione del melanoma primitivo e ad un follow-up trimestrale per I primi due anni, poi semestrale fino a 10 anni. Il confronto è stato eseguito con una coorte randomizzata di pazienti sottoposti a linfoscintigrafia preoperatoria nello stesso periodo, con esito positive e conseguente linfadenectomia selettiva radio-guidata.
Risultati: Nel campione esaminato di 2684 pazienti, il mancato drenaggio linfoscintigrafico è avvenuto solo in 49 casi (1.83%).
L'analisi del gruppo dei 49 casi non drenanti ha dimostrato che 41 (83,7 %) presentavano una localizzazione di melanoma primitivo nella regione cervicale posteriore e toracica sovrascapolare, interscapolare e sternale. In 6 (14,2%) si sono osservate metastasi a distanza, mentre solo in 1 caso (2%) una linfadenopatia metastatica tardiva ascellare. Nello studio vengono analizzati e confrontati I dati di follow-up in correlazione con le caratteristiche del melanoma primitivo.
Conclusioni: Lo studio dimostra che la regione cervicale postero-laterale e quella interscapolare presentano un maggior numero di casi di mancata impregnazione linfoscintigrafica. La frequenza di metastasi riscontrata è stata più elevata rispetto a quella osservata nella coorte di pazienti della casistica generale dei drenanti.

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Approccio C.O.R.E. nel trattamento dei tumori cutanei del distretto cervico-facciale

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INTRODUZIONE: La chirurgia dei tessuti molli ha come obiettivo primario la radicalità oncologica al fine di incrementare la sopravvivenza globale e la sopravvivenza libera da recidiva (1). I tumori cutanei, in particolare del distretto cervicofacciale, tuttavia, impattano spesso oltre che sulla sopravvivenza, anche sulla qualità di vita del paziente. Un approccio moderno è quello proposto dal Prof. Bruschi dell'Università di Torino nel concetto di Chirurgia Oncologica Ricostruttiva ed Estetica (C.O.R.E.) in cui l'operatore è in grado di padroneggiare sia le tecniche demolitive che quelle ricostruttive-estetiche, assegnando al tempo ricostruttivo un ruolo paritario alla rimozione della neoplasia (2).
MATERIALI E METODI: Abbiamo analizzato casi clinici di pazienti con tumori del distretto cervico-facciale (sia melanoma che non-melanoma skin cancer) trattati presso la Chirurgia Plastica dell'Azienda ospedaliera di Padova e presso l'istituto Oncologico Veneto di Padova negli ultimi 5 anni. Abbiamo considerato due gruppi: nel gruppo A sono stati inclusi i pazienti trattati solo dal chirurgo generale, nel gruppo B i pazienti trattati da chirurgo oncoplastico o da chirurgo generale e plastico previa pianificazione condivisa della strategia operatoria complessiva (secondo i concetti di C.O.R.E.). I criteri di inclusione allo studio erano i seguenti: diagnosi di melanoma o non melanoma skin cancer del distretto cervico-facciale trattati presso la Chirurgia Plastica dell'Azienda ospedaliera di Padova e presso l'Istituto Oncologico Veneto di Padova negli ultimi 5 anni, regolari follow-up post-operatori per almeno i successivi 6 mesi.
RISULTATI: Abbiamo analizzato nei due gruppi la conformità del trattamento relativa a radicalità oncologica (ottenuta in 1 o 2 tempi), utilizzo delle corrette tecniche ricostruttive, rispetto delle unità estetiche, complicanze.
CONCLUSIONI: Nella visione della chirurgia C.O.R.E. la chirurgia ricostruttiva non deve essere solo la fase successiva della chirurgia demolitiva ma parte integrante di un percorso chirurgico e terapeutico complessivo. In questo studio abbiamo riscontrato che l'applicazione di questi Principi porta ad un vantaggio complessivo in termini di risultato estetico e soddisfazione del paziente, mantenendo inalterata la radicalità della asportazione della neoplasia.

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METASTASI DI MELANOMA IN SEDE ATRIALE : CASE REPORT

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INTRODUZIONE
Si espone un caso di localizzazione secondaria di melanoma in sede atriale cardiaca dx, in donna di 65 anni sottoposta a valutazione chirurgica polmonare per episodio di emoftoe (febbraio 2019)
MATERALI E METODI
Le indagini radiolgiche (PET, TC torace, Ecocardiogramma), hanno evidenziato due lesioni eteroformative nel segmento posteriore del LSD e a sede ilare dx non ancora tipizzate e altresì eteroplasia in sede atriale cardiaca dx di dimensioni 29*24 mm adesa al setto interatriale, peduncolata e mobile.
RISULTATI
Il focus della esposizione, viene incentrato sul rarissimo riscontro in letteratura di metastasi da melanoma in sede settale atriale cardiaca, da noi istologicamente definita dopo eradicazione cardiochiurgica per presunto mixoma[1,2].
CONCLUSIONI
La peculiarità del caso é proprio nel raro riferimento bibliografico che riporta esclusivamente manifestazioni metastatiche muscolari cardiache da melanoma [3], in stati avanzati di malattia associati a prognosi infausta.

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RUOLO DELLA LINFOADENECTOMIA RADICALE E SUE COMPLICANZE NEI MELANOMI AL TERZO STADIO

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Introduzione: Nei linfonodi sentinella (LNFS) positivi la dissezione linfonodale di completamento si considera come opzione, considerando le possibili complicanze, mentre la terapeutica s'impone nelle metastasi clinicamente evidenti -evidenza 3- (AIOM,1).L'estensione, correlata alla regione anatomica, ed il numero dei linfonodi, definiscono la sua adeguatezza.Secondo IMI: 7(<3livelli)/14 (>4 livelli) linfonodi per la laterocervicale, 12 per l'ascellare (3 livelli), 6 per la sola inguinale e 13 per l'inguino-iliaco-otturatoria (Rossi, 2).Per lo stadio III è indicata la dissezione indipendentemente dal tipo di metastasi presenti nel LNFS (River, 3).Il tempo tra diagnosi e terapia non impatta sulla prognosi (Conic, 4).
Materiali e metodi: Su 591 pazienti (318 M, 273 F), abbiamo eseguito per positività LNFS/recidiva locale 186 linfoadenectomie radicali:116 ascellari, 63 inguino-iliaco-otturatorie,7 cervicali.Nei LNFS positivi(60), dopo discussione multidisciplinare onco-chirurgica,41 pazienti hanno eseguito la dissezione;19 no (bulky< 0.5, polipatologie, scelta personale).
Risultati: Il numero di linfonodi medi asportati è in linea con la Letteratura:14 cervicali, 16 ascellari, 19 inguino-iliaco-otturatori (Rossi, 5). Le complicanze osservate (71%) sono state: 121 sieromi (91%), 34 deiscenze/infezioni della ferita chirurgica (34%), 6 linfedemi (5%) (Moody,6).Il survival time medio è stato di 51,7 mesi.
Conclusioni: La dissezione radicale è raccomandata nei LNFS positivi, anche se non vi è evidenza di miglior prognosi.In attesa di chiari criteri clinico-patologici, dopo discussione multidisciplinare, proponiamo lo stretto follow up nei pazienti a basso rischio, la linfoadenectomia nell'alto rischio.

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8ª edizione AJCC: quale impatto in termini clinico-assistenziali? Analisi della nostra casistica di melanomi sottili.

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Introduzione: Nella 8th AJCC staging ed.(1) per il melanoma sono stati introdotti alcuni cambiamenti nei criteri di stadiazione. La biopsia del linfonodo sentinella (SLNB), pur considerata gold standard per lo staging, rimane controversa nei melanomi sottili (Breslow ≤1,0 mm). Lo studio si propone di analizzare l'impatto in termini clinico-assistenziali della nuova classificazione TNM nei pazienti con melanoma sottile.
Materiali e metodi: Studio clinico retrospettivo su 446 pazienti con melanoma cutaneo di Breslow ≤1 mm, operati presso l'U.O. di Chirurgia Plastica-Policlinico Sant'Orsola-Malpighi dal 2009 al 2017. Nella popolazione di studio sono state effettuate diverse analisi. 1) Riclassificazione di tutti i pazienti secondo i nuovi criteri di stadiazione. 2) Analisi dell'incidenza delle metastasi linfonodali, della loro distribuzione nelle sottocategorie pT1a e pT1b, nonché dell'incidenza delle complicanze. 3) Analisi dei diversi parametri istopatologici del melanoma primitivo.
Risultati: L'introduzione della nuova classificazione comporterà un decremento del numero di pazienti stadiati come pT1b. Il tasso di incidenza di metastasi linfonodali nei pazienti con melanoma sottile si attesta a circa il 5%, senza una netta differenza tra le sottocategorie pT1a e pT1b, mentre quello delle complicanze chirurgiche per la procedura è del 19% circa. Analizzando i parametri istopatologici del melanoma, sono state riscontrate delle associazioni tra la presenza di un infiltrato infiammatorio, la regressione tumorale, l'ulcerazione e la presenza di metastasi linfonodali.
Conclusioni: La nuova classificazione comporterà una diminuzione dei pazienti eleggibili alla SLNB; tuttavia, considerato il basso tasso di linfonodi metastatici, equiparabile tra le sottocategorie pT1a e pT1b, questa stessa non sembra apportare un reale cambiamento. Tenendo conto delle complicanze chirurgiche della procedura e della presenza di falsi negativi sembrerebbe che, anche nei pazienti in stadio pT1b, l'indicazione della SLNB non sia così forte, ma che vada discussa con il paziente valutando il rapporto rischio-beneficio. La presenza dell'ulcerazione, dell'infiltrato infiammatorio e della regressione tumorale sono maggiormente correlati con la possibilità di riscontrare un linfonodo metastatico.

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AREA TERAPIA MEDICA

Linfonodo sentinella nel melanoma spesso (Breslow > 4mm): la nostra esperienza chirurgica

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Introduzione: La biopsia del linfonodo sentinella (BLS) è una procedura diagnostica con elevata sensibilità e specificità per valutare metastasi linfonodali subcliniche in pazienti senza evidenze di secondarismi linfonodali (1).
La valenza prognostica e terapeutica della BLS in pazienti con riscontro di melanomi spessi (Breslow > 4mm) è ancora oggetto di discussione (2).
Materiali e Metodi: Tutti i pazienti che dal 2003 al 2015 sono afferiti al nostro centro (Policlinico di Sant'Orsola) con nuovo riscontro di melanoma con Breslow > 4mm (N = 82) e sottoposti a BLS sono stati inclusi nella seguente analisi. Gli end-point da noi valutati sono stati: a sopravvivenza libera da malattia a 5 anni, il tasso di recidive e l'impatto delle complicanze chirurgiche. I dati ottenuti sono stati confrontati a coorti storiche riportate in letteratura (3).
Risultati: I pazienti inclusi sono stati stratificati in 3 gruppi, a seconda dell'esito della BLS. Gruppo A: BLS negativo; Gruppo B: riscontro alla BLS di metastasi. In accordo con la letteratura è stata confermata la rilevanza prognostica della BLS, il cui esito si ripercuote in una differente sopravvivenza e una differente sopravvivenza libera da malattia (4).
Conclusioni: Il seguente studio descrive la rilevanza clinica della BLS nei melanomi spessi. Se in letteratura vi è un generale consenso sul sottoporre a BLS paziente con melanoma il cui Breslow è compreso tra 0,8mm e 4,0mm, per spessori maggiori la procedura è ancora dibattuta. Confrontando la sopravvivenza dei nostri pazienti sottoposti a BLS con coorti storiche presenti in letteratura di pazienti non sottoposti a tale procedura, si conferma il vantaggio in termini di aumentata sopravvivenza e riduzione delle riprese di malattia. Se l'aumentata sopravvivenza è attribuibile ad un più precoce e corretto inquadramento diagnostico, la riduzione di secondarismi sembrerebbe legala alla rimozione delle cellule neoplastiche con potenziale metastatico presenti nel linfonodo sentinella. Alla luce di questi dati, la BLS dovrebbe routinariamente essere eseguita anche noi pazienti con Breslow < 4mm.

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Role of 18F- fluorodeoxyglucose positron emission tomography/computed tomography (18FDG- PET/CT) baseline metabolic parameters as prognostic factors in melanoma patients treated with immunotherapy: a retrospective analysis.

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Background: Ipilimumab, Nivolumab and Pembrolizumab have proved efficacy in melanoma treatment, inducing long-term remissions in more than 20% of patients (pts).(1-5) Association of Nivolumab and Ipilimumab further improved this outcome. (6) Despite this, 20-30% of pts treated with single-agent immunotherapy develop severe immune-related adverse events, with a percentage even higher for the combination. (7) Since here, the need of predictive factors to best select patients who can really benefit and customize treatment.
18FDG- PET/CT metabolic parameters and blood count indices (BCI) have been investigated as prognostic factors in different malignancies, but few data are available on immunotherapy. (8-12)
Aim of this analysis was to investigate the role of some of these baseline parameters as response factors to immunotherapy in melanoma pts.
Methods: We retrospectively analyzed 23 melanoma pts treated with Ipilimumab, Nivolumab or Pembrolizumab from 2010 to 2018 who had basal 18FDG- PET/CT scan and complete blood count before treatment. Whole-body metabolic tumor volume (wMTV) and total lesion glycolysis (wTLG) were calculated for each patient as well as the higher standardized uptake volume maximum (SUVmax) and mean (SUV mean). Baseline neutrophil/ lymphocyte (NLR), lymphocyte/monocyte (LMR) and platelet/lymphocyte (PLR) ratio were calculated. We investigated the association of these parameters (dichotomized on their median) with best response and progression free survival (PFS).
Results: 21/23 patients were treated with immunotherapy in first line. 12 patients received Pembrolizumab, 7 Nivolumab and 4 Ipilimumab. Two pts had BRAF V600E mutation, 21 were wild-type. Overall response rate (ORR) was 43,4%;median PFS was not reached. wMTV and wTLG were associated with response (respectively p= 0.05 and p= 0.03, Mann- Whitney test), while no significant differences were found for SUV values. Pts with low wTLG had longer PFS (Cox-model HR per 100 units increase: 1.106, 95%IC 1.01-1.21; p= 0.03). Low basal NLR and PLR correlates with improved PFS (p= 0,03 for both), while no relation was found with ORR nor between LMR and ORR and PFS.
Conclusions: With the limit of a small sample, our preliminary data show that wMTV and wTLG may have a role in predicting outcomes to immunotherapy in melanoma pts and they could be further investigated in prospectical studies. Also BCI impact should be assessed in larger studies, as they may reflect the systemic immunological status.

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Attività sinergica degli inibitori di ATR e di PARP in linee cellulari di melanoma con mutazione di BRAF

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Introduzione: Il melanoma in stadio metastatico, nonostante i recenti progressi terapeutici, è ancora caratterizzato da elevata mortalità, specialmente in presenza della mutazione puntiforme di BRAF codone V600. L'elevata instabilità genetica riscontrata nel melanoma, che spiega l'alto carico mutazionale riscontrato in questa patologia e la conseguente risposta terapeutica agli inibitori del checkpoint immunitario, rappresenta un potenziale bersaglio farmacologico per farmaci che inibiscono i meccanismi di riparo del DNA. Tuttavia, gli inibitori di PARP (poli-ADP ribosio polimerasi), già approvati per il trattamento del carcinoma sieroso ovarico, non hanno mostrato un'attività significativa in pazienti affetti da melanoma, sia da soli che in associazione alla chemioterapia. ATR (atassia-teleangectasia legata a Rad3) è una proteina coinvolta nel meccanismo di riparo del DNA in risposta alle rotture della doppia elica e costituisce un bersaglio farmacologico di nuovo interesse. Lo scopo di questo lavoro è di valutare l'attività di un inibitore di ATR (AZD6738) da solo o in combinazione con un inibitore di PARP (Olaparib) in linee cellulari di melanoma con mutazione di BRAF.
Materiali e metodi: Due linee cellulari di melanoma BRAF mutate (A375 e SAN) e le loro corrispettive linee rese resistenti in vitro a vemurafenib e cobimetinib (A375-VRCR e SAN-VRCR) sono state trattate con AZD6738, Olaparib e la loro combinazione. Sono stati eseguiti saggi di MTT e di formazione di colonie al fine di valutare l'attività di questi farmaci in vitro.
Risultati: I saggi di MTT hanno evidenziato che tutte le 4 linee cellulari esaminate sono ugualmente sensibili ad AZD6738 (IC50: 1-1,5 μM), indipendentemente dalla resistenza acquisita in vitro a vemurafenib e cobimetinib. L'associazione di AZD6738 e Olaparib mostra sinergismo farmacologico in tutte e 4 le linee cellulari esaminate; tale risultato è stato confermato dal saggio di formazione di colonie, in cui dopo 10 giorni di esposizione alla combinazione di 0,4 μM di AZD6738 e 2 μM di Olaparib si è osservata una mortalità superiore al 94% in tutte le linee cellulari analizzate.
Conclusioni: L'inibizione di ATR determina mortalità in linee cellulari di melanoma con mutazione di BRAF indipendentemente da un trattamento precedente con inibitori di BRAF e MEK e, in tale modello preclinico, l'associazione di inibitori di ATR e di PARP mostra sinergismo farmacologico (meccanismo di letalità sintetica) costituendo un potenziale nuovo approccio terapeutico per questa neoplasia.

Concomitant medications during immunotherapy may influence immune related adverse events (irAEs) onset

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Background: There was still little evidence on potential baseline risk factors for immune related adverse events (irAEs) onset in patients (pts) treated with immune checkpoint inhibitors (ICI), both anti CTLA-4 and anti PD-1/PD-L1 agents. It was known that the drug-induced autoimmunity is an immune related drug reaction associated to continuous drug exposure. Aim of the study was to evaluate the potential role of concomitant use of drugs on the development of irAE (1) in pts treated with ICI. Furthermore, ECOG performance status (PS) and the presence of comorbidities were evaluated as potential factors associated to irAEs.
Methods: A retrospective series of 73 consecutive pts treated with ICI for metastatic melanoma from 2012 to 2018 in our centre was included. IrAEs were graded according to CTCAE v.4.0. Comorbidities were rated as per the Charlson Comorbidity Index (CCI) score (2). Concomitant use of drugs was reported specifying pharmacological class and total number of drugs taken. Statistical analysis were performed using the Mann-Whitney test. Concomitant drugs, CCI and PS were analysedas continuous variables.
Results: At baseline, the median age was 70,9 years and ECOG PS was ≤ 1 in 94,5% pts. CCI median score was 9. Concomitant drugs were recorded in 79,5% of pts with ≥ 3 drugs taken in 49,3% of cases. Main concurrent drugs were: antihypertensives (diuretics and beta-blocker) 68,5%, PPI 26,0%, neuropsychiatric drugs 23,3%, statins 13,7%, ASA 15,0%, warfarin 6,8%. All pts were treated with ICI, 57.6% as first line, 39.7% as second and 2.7% as a subsequent line of therapy. Most pts were treated with anti PD-1/PDL-1 inhibitors (pembrolizumab 43,8%, nivolumab 20,5%) whether 35,6% received ipilimumab. Overall, irAES onset in 29 pts (39.7%). Into detail, 46.8% of toxicity were grade 1, 28.1% grade 2, 18.8% grade 3 and 6.3% grade 4. The occurrence of irAEs was significantly associated with the number of concomitant drugs (p=0.0003). ECOG PS (p=0.1586) and CCI (p=0.4722) were not significantly associated with irAE.
Conclusions: Our results suggest that polypharmacy may be related to irAEs development. Further prospective studies are needed to confirm these data.

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A RETROSPECTIVE REAL-WORLD STUDY OF CUTANEOUS TOXICITY OF IMMUNE CHECKPOINTS INHIBITORS IN PATIENTS WITH ADVANCED MELANOMA

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Background: Immune checkpoint inhibitors (ICI) have significantly improved the survival of patients with metastatic melanoma. However, treatment with ICIs is associated with immune-related adverse events (irAEs). Skin irAEs are among the most frequent adverse events (AEs) observed by patients treated with ICIs and usually develop early in the course of treatment (within the first few weeks after initiation) [1-3]. However, serious skin AEs are rare and do not usually require treatment discontinuation.
Methods: We retrospectively analysed all consecutive patients who received immune checkpoint inhibitors (ICIs), such as Pembrolizumab, Nivolumab or Ipilimumab, for advanced melanoma between 2013 and 2018 at our institution.
Results: Of the 91 patients enrolled, 41 (45%) developed cutaneous toxicity of any grade. 23 out of 44 patients who received Pembrolizumab (52%) had toxicity, 5 out of 20 patients treated with Nivolumab (25%) and 13 out of 27 (48%) among patients who received Ipilimumab. 10 patients experienced ≥1 skin irAEs. Cutaneous irAEs were mostly mild: grade 1 in 51% of cases (29/57), grade 2 in 42% (24/57) and grade 3 in 7% (4/57). The most common cutaneous toxicities were pruritus (28%) and erythematous rash (25%). Mean time of onset of irAEs was 9.5 weeks (95% confidence interval CI 6.8-12.2). Systemic corticosteroid therapy was necessary in 31,6% of cases (18/57). Mean duration of irAEs was 6,9 weeks (95% CI 4.5-9.3). Permanent discontinuation of ICIs therapy was necessary only in one case. A landmark analysis after 3 months of treatment revealed no difference in overall survival between patients with and without cutaneous irAEs.
Conclusions: The values obtained in our study are consistent with data reported by others in the literature. Knowledge of these findings and early and multidisciplinary management are critical for maintaining dose intensity, and health-related quality of life in cancer patients receiving ICIs.

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Combined inhibition of MEK and Notch blocks migration and triggers senescence in GNAQ^{Q209L} mutated uveal melanoma cells

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Background: Activating mutations in genes *GNAQ* or *GNA11* promote uveal melanoma (UM) carcinogenesis and metastasis through the activation of MAPK and even Notch signaling. The aim of this study was to ascertain the effects of a combinatorial inhibition of MEK and Notch signaling by using cobimetinib and the γ-secretase inhibitor nirogacestat, on the GNAQ^{Q209L}UM cell line 92.1.
Methods: 92.1cells were treated with cobimetinib and nirogacestat alone and in combination. Drug(s) cytotoxicity was evaluated by MTT and the combination index by Calcusyn software. FACS analysis was used to assess cell cycle distribution and apoptosis induction by Annexin V staining. Cell targets modulation was analyzed by western blotting and real-time PCR. Induction of senescence was determined by the beta galactosidase detection kit. UM migration,toward liver cancer cells, was detected by the transwell migration assay.
Results: The combination of drugs was synergic in inhibiting cells proliferation (CI=0.4). MEK inhibition by cobimetinib resulted in apoptosis induction as a consequence of the arrested state of the cells at G0/G1 phase of cell cycle. The drugs combination synergistically repressed cell proliferation because it promoted cell senescence, particularly evident in long-term cultureas senescence-associated expression of β-galactosidase (SA-β-Gal). The analysis of target proteins evidenced that drugs combination strongly reduced the level of cyclin D1 and Hes-1, inactivated the retinblastoma protein (RB) and increased the level of p27^{KIP1}. Interestingly both drugs prevented Notch signaling activation, unveiling a cooperative mechanism between MAPK and Notch pathway in driving 92.1 cells proliferation. Indeed cobimetinib did not achieve the inhibition of p-ERK1/2, nirogacestat stimulated it, whereas the drugs combination, only, achieved the strongest inhibition on both c-jun(Ser63) and ERK1/2 activation
and transcriptionally repressed the expression of cyclin D1, Notch1/3 and Hes1. Of note, such drugs combination blocked the migration of UM cells towards liver cancer cells.
Conclusion: Here, we showed that in such GNAQ^{Q209L} mutated cells the mitogenic stimuli were preferentially transduced through a rout that involved the MAPK and Notch signaling to promote proliferation, migration and escape cell senescence. In addition we demonstrated, for the first time, that the simultaneous inhibition of Notch and MAPK pathways prolonged the treatment efficacy of MEKi in UM cells.

SURVEY IMI: Experience about management of immunotherapy toxicities

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BACKGROUND: Checkpoint inhibitors, immunomodulatory antibodies that are used to enhance the immune system, have substantially improved the prognosis for patients with advanced malignancy. The management of toxicities due to immunotherapy is an emergent topic. We explored individual medical experience and practice.
METHODS: Italian medical doctor members of the Italian Melanoma Intergroup were invited to participate in an online survey addressing management of toxicities due to immunotherapy.
RESULTS: A 18-item questionnaire was delivered to 31 medical doctor: 74% aged 30-40 years, 80% oncologist, 16% dermatologist, 35% still in training, 67% works in Universities or Research Institutes. A 32% has prescribed immunotherapy for at least 6 years, 93% has participated in Clinical Trials or Expanded Access Program, 51% has enrolled patients in study with combo-immunotherapy (median 10 patients, range 2-50). 50% of doctors cure more than one cancer, 87% treat melanoma, 32% lung cancer. To manage immunotherapy toxicity, doctors use guidelines, the most common is ASCO guide lines (45%). In most Centre (71%) there are more specialists, at least 2 or 3, dedicated to manage collateral effects or radiological response of therapy (endocrinologist 51%, dermatologist 51%, radiologist 45%, gastroenterologist 35% etc).
The most frequent toxicities due to anti-CTLA4 are gastrointestinal 48%, dermatological 29%, 52% of physician treated at least 5 or more patients who experienced ≥G3 toxicity. The most frequent toxicities due to anti-PD1 are thyroiditis 67%, dermatological 25%, 41% of physician treated at least 5 or more patients who experienced ≥G3 toxicity. The most frequent toxicities due to Combo-immunotherapy are gastrointestinal 26%, Hepatitis 13%, 41% of physician treated at least 5 or more patients who experienced ≥G3 toxicity. An average of 3 patients per centre for each treatment had a need for hospitalization.
A 61% of physicians used Infliximab or Mycofenolato Mophetile to manage immunotherapy toxicities at least one time.

CONCLUSIONS: This is a preliminary evaluation, the doctors who took part have a high experience on the treatment, so we need to extend the analysis to a more general sample to have an assessment of the national experience on the management of immunotherapy toxicities.

Sustained complete response to Nivolumab in two cases of GNAQ mutant uveal melanoma with non-hepatic metastatic disease.

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Introduction: Uveal melanoma is a rare entity among malignant melanomas, with a very unfavorable prognosis [1]. Despite excellent rates of local disease control for the primary cancer, up to 50% of patients affected by uveal melanoma develop metastatic disease, leading to a median overall survival less than ten months [2]. According to literature, liver is the most frequent initial site of disease spread as 90% of patients with metastatic disease present hepatic involvement [3]. For metastatic disease, several systemic treatments have been tested to date, with no proven benefits and unsatisfactory response rates [4]; immunotherapy with anti-CTLA-4, anti-PD-1 and anti-PD-L1 antibodies has been evaluated in uveal melanoma failing to show significant efficacy so far [5].
Methods and materials: We present the case of two patients with treatment-naïve, metastatic uveal melanoma harboring GNAQ mutations. The first patient was a 37-year-old man who presented axillary lymph nodes, right internal iliac lymph nodes and bone metastases; intravesical and pancreatic metastases were detected in the second patient, a 49-year-old woman. CT and FDG-PET scans showed no evidence of hepatic involvement while the NGS panel revealed the presence of GNAQ exon 5 mutations (codon 209) and no mismatch repair deficiency in both patients. No evidence of PD-L1 expression was found. Given the stage of the disease, the two patients started a first-line treatment with Nivolumab in September 2016 and October 2016, respectively.
Results: The two patients achieved a complete response with Nivolumab treatment after 4 and 8 cycles, respectively. They are currently continuing Nivolumab 480 mg every 4 weeks without signs of clinical and instrumental disease recurrence.
Conclusions: Despite the disappointing results of immune checkpoint-inhibition therapy in metastatic uveal melanoma, we underline the exceptional findings of two patients harboring GNAQ mutation who experienced a sustained complete response to Nivolumab. To our knowledge, the two patients represent the first reported cases of complete response to Nivolumab treatment in GNAQ mutation positive non-hepatic metastatic uveal melanoma.

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ErbB3 phosphorylation as central event in adaptive resistance to BRAF/MEK inhibitors in metastatic melanoma: early detection in CTCs during therapy and insights into regulation by autocrine Neuregulin

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Background: In recent years the introduction of target therapies with BRAF and MEK inhibitors (MAPKi) and of immunotherapy with anti-CTLA-4 and anti-PD-1 monoclonal antibodies has dramatically improved survival of metastatic melanoma patients [1]. Despite these changes drug resistance remains a major hurdle. Several mechanisms are at the basis of drug resistance [2]. Particular attention has been devoted over the last years to unravel mechanisms at the basis of adaptive/non genetic resistance occurring in BRAF mutated melanomas upon treatment with to MAPKi [2]. In detail we focus on the involvement of activation of ErbB3 receptor following early exposure of melanoma cells to BRAF or MEK inhibitors, and the following induction of PI3K/AKT pathway.
Methods: Human melanoma cell lines, WM266, LOX IMVI, and WM115 were cultured in RPMI supplemented with 10% FBS. To evaluate ErbB3, AKT and ERK 1/2 signalling melanoma cells were starved and treated with vemurafenib (0.5 μM) for 2h, 8h and 24h. Unstimulated cells were treated with conditioned medium (CM) from BRAF inhibitor-stimulated melanoma cells. Moreover melanoma cells were also treated from 2h to 72h in order to study the activation kinetics of the ErbB3/Akt axis by western blotting assay.
Results: We show here with a combination of approaches that autocrine production of neuregulin by melanoma cells is a major factor responsible for ErbB3 phosphorylation and downstream AKT activation. Interestingly the kinetic of neuregulin production and of the ensuing ErbB3 phosphorylation is different in different melanoma cell lines which underscores the high degree of tumor heterogeneity. Moreover, heterogeneity is further highlighted by the evidence that in different cell lines neuregulin upregulation can occur at the transcriptional or at the post-transcritpional level. Finally we complement our study by showing with a liquid biopsy assay that circulating tumor cells (CTCs) from melanoma patients undergo upregulation of ErbB3 phosphorylation in vivo shortly after initiation. of therapy.
Conclusions: Our new findings could have potential diagnostic implications in the field of liquid biopsy, as the activation of the ErbB3-NRG1 axis could be implicated as a new early biomarker able to predict the response to the targeted therapies in metastatic melanoma patients.

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The prognostic factor of early loss of muscle mass in patients with metastatic melanoma treated with immunotherapy

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Background: Higher BMI is associated with better outcomes in metastatic melanoma patients (MM pts), while the prognostic value of sarcopenia is little known in these pts (1).
The aim of this study was to examine the prognostic impact of body-mass index (BMI), baseline sarcopenia, loss of skeletal muscle mass (LSMM) on overall survival (OS) in MM pts who received immunotherapy (IT).
Methods: We conducted a retrospective study of a consecutive series of 42 MM pts (Jan 2011-Dec 2018) treated with IT in a single referral center. Sarcopenia was defined according to Prado's criteria (2). Skeletal muscle index (SMI) was calculated as cross-sectional-area of muscle (cm^2), using CT-scan, at the L3 level divided by the square of the height (m^2). Early LSMM, during IT, was defined as a decrease in SMI□10% from baseline at first evaluation. BMI was calculated as weight (kg) divided by the square of height (m^2) and categorized according to standard WHO definitions. Weight loss was analyzed as continuous variable.
Results: At baseline, 27 pts (64,3%) were male, 26 pts (61.9%) were < 70 years and 31 pts (73.8%) had ECOG PS=0. Overall, 26 pts (61.9%) had LDH <ULN, 24 pts (57.1%) had □3 metastatic sites ,10 pts (23%) had CNS metastases, BRAF was mutated in 17 pts (40,4%), 22 pts (52%) had previously received at least one line of systemic therapy. As a first line IT treatment, 16 pts (38.1%) received an antiCTLA-4 agent and 26 pts (61.9%) a PD1 inhibitor. Of note, 23 pts (54.8%) had a sarcopenic state, and 23 pts (54,8%) had a BMI □25. Out of 42 pts, 30 (71.4%) had a CT-scan at first evaluation, and 30% of them had an early LSMM. Median OS was 11.38 months and 9.37 months in pts with early LSMM □□□□ Both in univariate and multivariate analysis, ECOG PS□1, and early LSMM □10% were significantly associated with worse OS. Low albumin levels were not associated with a sarcopenic state. Interestingly, pts with weight loss had better outcome.
Conclusions: Early LSMM □10% and ECOG PS□1 may negatively influence the outcome of MM pts treated with IT. Further prospective investigation are needed to confirm these preliminary data.

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BRAF INHIBITORS MAY PRODUCE A LATE-ONSET, DUAL TOXICITY ON THE RENAL FUNCTION: A CASE REPORT

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Introduction: Tyrosine kinase inhibitors (TKIs) Dabrafenib and Trametinib represent the standard of care in BRAF mutated melanoma, which accounts for 40-50% of melanomas (1). Renal toxicity is reported to occur in less than 1% of the patients (2) and it's usually caused by indirect mechanisms leading to dehydration and prerenal acute kidney injury (AKI).
Case report: We report the case of an 83-year-old man diagnosed with melanoma of the leg in 1980, who has been locally treated until 2016, when he started the combination therapy with TKIs Dabrafenib and Trametinib at a reduced dose. The therapy obtained a complete response, although, after 2 years of treatment, the patient suffered from an episode of AKI, associated with diffuse itch, nausea, abdominal pain and proteinuria, that required hospitalization. He was then diagnosed with drug induced renal injury and treated with steroids, with rapid relief. The patient didn't take any new drug that could interfere with the metabolism of TKIs. Interestingly, he had an increased frequency of rosacea flares during the treatment, with one of these episodes occurred almost simultaneously with the onset of AKI. Moreover, eosinophil and monocyte count followed the trend of creatinine, although it didn't get over the range limit.
Discussion: We reviewed the literature and only found a recent case report describing a granulomatous nephritis associated with Dabrafenib and Trametinib that occurred after 18 months of treatment (3), which interestingly have some common traits with our case. We speculate that TKIs Dabrafenib and Trametinib could have produced a dual toxicity on the renal function: a direct toxic effect on podocytes due to the expression of BRAF by these cells (4), which determined proteinuria, and a systemic, immune-mediated toxicity that appeared in the form of interstitial nephropathy (5).
Conclusion: in patients who have predisposing factors or who need to take potentially nephrotoxic drugs, the risk, although rare, of developing AKI should be considered before starting the treatment with TKIs Dabrafenib and Trametinib. For this reason, measuring creatinine and proteinuria before the treatment start and during the therapy could be recommended in these patients.

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SUDDEN RELAPSE/PROGRESSION OF DISEASE AND RAPID DEATH SHORTLY AFTER THE OCCURRENCE OF VITILIGO-LIKE DEPIGMENTATION DURING TARGETED THERAPY

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Vitiligo-like depigmentation is a relatively common cutaneous side effect in patients with metastatic melanoma during treatment with immunotherapy (anti-CTLA4 and anti-PD1).
Recent studies suggest that BRAFi/MEKi targeted therapies also induce an immune response against melanoma, via multiple mechanisms involving the immune microenvironment. In particular, the MAPK pathway is implicated in the immune cell function and survival, therefore BRAFi and MEKi influence immune functions. The immunologic effects of BRAFi increase antigen presentation and antigen-specific T cell recognition, and improve T cell effector functions. Moreover, BRAFi induce an immune stimulation via the upregulation of melanocyte differentiation antigens (MDA) and MHC expression in BRAF mutant melanoma.
We report two cases of vitiligo-like depigmentation in stage IV melanoma under targeted therapy, both followed by the sudden occurrence of relapse/progression rapidly eventuating into death. The first case concerns a 48 y.o. woman with stage IV (M1b. lung), while the second a 60 y.o. man with stage IV (M1c, lung and bone), both treated by the association of dabrafenib and trametinib. Both patients obtained a very good and persistent partial remission, developing a vitiligo-like depigmentation on the face & neck after approximately 24 months of treatment. After 4 and 6 months, respectively, both patients experienced the sudden occurrence of relapse/progression of disease, with multiple site spread of disease including CNS. We would like to stress the interesting time correlation between the development of vitiligo-like depigmentation, presumably related with melanoma cell destruction as a consequence of enhanced immune response to melanoma and mostly considered a good prognostic sign, and a dramatic change in the course of disease. This evenience, apparently hard to explain, could be interpreted as the result of immune escape rapidly following a strong immune reaction.

Relevant and durable response to pembrolizumab in a case series of patients with metastatic ocular melanoma

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Background. Ocular melanomas (OMs) are a rare form of malignancy arising from the melanocytes of the uveal tract, conjunctiva, or orbit. OM is the second most common type of melanoma after cutaneous and the most common primary intraocular malignant tumor in adults (1). Uveal melanoma (UVM) is the most common type of OM and is characterized by activation of the MAPK pathway via mutations in GNAQ or GNA11, while conjunctival melanomas (CM) are far less frequent. The biologies of UVM and CM are distinct from each other, as well as from that of cutaneous melanoma. No standard treatment has been defined for either metastatic UVM or CM. Antibodies inhibiting the programmed death receptor 1 (PD-1) have demonstrated significant activity in the treatment of advanced cutaneous melanoma, while the efficacy and safety of PD-1 blockade in patients with OM has not been well characterized and not yet shown convincing efficacy (2).
Methods. Herein we report our experience with 3 patients with metastatic OMs (uveal tract, n=2 and conjunctiva, n=1) treated with anti PD-1 antibody pembrolizumab as first-line therapy. Therapy was administered at the approved dosing schedule of 2 mg/kg q3w. The efficacy was evaluated in terms of progression-free survival (PFS) and response rate. Toxicity was also assessed.
Results. All cases have shown responses. No patients developed ocular toxicity or loss of vision. Toxicity was mild, without grade 3-4 side effects.
Conclusions. As patients with OMs were excluded by clinical trials of ICIs in melanoma, data with ICIs in OM are mainly based on retrospective studies. However, the immune system seems to play a remarkable role also in this disease as evidenced by better survival outcomes in patients with some types of autoimmune disease. Further knowledge on the immunological backbone of OM could allow the selection of patients who may benefit more from immunotherapy. Additional studies are needed to identify new targets to enhance anti-tumor immunoreactivity. Although this cohort of patients is small, to our knowledge this is the first case series of patients with different OMs being treated with anti-PD1 therapy. In the absence of a clinical trial, treatment with pembrolizumab appears to be a viable option for patients with OMs.

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COMUNICAZIONI ORALI SELEZIONATE

SESSIONE 1 EPIDEMIOLOGIA, GENETICA E PATOGENESI

Mutation screening comparison between primary and metastatic melanomas

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Background. Cutaneous malignant melanoma (CMM) is one of the most common skin cancers worldwide. Limited information is available in the current scientific literature on the concordance of genetic alterations between primary and metastatic CMM. In the present study, we performed next-generation sequencing (NGS) analysis of the main genes participating in melanoma pathogenesis and progression, among paired primary and metastatic lesions of CMM patients, with the aim to evaluate levels of discrepancies in mutational patterns.
Methods. Paraffin-embedded tumor tissues of the paired lesions were retrieved from the archives of the institutions participating in the study. NGS was performed using a specific multiple-gene panel constructed by the Italian Melanoma Intergroup (IMI) to explore the mutational status of selected regions (343 amplicons; amplicon range: 125-175 bp; coverage 100%) within the main 25 genes involved in CMM pathogenesis; sequencing was performed with the Ion Torrent PGM System.
Results. A discovery cohort encompassing 30 cases, and a validation cohort including eleven Sardinian patients with tissue availability from both the primary and metachronous metastatic lesions were identified; the global number of analyzed tissue specimens was 90. A total of 829 genetic non-synonymous variants were detected: 101 (12.2%) were pathogenic/likely pathogenic, 131 (15.8%) were benign/likely benign, and the remaining 597 (72%) were uncertain/unknown significance variants. Considering the global cohort, the consistency in pathogenic/pathogenic like mutations was 76%. Consistency for *BRAF* and *NRAS* mutations was 95.2% and 85.7% respectively, without statistically significant differences between the discovery and validation cohort.
Conclusions. Our study showed a high level of concordance in mutational patterns between primary and metastatic CMM, especially when pathogenic mutations in driver genes were considered.

The Melanoma Unit of Sassari (MUS) includes the following members who participated as investigators in this study: Maria Filomena Dedola, Maria Antonietta Fedeli, Maria Antonietta Montesu, Stefano Profili, Corrado Rubino, Rosanna Satta, Tiziana Scotto, Germana Sini (Sassari, Italy). The Italian Association for Cancer Research (AIRC) Study Group includes the following members who participated as investigators in this study: Michele Maio (Siena, Italy), Daniela Massi (Florence, Italy), Andrea Anichini (Milano, Italy), Ulrich Pfeffer (Genoa, Italy). The Italian Melanoma Intergroup (IMI) includes the following additional members who participated as investigators in this study: Anna Maria Di Giacomo (Siena, Italy); Paola Ghiorzo (Genova, Italy), Paola Queirolo (Milan, Italy); Mario Mandalà (Bergamo, Italy); Pietro Quaglino (Torino, Italy), Vanna Chiarion Sileni (Padova, Italy); Ignazio Stanganelli (Meldola, Italy).

Analisi età-periodo-coorte dei trend d'incidenza del melanoma cutaneo in Italia

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Introduzione/Background. Questo studio, parte di un progetto collaborativo fra l'Intergruppo Italiano Melanoma (IMI) e i Registri tumori di popolazione italiani, aveva lo scopo di valutare i tassi di incidenza del melanoma cutaneo maligno in Italia, per sesso e area geografica, e le loro tendenze temporali.
Materiali e metodi. I Registri tumori di popolazione italiani aderiscono ad un'associazione (AIRTUM) che ne valuta la qualità e gestisce una banca dati comune. Sono stati calcolati i tassi d'incidenza per 100.000 abitanti/anno del periodo 1994-2013, standardizzati sulla popolazione europea 2013. Utilizzando modelli di regressione joinpoint, le tendenze temporali sono state espresse come variazione percentuale annua stimata (APC). I dati d'incidenza, inoltre, sono analizzati con un approccio età-periodo-coorte.
Risultati. Hanno aderito 38 Registri che coprono una popolazione residente pari a circa 20.000.000 di abitanti. Nel periodo 1994-2013, sono stati diagnosticati 55.393 nuovi casi di melanoma cutaneo maligno (45.995 al Centro-Nord e 9.398 al Sud). Il tasso d'incidenza complessivo, riferito al 2010, è di 18.0/100.000 (uomini) e 15.4 (donne). È presente un forte gradiente geografico in entrambi i sessi, con tassi che variano per gli uomini tra 20.8 (Nord), 24.9 (Centro) e 11.3 (Sud) e per le donne, rispettivamente 17.5, 19.8 e 10.6. In entrambe le aree geografiche (Centro-Nord e Sud) e in entrambi i sessi, l'incidenza è aumentata regolarmente (anche se con intensità diversa) in tutte le fasce d'età (15-39, 40-59, 60-79, 80+ anni). L'analisi età-periodo-coorte mostra significativi effetti (non lineari) di periodo e di coorte per gli uomini del Centro-Nord. Nell'ultimo periodo (2009-2013) l'aumento del rischio è più modesto e per l'ultima coorte di nascita (anno mediano 1994) il rischio è inferiore rispetto alle coorti precedenti. Per quanto riguarda le donne, i risultati sono simili. Anche per l'Italia meridionale, in entrambi i sessi, si osserva un significativo effetto di coorte con una diminuzione dell'incidenza per la coorte più recente.
Conclusioni. L'incidenza totale di MMC in Italia è aumentata costantemente durante il periodo di studio. La tendenza in corso per le coorti recenti, tuttavia, è compatibile con l'inizio di una diminuzione dipendente dalla coorte di nascita nel rischio di malattia. Questo andamento, possibile effetto di interventi di prevenzione primaria (consapevolezza del rischio da UV, minore esposizione e maggior protezione), dovrà essere monitorato e confermato nel tempo.

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SESSIONE 2 PREVENZIONE E STRATEGIE DIAGNOSTICHE

Screening mutazionale multigenico basato su approccio NGS in melanomi escissi dopo valutazione con microscopia confocale a riflettanza (RCM)

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Introduzione: La Microscopia Confocale a Riflettanza (RCM) rappresenta una metodologia non invasiva per la diagnosi precoce dei tumori cutanei ed in particolar modo ha incrementato sia la accuratezza diagnostica del melanoma, mediante un incremento della sensibilità e specificità diagnostica delle lesioni cutanee pigmentate e non, sia il rapporto benigno/maligno delle lesioni cutanee escisse (B/M ratio) che il rapporto tra i melanomi spessi/sottili. Ulteriori potenziali informazioni potrebbero essere ottenute attraverso la correlazione tra le caratteristiche fenotipiche RCM dei melanomi e le varianti genetiche dei principali geni coinvolti nella patogenesi molecolare del melanoma.
Metodi: Abbiamo selezionato 16 pazienti (10 m, 6 f) di età compresa tra 33 e 89 anni, che presentavano lesioni pigmentate sospette per melanoma in dermoscopia, sottoposte a valutazione RCM ed escissione chirurgica. I tessuti tumorali inclusi in paraffina sono stati sottoposti ad analisi mutazionale di *next-generation sequencing* (NGS) con specifico pannello dell'Intergruppo Melanoma Italiano (IMI), contenente i 25 principali geni coinvolti nella melanomagenesi; l'analisi NGS è stata eseguita su piattaforma Ion S5-GeneStudio.
Risultati: Abbiamo esaminato 16 melanomi (8 a diffusione superficiale, 1 nodulare, 6 in situ, 1 lentigo maligna), localizzati a: tronco (N=8), arti superiori (N=2) e inferiori (N=5), volto (N=1). Le lesioni sono state valutate con RCM secondo criteri di Pellacani et al. 2009. Nello strato epidermico, 87,5% mostra pattern regolari tipo a nido d'ape; solo in 2 lesioni è stato riscontrato un pattern epidermico disorganizzato (12,5%). Le cellule pagetoidi nello strato epidermico sono presenti solo in 4 lesioni con aspetti prevalentemente rotonde/poligonali, di bassa o moderata densità, e prevalentemente localizzate. A livello della giunzione dermo-epidermica, si evidenzia un pattern prevalentemente ad anello (62,5%), di cui il 40% atipico, seguito da un pattern aspecifico nel 31,25% delle lesioni; solo una lesione presentava un pattern a zolla. La valutazione degli aggregati cellulari evidenzia una lieve predominanza di nidi giunzionali tipici, mentre per quanto riguarda i nidi dermici si osserva una dominante presenza di aggregati disomogenei (50%) seguiti da aggregati di tipo omogenei (33,3%) ed una lesione con aspetti cerebriformi (16,6%). Il 37,5% delle lesioni evidenziava la presenza di aggregati cellulari in strutture tipo-foglio. In 15/16 (93,75%) melanomi esaminati sono state evidenziate cellule atipiche a livello della giunzione dermo-epidermica con aspetti prevalentemente di tipo rotondo/poligonale (53,3%) e polimorfo (46,66%), con densità moderata (40%) ed elevata (40%) e prevalentemente sparse (40%) e diffuse (53,3%). Nello stroma è possibile osservare melanofagi e cellule infiammatorie rispettivamente nel 33,3% e 75% delle lesioni esaminate, mentre solo il 18,75% dei melanomi evidenzia vasi ematici. Considerando come criteri di selezione delle

varianti nucleotidiche il coverage >100 reads ed una frequenza allelica >5%, abbiamo identificato un totale di 482 varianti (SNV, MNV, INDEL). I geni maggiormente trovati mutati nella nostra serie sono: ARID2, BAP1, DDX3X, NF1 e TP53. Tra i geni del pathway MAPK, solo 4 (25%) casi presentano una mutazione patogenica in BRAF (tre casi: V600E) o NRAS (Q61L).
Conclusioni: Le analisi di correlazione statistica sono in corso.

Impatto dell'uso di farmaci con proprietà fotosensibilizzanti nella progressione del melanoma: studio retrospettivo bicentrico

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Introduzione: La terapia farmacologica per patologie sistemiche è stata recentemente oggetto di numerosi studi epidemiologici volti ad individuare un loro ruolo nei soggetti affetti da melanoma. Alcuni farmaci usati per il trattamento di patologie molto comuni, quali antipertensivi, anticoagulanti, antidiabetici presentano un noto effetto fotosensibilizzante sulle cellule cutanee; tale proprietà determina un'anomala risposta cutanea alla radiazione solare,quest'ultimo noto ed importante fattore di rischio per l'insorgenza di melanoma cutaneo.
Materiali e metodi: E' stato effettuato uno studio retrospettivo sui dati clinici ed anamnestici di pazienti afferenti all'Ambulatorio Melanoma dell'U.O. di Dermatologia del Policlinico S.Orsola Malpighi, Bologna e dell' IDI - IRCCS (Roma).
Risultati: Dal nostro database sono stati identificati 590 con dati clinico-anamnestici completi e un follow-up di almeno 5 anni. Di questi 383 (65.0%) utilizzavano regolarmente almeno un farmaco. Fra di essi 288 (75.2%) erano in trattamento con almeno un farmaco con capacità fotosensibilizzante. All'interno di quest'ultimo gruppo, 162 pazienti (56.3%) assumevano un solo farmaco fotosensibilizzante e 126 (43.7%) facevano uso di 2 o più di questi. Analizzando i pazienti che usavano due o più farmaci si è rilevato un rischio tre volte superiore di progressione della neoplasia, specialmente nei pazienti di sesso femminile.
Conclusioni: L'obiettivo di questo studio è stato quello di valutare un'eventuale correlazione fra l'assunzione cronica di farmaci con proprietà fotosensibilizzanti e l'insorgenza di melanoma valutando l'impatto sui suoi principali parametri prognostici istopatologici. Dai risultati emersi sembrerebbe che esista un maggior rischio di progressione nei pazienti che assumono contemporaneamente più di due farmaci con effetto fotosensbilizzante.Tale dato se confermato su casistiche multicentriche più ampie, avrebbe un ruolo importante nella gestione del paziente con pregresso melanoma.

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SESSIONE 3 CLASSIFICAZIONE PATOLOGICA E MOLECOLARE

Prognostic impact of the extent of ulceration in cutaneous melanoma: a multi-institutional Italian study of 477 cases.

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Background. Ulceration has been recognized as an adverse prognostic factor in primary cutaneous melanoma (PCM) with associated increased risk for recurrence and mortality (1-5). The aim of this study was to retrospectively investigate whether the extent of ulceration (EU) has a prognostic impact on relapse free survival (RFS) and overall survival (OS) in PCM.
Methods. Consecutive patients with primary cutaneous ulcerated melanoma included in prospectively collected IMI databases were enrolled in this study. EU and the percentage of ulceration (defined as the ratio of the EU to the maximum diameter of the dermal-invasive component) were evaluated on H&E sections

representative of the primary melanoma. Breslow thickness (BT) was categorized as equal or lower than 2 mm, between 2 mm and 4 mm and higher than 4 mm. Univariate and multivariable Cox proportional hazard models stratified by center were used to analyse the independent impact of the EU on RFS and OS.
Results. 477 patients diagnosed with primary cutaneous ulcerated melanoma during 1993-2016 were included. The mean EU was 2.2 mm, 4.8 mm and 9.0 mm in the lower (equal or lower than 2 mm), intermediate (between 2 and 4 mm) and higher (more than 4 mm) BT category. A significant negative impact of the increase of the EU on RFS (HR[1 mm increase] 1.32, 95% CI 1.16 – 1.51, p<0.0001) and OS (HR 1.27, 95% CI 1.11 – 1.45, p=0.0006) was found in patients with BT ≤ 2 mm, after stratifying by center and adjusting for TILs, regression, age and gender. The ulceration percentage was also detected as a risk factor for RFS (HR 1.01, 95% CI 1.00 – 1.02, p=0.0125) and OS (HR 1.01, 95% CI 1.00 – 1.02, p=0.0314). No impact of the EU or ulceration percentage was detected in patients with BT between 2 and 4 mm and higher than 4 mm. The presence of TILs improved the RFS and OS in melanomas with BT between 2 and 4 mm and >4 mm.
Conclusions. In our cohort we demonstrate the significant prognostic impact of the EU in patients with BT ≤2 mm. Incorporating this parameter in pathology reports could serve as a better stratification criterion for staging and management of patients with cutaneous melanoma.

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MICROENVIROMENT IN PRIMARY MELANOMA: IMMUNOPROFILING NANOSTRING ANALYSES

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Introduction: Histologic regression (HR) in melanoma has been defined as the replacement of tumor cells by an inflammatory (mainly lymphocytic) infiltrate, non-laminated dermal fibrosis, melanophagocytosis, and telangiectasia. A specific subsets of T-helper lymphocytes are associated with anergy and hampering CD8+ immune response against cancer cells.
Materials: The study is part of a ministerial grant for the Department of Medical Sciences (University of Turin) (TESEO).96 consecutive patients were included (46 HR melanoma and 50 not HR melanoma). NanoString nCounter technology was used to measure relative expression levels of immune genes within the tumor microenvironment: 300 ng of total RNA from each sample were hybridized to the nCounter PanCancer Immune Profiling panel. This panel detects the expression of 770 mRNA targets: 730 immune related genes and 40 housekeeping genes.
Results: Out of the 19 candidate genes differently expressed in HR melanoma towards not HR ones,12 resulted up-regulated in melanoma samples with HR (*RPS6,IL11RA,TP53,NOTCH1,EGR2,EGR1,ABL1,CFD,ZNF205,NFATC1,ICOSLG,ECIST*) and 7 up-regulated in melanomas without HR*(IL1B*,*BIRC5*,*PBK*,*CDK1*,*CXCL1* e *CD47)*.In particular the higher expression of *RPS6, TP53, NOTCH1, ABL1* suggests a more conserved cell cycle control, apoptosis and proliferation in HR melanomas.
HR melanomas showed a higher expression in term of mRNA normalized count of *CD3E*, *CD4*, *CD8B*, *FOXP3* and *FOXP3/CD4* ratio than not HR melanomas.
HR melanomas showed a higher score of expression profile genes referred to Th1 cells in term of Th1 cells score and also as ratio between Th1 cells and total TIL. Looking at Tumor Associated Macrophages, HR melanomas were characterized by an higher expression of *IL11RA* and *LTBR*, whereas an higher expression of *IL1B* and *CXCL1* was observed in melanomas without HR.
Conclusion: HR Melanomas are characterized by an higher expression of genes related to a more conserved and regulated environment in term of cell cycle regulation, proliferation, and efficient immunity against tumor supporting the hypothesis of a better outcome of HR melanomas.

HIGH MELANOMA RISK IN NON-MELANOMA SKIN CANCER PATIENTS UNDER AGE 40: A LARGE RETROSPECTIVE COHORT STUDY

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Background. Patients with a history of non-melanoma skin cancer (NMSC) are at increased risk for other primary cancers(1), in particular for cutaneous melanoma(2). However rarely such studies are able to identify age-specific risks due to the lack of statistical power(3). Our study was performed to compare the risk of melanoma within age groups in a large cohort of NMSC patients and in a control group of non-dermatological patients of the same hospital.
Methods. A retrospective linkage analysis was performed between records of hospitalizations and the occurrence of melanoma was compared within 10-year age group by computing the relative risk (RR) and modeled using multiple logistic regression.
Results. The linkage procedures identified 30,929 individuals with NMSC and 25,956
control patients. Overall, NMSC patients had RR for melanoma of 6.2 compared to controls. The overall RR for melanoma was approximately the same in males and females (6.1 and 5.6, respectively). The most striking result concerns the age-specific RR for melanoma, in particular in the younger age groups. In fact, patients with NMSC and less than 40 years of age have a RR of melanoma of 25.1 compared to vascular surgery patients of the same age. The RR for the age group 40-49 was 10.4, and in the older age groups it progressively decreases to 4.2 in subjects 70-year old or older.
Limitations. Our study is a retrospective analysis, and our ICD-9 codes do not distinguish between Basal Cell Carcinoma and Squamous Cell Carcinoma, nor between subtypes of melanoma.
Conclusions. Our large study suggests that prevention of melanoma in NMSC patients is mandatory, especially for patients which develop a NMSC under 40 years of age.

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SESSIONE 5 LA GESTIONE INTEGRATA DELLA FASE AVANZATA DI MALATTIA

Efficacia del trattamento locale del melanoma primario con elettrochemioterapia intraoperatoria.

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Introduzione: L'elettrochemioterapia (ECT) si è dimostrata un'efficace modalità di trattamento nei confronti di diverse tipologie tumorali (1) come trattamento palliativo, ma anche come neoadiuvante con finalità citoriduttve (2,3). Tuttavia, nessuno studio, ha valutato l'efficacia dell'ECT nei melanomi primitivi. L'obiettivo di questo studio è valutare l'efficacia dell'ECT nel ridurre il rischio di recidiva locale e metastasi in transit, oltre a quello di metastasi a distanza nei melanomi primitivi con spessore > o uguale a 3mm sec. Breslow.
Materiali e Metodi: Sono stati inclusi nello studio i pazienti operati presso l'U.O. di Chirurgia Plastica del Policlinico Universitario Sant'Orsola-Malpighi dal 2012 al 2015 per allargamento di melanoma con spessore > o uguale a 3mm sec. Breslow (associato o meno alla ricerca del linfonodo sentinella). Questi pazienti sono stati suddivisi in 2 gruppi: al primo è stata associata l'esecuzione di ECT con infusione di Bleomicina; il secondo ha eseguito solo la procedura di allargamento.
Risultati: I pazienti inclusi nello studio sono stati 59; 27 pazienti sono stati inclusi nel gruppo con ECT, 32 pazienti invece nel gruppo senza ECT. Nel gruppo senza ECT sono state diagnosticate 11 recidive locali o metastasi in transit (34.4%) con un tempo libero da malattia di 32.8 mesi; nel gruppo con ECT sono state diagnosticate 5 ricorrenze di malattia (18.5%) con periodo libero da malattia medio di 40.9 mesi. Queste differenze purtroppo non raggiungono la significatività statistica. Per quanto riguarda le metastasi a distanza, linfonodali o viscerali, i casi totali evidenziati sono stati 18, con una incidenza del 22.2% nel gruppo con ECT contro il 37.5% del gruppo senza ECT. Il tempo medio libero da metastasi risulta di 10 mesi maggiore nel gruppo con ECT. Anche in questo caso non viene raggiunta la significatività statistica.
Conclusione: Nonostante non sia stato possibile raggiungere la significatività statistica, verosimilmente per il ridotto numero di pazienti arruolati, l'ECT potrebbe risultare un trattamento efficace per melanomi primitivi del ridurre sia il rischio di recidive locali o metastasi in transit, sia di metastasi a distanza.

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La biopsia del linfonodo sentinella nel melanoma dei genitali

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Introduzione
Il melanoma dei genitali è un tumore estremamente raro. Il melanoma vulvare rappresenta circa il 5% dei tumori localizzati in questa sede e il melanoma del pene circa lo 0,7% dei tumori del pene e lo 0,18% dei casi di melanoma (1, 2). Il melanoma dei genitali è caratterizzato da una scarsa sopravvivenza e da alti tassi di recidiva, tanto che il melanoma vulvare viene considerato come un'entità autonoma di melanoma mucosale. Il trattamento chirurgico rappresenta la principale opzione terapeutica, mentre la gestione dei linfonodi loco-regionali è dibattuta. La biopsia del linfonodo sentinella (BLS) è divenuta lo standard of care per la stadiazione del melanoma cutaneo, ma il suo ruolo nei tumori dei genitali è controverso.
Materiale e metodi
La BLS e' stata effettuata su 8 pazienti con melanoma dei genitali, 5 maschi e 3 femmine di eta' <80 anni, melanoma >1 mm, in assenza di segni clinici ed ecografici di malattia. Tutti i pazienti hanno effettuato linfoscintigrafia ed iniezioni di colorante vitale pre-operatorie. Sono stati asportati i linfonodi blu e i linfonodi con conta ≥10% rispetto al linfonodo maggiormente radioattivo ex-vivo.
Risultati
L'età media dei pazienti è stata di 55 anni e lo spessore medio del melanoma 2,6 mm. Il linfonodo sentinella (LS) è stato identificato in tutti i pazienti. In tre pazienti il drenaggio è risultato essere bilaterale, in cinque pazienti monolaterale. In tre casi il LS è risultato positivo. I depositi metastatici nel LS sono risultati di dimensioni >1 mm o parenchimali multifocali.
Conclusioni
La BLS nel melanoma dei genitali è ancora oggetto di studio e i dati a disposizione in letteratura sono limitati. Nella nostra esperienza la tecnica è risultata applicabile con successo anche in questa sede anatomica permettendo di identificare tre casi altrimenti sottostadiati. In considerazione dell'elevata aggressività del melanoma in tali sedi, la BLS puo' risultare utile per selezionare i pazienti che possono maggiormente beneficiare di trattamenti chirurgici di completamento e adiuvanti precoci.

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SESSIONE 7 PROBLEMATICHE DEL TRATTAMENTO SISTEMICO NELLA MALATTIA AVANZATA

Get your act together: the management of oligoprogression in the landscape of new therapies for metastatic melanoma

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Background: A limited degree of progression after a response to systemic treatment is labelled as oligoprogression. The rogue progressive metastases could benefit from local treatment which could allow to continue the ongoing systemic therapy beyond progression (TBP).
We aimed to define the incidence of oligoprogression among the entire population of metastatic melanoma (MM) treated with targeted or immunotherapy and how long the local therapies share to disease control and survival. We also find out which patients benefit from TBP.
Methods: We retrospectively reviewed 214 MM from our Institution and selected patients who developed oligoprogression during BRAF/MEK or PD1 inhibitors and received a local treatment while continuing TBP. We performed a univariate and multivariable analysis to assess the association between therapy outcomes and a series of clinical and biological features.
Results: We identified 27 oligoprogressed patients (incidence 10%) treated locally with surgery (14), radiosurgery (11) and electrochemotherapy (2). TBP included PD-1 inhibitors (13) and BRAF/MEK inhibitors (14). The median post-oligoprogression progression free survival (POPFS) was 14 months (5-19 95% C.I.). In the univariate analysis, a longer POPFS was associated with complete response (CR) (p=0,001 HR 95% C.I. 2,9 (1,1-7,7)), ECOG PS 0 (p=0,0008, HR 95% C.I. 8,5 (2,4-30)), neutrophils/lymphocytes ratio (N/L) <2 (p=0,02 HR 95% C.I. 3,1 (1,1-8,7)), and PFS from beginning of treatment >11 month (p=0,03 HR 95% C.I. 2,8 (1,05-7,9)). Nevertheless, in multivariable analysis, only CR (p=0,004, HR 95% C.I. 4,1 (1,5-10,8)) and N/L <2 (p=0,03, HR 95% C.I. 3,1 (1,09-8,8) were found associated with POPFS. The mOS post-oligoprogression was 19 months (range 11-25; 95% C.I.) while the mOS was 38 months (range 16-38 95% C.I.) with 48% of patient alive at the time of the analysis. In multivariable analysis a longer OS was associated with ECOG PS, LDH <ULN, N/L <2, PFS>11 months and surgery as local treatment.
Conclusions: In selected patients, local treatments are able to control oligoprogression for a long time permitting to continue systemic treatment and prolong OS. Increasing biological knowledge and clinical experiences are improving the accuracy in identifying patients to apply for local ablative therapies to propose the right treatment to the right patient at the right time.

Clinically Occult Metastases in Sentinel Lymph Nodes from Melanoma Patients are associated with the presence of IDO+ Tolerogenic Langerhans Cells

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Background. Langerhans cells (LCs) play crucial roles in skin immune responses, driving immunity or self-tolerance depending on their maturation state. However, many tumours, particularly melanoma, are able to evade the immune system setting up tumour tolerance through different escape mechanisms, mainly altering DC functions and inducing the expression of the tolerogenic enzyme indoleamine 2,3-dioxygenase (IDO1) (1).
IDO1 expression has been detected in sentinel lymph node (SLN) of melanoma patients, associated with melanoma metastases thus with a negative prognostic role (2), particularly in dermal- and plasmacytoid- dendritic cells subsets. IDO1 expression in SLN LCs is unknown. SLN LCs exhibit an immature immunophenotype in melanoma patients, expressing low CD83 levels, the typical DC maturation marker (3). Notably, only a fraction of mature *in-vitro* migrated LCs from healthy human skin expressed IDO1 (4).
Methods. To elucidate the relation between tolerance and maturation, we analyzed IDO1 and CD83 expression in SLN LCs from melanoma patients, using specific monoclonal antibodies, flow cytometry and fluorescent immunohistochemistry.
Results. Beside few IDO1+ SLN LCs, the simultaneous analysis of IDO1 and CD83 expression revealed the presence of four different SLN LCs subsets: *real mature* $IDO1^{-}CD83^{+}$; *real immature* $IDO1^{-}CD83^{-}$; *tolerogenic mature* $IDO1^{+}CD83^{+}$; and *tolerogenic immature* $IDO1^{+}CD83^{-}$. Only the latter subset was significantly increased in SLNs with melanoma metastases, as compared to SLNs without metastases ($p<0.05$) and in SLN LCs from patients with primary melanoma with mitosis rate (MR) ≥ 2 as compared to MR ≤1 ($p<0.05$).
Conclusion. These results extend the current knowledge on SLN LCs and tumour tolerance and might represent a key point for designing novel immunotherapeutic approaches in melanoma patients, involving IDO1 inhibitors.

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Body-mass index (BMI) and outcome of metastatic melanoma patients receiving targeted therapy and immunotherapy: a multicenter international retrospective study

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Background: Obesity is a risk factor for malignancy, however its prognostic role on survival of metastatic melanoma (MM) patients is controversial. We aim to investigate the role of body mass index (BMI) in MM patients receiving targeted and/or immunotherapy alone or as a sequence.
Methods: Data on MM patients receiving ≥ 1 line of systemic treatment were retrieved from prospectively collected databases. Progression free (PFS) and overall survival (OS) were analyzed by means of multivariable stratified Cox regression models; disease control rate (DCR) was analyzed by multivariable stratified logistic regression models. A subgroup analysis was planned according to the treatments received and the sequential strategy. All multivariable models included BMI, age, sex, AJCC VIII edition stage, performance status, LDH and treatment sequence strategy as covariates.
Results: Between November 2010 and November 2018, 688 patients from 3 Italian and 2 Polish centers were enrolled. 403 (57%) patients had M1c/d disease, 273 (41%) were female and the mean BMI was 27.05 (sd=4.89). BMI impacted differently on OS in patients who received targeted or immunotherapy: in the immunotherapy subgroup the hazard ratio [HR for 5-units increment] increased from 1.03 [95%CI: 0.87-1.22] at 6, to 1.18 [95%CI: 0.99 -1.40] at 12, up to 1.35 [95%CI: 1.04-1.74] at 18 months; while decreased from 0.94 [95%CI: 0.65-1.37] at 6, to 0.65 [95%CI: 0.41-1.02] at 12, up to 0.45 [95%CI: 0.21-0.96] at 18 months in those who received targeted therapy. No significant effect of BMI on PFS and DCR was found in any of the subgroup analyses.
Conclusions: In patients with MM the prognostic role of BMI on survival varies over time and differs according to the treatment received. The biological reason for this opposite effect is unclear and needs to be further investigated.

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