Abstract. Li-Fraumeni syndrome (LFS) is a cancer-prone, autosomal dominant syndrome caused by underlying germline gene mutations of \textit{TP53}, a tumor-suppressor gene encoding the p53 protein with a major role in apoptosis, DNA repair and cell cycle regulation. Cumulative cancer incidence for LFS patients by the age of 70 years is 80-100%, mostly involving adrenocortical carcinoma, brain tumors, bone and soft tissue sarcomas, leukemia and female breast cancer from the age of 20 years. Dominant negative \textit{TP53} variant is correlated with an increased tumorigenesis risk in LFS. Sporadic \textit{TP53} mutations are related to almost half of global cancers since p53 in addition to p73 protein represent essential players in anticancer cellular protection. Epidemiological aspects concerning skin cancers, especially malignant melanoma (MM), in LFS are less clear. A low level of statistical evidence demonstrates LFS cases with pediatric MM, multiple MM, spitzoid MM, atypical presentations, mucosal and uveal MM. Retrospective cohorts indicate a higher cumulative risk than the general population by the age of 70 years for MM and basal cell carcinoma. Non-syndromic and syndromic \textit{TP53} mutations are a major pathway of metastasis, including MM. In LHS, an important level of awareness involves skin cancers despite not being a part of the typical malignancy-containing picture. Additional data are crucially needed. However, at least one dermatologic control is a step in the multidisciplinary panel of surveillance of these patients; but in cases with benign and pre-malign pigmentation, serial dermatoscopy and full body photography are recommended for early melanoma detection in order to improve the prognosis and to reduce the overall malignancy burden.

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1. Introduction

Li-Fraumeni syndrome (LFS) is a cancer-prone, autosomal dominant, hereditary syndrome (1). Patient with LFS have a very early onset of underlying neoplasia during life; 10-15% of all malignancies in the pediatric population are found associated with LFS in addition to more than 100 gene anomalies, including the \textit{TP53} gene (1,2). Starting from childhood, early diagnosis of brain cancer, leukemia in addition to sarcomas of the skeleton and soft tissue, and adrenocortical cancer have been reported (3). In young females, there is a higher risk of mammary cancer (1). This particular aspect needs to be differentiated from other gynecological cancers with a hereditary pattern such as Peutz-Jeghers syndrome, Lynch syndrome, \textit{BRCA1-} and \textit{BRCA2}-associated disease, and Cowden syndrome (4).

Specific protocols of screening, management and lifelong surveillance for LFS patients have been developed (5). A large study on 286 subjects carrying a \textit{TP53} mutation (from
107 families) showed a cumulative cancer incidence of 100% (by the age of 70 years), and 50% by the age of 46 (males) and 31 years (females). Women have the most increased incidence of malignancy after the age of 20 years (because of mammary cancer, with a cumulative incidence of 54% by the age of 70) while men exhibit a high incidence early during childhood and later during adulthood. The cumulative incidence (by the age of 70 years) for females and males was found to be 15 and 22% respectively for soft tissue sarcoma, 5 and 11% respectively for osteosarcoma, 6 and 19% respectively for central nervous system tumors; with a second tumor diagnosed after a median of a decade in almost half of patients (6).

2. Aim of the review

The present review was designed with an aim to introduce a practical overview of published data regarding LFS and associated malignancies focusing on melanoma. This is a brief narrative review of literature underlying a PubMed research on LFS and associated malignancies, especially malignant melanoma (MM). Most of the published papers involving specific data on LFS and melanoma were found to be of a low level of evidence, mainly case reports or cases series, but also we found two retrospective studies. The perspective of approach was clinical and multidisciplinary. The inclusion criteria of the citations were full-length English papers that were recently published with the majority of the 61 articles published within the last three years. Due to the rarity of the topic, a heterogeneous level of statistical evidence was used in order to offer a real-life medical picture of the selected topic.

3. Genetic background: TP53 mutations

LFS is related to germline mutations of the TP53 gene (chromosome 17) with high penetrance. TP53 is a tumor-suppressor gene that encodes the p53 protein with a major role in apoptosis, DNA repair and cell cycle regulation (7). While germline mutations cause LFS, sporadic mutations are related to almost half of global cancers (mostly non-syndromic presentation), because the p53 protein in addition to p73 protein represent essential players in human body anticancer protection at the cellular level (8). The p53 protein is responsible for cell cycle function in order either to maintain adequate homeostasis or to induce cell cycle arrest thus causing cell death (9).

The mutation profile is a prognostic factor in associated malignancies; tumor heterogeneity being related to incomplete protein inactivation (7). Hotspot variant and truncating variants are correlated with a higher incidence of cancer and an earlier age at presentation (10). Dominant negative variant is generally recognized with an overall higher cancer risk (1). TP53 (R337H) mutation is particularly prevalent in Brazil where population clusters of pediatric adrenocortical carcinomas or sarcomas have been described (11). Not all TP53 carriers develop tumors through their entire lifespan, but those who do, are associated with a clinical picture of an 80-100% penetrance by the age of 70 years (12). Some aspects of the genotype-phenotype correlations are well known until present but there are still open issues (12). The timing of tumors in LFS includes the following: between birth and 15 years, adrenocortical carcinoma in association with choroid plexus carcinoma are prominent; between 16 and 50 years, breast cancers in females, sarcomas, astrocytoma, and leukemia are prominent; between 51 and 80 years, pancreatic carcinoma in both sexes and prostate cancer in males are prominent (12).

4. Tumorigenesis in Li-Fraumeni syndrome

We mention the importance of a general picture in LFS, which represents a standard multidisciplinary approach, both in terms of diagnosis and therapy (1). Yearly magnetic resonance imaging (MRI) is recommended for tumor screening (13). Whole-body sequences are mostly useful and, since the technique is not radiant, it is feasible in the pediatric population (14). In subjects with positive TP53 mutations, the protocol of imaging follow-up during childhood includes: annual whole body and brain MRI from the first year of life (and bi-annual abdominal ultrasound). In adults, yearly brain MRI should be implemented until the age of 50 years in addition to annual whole body MRI. For women, this should include annual mammary MRI until the age of 65-70 years (1).

LFS-related cancers, especially pediatric cancers are highly sensitive to radiotherapy (15). On the other hand, an alarming risk of radiation-induced second malignancy has been reported in carriers of TP53 germline mutations, as well as a higher risk in tumorigenesis caused by conventional genotoxic chemotherapy (16). For instance, the prevalence of secondary sarcoma is higher than that noted in the general population (15). It is essential to identify the TP53 status in patients with different malignancies who otherwise would be candidates for radiotherapy and genotoxic chemotherapy, because these therapeutic procedures should be avoided, if possible (1).

As mentioned, the large area of LFS-related tumorigenesis is extended as following. Osteosarcoma, the most frequent primary malignancy of the skeleton in children and teenagers and the third most frequent in adults, involves TP53 mutations in the majority of cases (17). RB1 mutations (retinoblastoma syndrome) are described in almost one-fifth of osteosarcoma cases, while other rarer syndromic circumstances involve Werner syndrome or Bloom syndrome (18).

Hereditary syndrome-related primary genitourinary rhabdomyosarcoma needs to be differentiated from DICER1 mutations, Noonan syndrome, Costello syndrome, neurofibromatosis type 1, and Beckwith-Wiedemann syndrome (19,20).

Since TP53 mutations represent an important cause of breast cancer before the age of 31 years, for cases with a positive TP53 mutation, annual screening should be performed as well as in TP53-positive patients who are survivors of mammary cancer (21). Overall, half of female patients with TP53 germline mutations present with breast cancer by the age of 70 years (22). On the other hand, in females presenting with a mammary malignancy at an early age and unknown genetic background, TP53 analysis should be assessed, especially if testing for BRCA1 and BRCA2 mutations is negative (23). A TP53 carrier, regardless of the full manifestation of LFS, has a 3 times higher risk of breast cancer when compared to the global population (except for BRCA1 and BRCA2 carriers) (24). Radiotherapy may be useful in breast cancer related to LFS or Li-Fraumeni-like syndrome, but the rate of radiotherapy-related malignancy represents a massive concern (25).
LFS is associated with a higher risk of tumors located in the central nervous system (such as astrocytoma, glioblas-
toma and choroid plexus carcinoma) and close surveillance is
necessary (26). Loss of TP53 function and gain of function in
mutant variants are both connected with brain cancers (27).

Hematologic malignancies associated with LFS have
also reported. These include leukemia of lymphoid type (acute
lymphoblastic leukemia) and of myeloid type (acute myeloid
or chronic myeloid leukemia), and myelodysplastic syndrome
and less often lymphoma (28). The potential of inducing these
disorders may be related to the actual therapy which is applied
for some concurrent solid cancers (such as radiotherapy or
certain types of chemotherapy) (29).

LFS has a dramatic impact on adrenocortical carcino-
ma incidence; 50–80% of subjects diagnosed with LFS
during infancy have syndromic TP53 mutation, while 10%
of adult cases have a genetic anomaly, either LFS or Lynch
syndrome (30). A high index of suspicion is necessary in
cases of children diagnosed with adrenal cancer and unknown
family medical history; TP53 analysis is indicated under these
circumstances (31,32).

5. Melanoma in patients with Li-Fraumeni syndrome

Patients with LFS have an increased lifetime cumulative rate
of different familial cancers as mentioned before; yet the exact
epidemiological data concerning skin cancers, especially MM,
are limited (33). Generally, it is considered that melanoma is
diagnosed less frequently in TP53 carriers when compared to
the previously mentioned neoplasias, but more frequent when
compare to the general population (33,34). Melanoma in the
pediatric population with LFS has also been reported (34).
Exceptional cases with multiple melanoma have been found,
as well (35,36). In addition, pediatric Spitzoid melanoma
which is not typically involved in syndromic associations,
was reported in a young patient with TP53 mutation, also
associated with choroid plexus carcinoma and myelodysplastic
syndrome (37).

Atypical forms of melanoma have been reported with a very
low level of evidence (38). A first case of mucosal melanoma
was reported in a female of 21 years as a first presentation of
LFS; hematologic malignancies were subsequently identified
among other family members caring the TP53 mutation (39).
Uveal MM has been described in a few cases (40). An analysis
of LFS and POT1 gene anomalies was assessed and incidental
diagnosis of melanoma was pointed out (41). A cases series
on two 28-year-old twins with LFS found familial melanoma,
suggesting that follow-up of moles based on dermoscopy and
total-body photography is helpful for early recognition of
melanoma in such cases (42). An unusual case of primary skin
leiomysarcoma was reported in 2018 in regards to a patient
with TP53 mutation (loss of heterozygosity) presenting with
LFS (43).

A retrospective Dutch study based on national registry data
included 71 patients diagnosed with different skin cancers from
33 families with LFS; 59% of the subjects with skin cancers
and LFS were females; the cumulative risk of skin cancers of
these patients depending on age was 10.4% at 40 years, 25.2%
at 60 years, and 44.6% at 70 years; the median age at diagnosis
of the dermatological malignancies was 41 years, independent
of other LFS-related cancers (44). In addition, by the age of
70 years, the cumulative risk for specific cancers was higher
than the general population for the same geographic area:
12.6% for melanoma and 34.6% for basal cell carcinoma (44).

Another retrospective single center study on 89 subjects
diagnosed between 2004 and 2015 with LFS showed a median
age at first tumor diagnosis (regardless of the site and the type)
of 25 years: 71% of individuals had primary multiple tumors
and 2/89 patients had skin cancer, with a similar incidence
for stomach, thyroid, lung carcinomas and leukemia in this
mentioned cohort (45).

For the differential diagnosis of a patient with melanoma
and tumors related to LFS including brain cancer, a case must
be mentioned concerning melanoma-astrocytoma syndrome
underlying CDKN2A tumor-suppressor gene mutations
(chromosome 9) (46).

On the other hand, non-syndromic mutations of the TP53
gene have been reported in many melanoma studies, as well as
the immunohistochemistry expression of p53 which generally
is associated with a poor prognosis (47). A genetic analysis
of 154 patients with metastatic disease from different carci-
nomas, adenocarcinomas and melanomas identified TP53
out of 790 mutations as the most common driven pathway
related with metastatic potential and drug resistance (48).
A study of 38 subjects with desmoplastic melanoma showed
a correlation between the depth of invasion and TP53 gene
mutation (P=0.002) (49). The p53 protein is related to skin
tumorigenesis, in terms of both melanoma and non-melanoma,
and it may represent a future target of standard therapy (50).
For instance, S-petasin is a molecule that activates the p53
pathway inducing anti-proliferative effects in melanoma cell
lines (51).

6. Future considerations

Overall, LFS represents a very challenging condition for
patients and physicians, as noted in other multiple endocrine
and non-endocrine tumor combinations based on a common
genetic background (52,53). The timing of surgery, whether
it includes adrenalectomy or melanoma removal, requires
a multidisciplinary team of evaluation for improving the
outcome but also the quality of life, not only the life span of
the patients (54,55). Whether or not hormonally active tumors
such as adrenal neoplasia and related neuroendocrine anoma-
lies promote the growth of MM, as suggested by some studies,
is still a matter of discussion (56,57). In addition, whether or not
the phenotype of MM is more severe or atypical in relationship
to the presence of other tumors and/or genetic anomalies is an
open issue; on the one hand the patient has multiple associ-
ted tumors thus a more severe overall prognosis; but, on the
other hand, since the patient has been diagnosed with a genetic
condition, he/she may be re-assessed more frequently for serial
check-ups (58,59). Various biomarkers such as the E-cadherin
family or TIMP proteins are suggested in order to be used as
prognostic factors for MM (60,61).

7. Conclusions

An important level of awareness involves skin cancer in LFS,
particularly melanoma, despite the fact that it is not a part of
the typical malignancy-containing picture. Patients with LFS seem to have a higher risk of developing MM when compared to the general population. The level of statistical evidence requires additional data to be conclusive. However, at least one dermatologic control is the first step in the multidisciplinary panel of surveillance of these patients; but in cases with benign and pre-malign pigmentations, serial dermatoscopy and full body photography are recommended for early melanoma detection in order to improve the prognosis and to reduce the overall malignancy burden.

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FS drafted the manuscript and critically revised the final form. MCD is the corresponding author and revised the references. AP researched the literature, MC drafted the manuscript in light of the literature data, RCP researched the literature data, and AG approved the final form after review of the literature data. All the authors read and approved the final form of the manuscript for publication.

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Competing interests

The authors declare they have no competing interests.

References

1. Frebourg T, Bajalica-Largercrantz S, Oliveira C, Magenheim R and Evans DG; European Reference Network GENTURIS: Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet 28: 1379-1386, 2020.
2. Miranda Alcalde B, Villa Alcázar M, Martínez Romera I and López Ibor J: The importance of Li-Fraumeni syndrome, a hereditary cancer predisposition disorder. Arch Argent Pediatr 119: e11-e17, 2021.
3. Fortuno C, Lee K, Olivier M, Pesaran T, Mai PL, de Andrade KC, Attard LD, Crowley S, Evans DG, Feng BJ, et al: Specifications of the ACMG/AMP variant interpretation guidelines for germ-line TP53 variants, Hum Mutat 42: 223-236, 2021.
4. Wade KS, Estes JM and Kline RC: Genetics and the Gynecologic Patient. Obscner J 20: 446-451, 2020.
5. Ueki A and Hirayama A: Molecular features and clinical management of hereditary gynecological cancers. Int J Mol Sci 21: 9504, 2020.
6. Mai PL, Best AF, Peters JA, DeCastro RM, Khincha PP, Loud JT, Bremer RC, Rosenberg PS and Savage SA: Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer 122: 3673-3681, 2016.
7. Monti P, Menichini P, Speciale A, Cutrona G, Fais F, Taiana E, Neri A, Bomben R, Gentile M, Gattei V, et al: Heterogeneity of TP53 Mutations and P53 Protein Residual Function in Cancer: Does It Matter? Front Oncol 10: 593383, 2020.
8. Zawacka-Pankau JE: The undervalued avenue to reinstate tumor suppressor functionality of the p53 protein family for improved cancer therapy-drug repurposing. Cancers (Basel) 12: 2717, 2020.
9. Levine AJ: p53: 800 million years of evolution and 40 years of discovery. Nat Rev Cancer 20: 471-480, 2020.
10. Fortuno C, Pesaran T, Mester J, Dolinsky J, Yussuf A, McGoldrick K, James PA and Spurdb ABL: Genotype-phenotype correlations among TP53 carriers: Literature review and analysis of probands undergoing multi-gene panel testing and single-gene testing. Cancer Genet 248-249: 11-17, 2020.
11. Volc SM, Ramos CRN, Galvão HCR, Felicio PS, Coelho AS, Berardinelini GN, Campacci N, Sabato CDS, Abrhaob-A-Machado LF, Santana IVV, et al: The Brazilian TP53 mutation (R337H) and sarcomas. PLoS One 15: e0227260, 2020.
12. Amadou A, Achatz MIW and Hainaut P: Revisiting tumor patterns and penetration in germline TP53 mutation carriers: Temporal phases of the Li-Fraumeni syndrome. Curr Opin Oncol 30: 23-29, 2018.
13. Consul N, Amini B, Ibarra-Rovira JJ, Blair KJ, Moseley TW, Taher A, Shah KB and Elsayes KM: Li-Fraumeni syndrome and Whole-body MRI screening: Screening guidelines, imaging features, and impact on patient management. AJR Am J Roentgenol 216: 252-263, 2021.
14. Grasparil AD II, Gottumukkala RV, Greer MC and Gee MS: Whole-body MRI surveillance of cancer predisposition syndromes: Current best practice guidelines for use, performance, and interpretation. AJR Am J Roentgenol 215: 1002-1011, 2020.
15. Iwasaki T, Mizumoto M, Numajiri H, Oshiro Y, Suzuki R, Moritani K, Eguchi M, Ishi E and Sakurai H: Re-irradiation using proton therapy for radiation-induced secondary cancer with Li-Fraumeni syndrome: A case report and review of literature. J Cancer Res Ther 16: 1524-1527, 2020.
16. Eulo V, Lesmana H, Doyle LA, Nichols KE and Hibre AC: Secondary sarcomas: Biology, presentation, and clinical care. Am Soc Clin Oncol Educ Book 40: 1-12, 2020.
17. Pang LK, Pena M, Zhao R and Lee DF: Modeling of osteosarcoma with induced pluripotent stem cells. Stem Cell Res 49: 102006, 2020.
18. Czarnecka AM, Synoradzki K, Firlej W, Bartnik E, Sobczuk P, Fiedorowicz M, Grieb P and Rutkowski P: Molecular biology of osteosarcoma. Cancers (Basel) 12: 2130, 2020.
19. Schneider KW, Cost NG, Schultz KAP, Svihovec S and Suttman A: Germline predisposition to genitourinary rhabdomyosarcoma. Transl Androl Urol 9: 2430-2440, 2020.
20. Sandru F, Carsote M, Valea A, Albu SE, Petca RC and Dumitrascu MC: Somatostatinoma: Beyond neurofibromatosis type 1 (Review). Exp Ther Med 20: 3383-3388, 2020.
21. Evans DG, Woodward ER, Bajalica-Largercrantz S, Oliveira C and Frebourg T: Germline TP53 testing in breast cancers: Why, when and how? Cancers (Basel) 12: 3762, 2020.
22. Le AN, Harton J, Desai H, Powers J, Zelley K, Bradbury AR, Nathanson KL, Shah PD, Doucette A, Freedman GM, et al: Frequency of radiation-induced malignancies post-adjuvant radiotherapy for breast cancer in patients with Li-Fraumeni syndrome. Breast Cancer Res Treat 181: 181-188, 2020.
23. Piombino C, Cortesi L, Lambrettini M, Punic K, Grandi G and Toss A: Secondary prevention in hereditary breast and/or ovarian cancer syndromes other than BRCA. J Oncol 2020: 6384190, 2020.
24. Fortuno C, James PA and Spurde AB: Current review of TP53 pathogenic germline variants in breast cancer patients outside Li-Fraumeni syndrome. Hum Mutat 39: 1764-1773, 2018.
25. Petry V, Bonadio RC, Cagnacci AQC, Senna LAL, Campos RDNB, Cotti GC, Hoff PM, Fragoso MCBV and Estvez-Diz MDP: Radiotherapy-induced malignancies in breast cancer patients with TP53 pathogenic germline variants (Li-Fraumeni syndrome). Fam Cancer 19: 47-53, 2020.
26. Orr BA, Clay MR, Pinto EM and Kesserwan C: An update on the central nervous system manifestations of Li-Fraumeni syndrome. Acta Neuropathol 139: 669-687, 2020.
27. Kong X, Zhang Y, Xiong S and Williams-Villalobo AE: A Glance of p53 functions in brain development, neural stem cells, and brain cancer. Biology (Basel) 9: 285, 2020.
28. Valdez JM, Nichols KE and Kesserwan C: Li-Fraumeni syndrome: A paradigm for the understanding of hereditary cancer predisposition. Br J Haematol 176: 539-552, 2017.

29. Swammanthan M, Bannon SA, Routhert M, Naqvi K, Kadia TM, Takahashi K, Alvarado Y, Ravandi-Kashani F, Patel KP, Champlin R, et al: Hematologic malignancies and Li-Fraumeni syndrome. Cold Spring Harb Mol Case Stud 5: a003210, 2019.

30. Jouinot A and Bertherat J: Diseases predisposing to adrenocortical malignancy (Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and carney Complex). Exp Suppl 111: 149-169, 2019.

31. Petr EJ and Else T: Adrenocortical carcinoma (ACC): When and why should we consider germline testing? Presse Med 47: e119-e125, 2018.

32. Carsote M, Gheorgian A, Terzea D, Gheorghian-Galateanu AA and Valea A: Cystic adrenal lesions: Focus on pediatric population (a review). Clujul Med 90: 5-12, 2017.

33. Kamihara J, Rana HQ and Garber JE: Germline TP53 mutations and the changing landscape of Li-Fraumeni syndrome. Hum Mutat 35: 654-662, 2014.

34. Baek YS, Seo JY, Song JY, Lee SY, Kim A and Jeon J: Li-Fraumeni syndrome presenting as cutaneous melanoma in a child: Case report and review of literature. J Eur Actad Dermatol Venereol 33: e174-e175, 2019.

35. Akay BN, Ocu Bepe A, Topcu V and Farabi B: A rare case of multiple cutaneous melanomas in Li-Fraumeni syndrome: A coincidental association or a component of the syndrome? Australas J Dermatol 60: e214-e216, 2019.

36. Curiel-Lewandrowski C, Speetzen LS, Cranmer L, Warneke JA and Loecher CJ: Multiple primary cutaneous melanomas in Li-Fraumeni syndrome. Arch Dermatol 147: 248-250, 2011.

37. Kolipara R, Cooley LD, Horii KA, Hetherton ML, Leboit PE, Singh V and Zwick DL: Spitzoid melanoma associated with Li-Fraumeni syndrome and atypical mole syndrome: Total-body digital photography, dermoscopy expression pattern in common melanocytic nevi. Virchows Arch 462 patients. J Fr Ophtalmol 22: 1054‑1063, 1999 (In French).

38. Jacqueim J, Perron E, Pissaloux D, Alberti L and de la Fouchardière A: Atypical cutaneous melanocytic tumours arising in two patients with Li-Fraumeni syndrome. Pathology 49: 801‑805, 2017.

39. Klein JD and Kupferman ME: Li-Fraumeni syndrome presenting as mucosal melanoma: Case report and treatment considerations. Head Neck 39: E20-E22, 2017.

40. Hajkova N, Höyj J, Nemecjova K, Dnndr P, Ulynych J, Jirsova K, Glezgova J and Ticha I: Germline mutation in the TP53 gene in uveal melanoma. Sci Rep 8: 7618, 2018.

41. Calvete O, Garcia-Pavia P, Domínguez F, Bougeard G, Kunke Z, Braeuninger A, Teule A, Rupi C, Lasa A, Ramón Y Cajal T, et al: The wide spectrum of POT1 gene variants correlates with multiple cancer types. Eur J Hum Genet 25: 1278-1281, 2017.

42. Giavedoni P, Rieh M, Carnera C, Puig S and Malvehy J: Familial melanoma associated with Li-Fraumeni syndrome and atypical mole syndrome: Total-body digital photography, dermoscopy and confocal microscopy. Acta Derm Venereol 97: 720-723, 2017.

43. Sabater-Marco V, Ferrando-Roca F, Morera-Faes A, García-Garcia JA, Bosch SB and López-Guérrero JA: Primary cutaneous leiomyosarcoma arising in a patient With Li-Fraumeni Syndrome: A neoplasm with unusual histopathologic features and loss of heterozygosity at TP53 Gene. Am J Dermatopathol 40: 275-227, 2018.

44. Nieuwenburg SA, Adan F, Ruijs MWG, Sonke GS, van Leerdam ME and Crijns MB: Cumulative risk of skin cancer in patients with Li-Fraumeni syndrome. Fam Cancer 19: 347-351, 2020.

45. Park KJ, Choi HH, SuH SP, Ki CS and Kim JW: Germline TP53 mutation and clinical characteristics of Korean patients with Li-Fraumeni syndrome. Ann Lab Med 36: 463-468, 2016.

46. Chan AK, Han SJ, Choy W, Beleford D, Aghi MK, Berger MS, Shieh JT, Bollen AW, Perry A, Phillips JJ, et al: Familial melanoma-astrocytoma syndrome: Synchronous diffuse astrocytoma and pleomorphic xanthoastrocytoma in a patient with germline CDKN2A/B deletion and a significant family history. Clin Neuropathol 36: 213-221, 2017.

47. Hsieh CC and Shen CH: The potential of targeting P53 and HSP90 overcoming acquired MAPK-resistant melanoma. Curr Treat Options Oncol 20: 22, 2019.

48. Pandey R, Johnson N, Cooke L, Johnson B, Chen Y, Pandey M, Chandler J and Mahadevan D: TP53 Mutations as a driver of metastasis signaling in advanced cancer patients. Cancers (Basel) 13: 597, 2021.

49. Alos L, Fuster C, Castillo P, Jares P, Garcia-Herrera A, Marginet M, Agreda F, Arance A, Gonzalo E, Garcia M, et al: TP53 mutation and tumoral PD-L1 expression are associated with depth of invasion in desmoplastic melanomas. Ann Transl Med 8: 1218, 2020.

50. Loureiro JB, Abrantes M, Oliveira PA and Saraiva L: P53 in skin cancer: From a master player to a privileged target for prevention and therapy. Biochim Biophys Acta 1874: 184834, 2020.

51. Guo L, Kang JS, Kang NJ and Choi YW: S-petasin induces apoptosis and inhibits cell migration through activation of p53 pathway signaling in melanoma B16F10 cells and A375 cells. Arch Biochem Biophys 692: 108519, 2020.

52. Carsote M, Valea A, Dumitru N, Terzea D, Petrova E, Albu S, Buruiana A and Gheorgian A: Metastases in daily endocrine practice. Arch Balkan Med Union 51: 478-482, 2018.

53. Balosescu R, Carsote M, Albu SE and Valea A: Multiple surgeries and long-term endocrine follow-up in a MEN2A syndrome. J Surgical Sciences 4: 1-4, 2015.

54. Padurarun DN, Nica A, Carsote M and Valea A: Adrenalecotomy for Cushing's syndrome: Do's and don'ts. J Med Life 9: 334-341, 2016.

55. Poiu C, Carsote M, Chirtia C, Terzea D, Paun S and Beuran M: Giant adrenal cyst: Case study. J Med Life 3: 308-313, 2010.

56. Caruntu C, Boda D, Constantin C, Caruntu A and Neagu M: Catecholamines increase in vitro proliferation of murine B16F10 melanoma cells. Acta Endocrinol (Basel) 13: 597, 2021.

57. Lupu M, Caruntu A, Caruntu C, Papagheorghe LML, Ilie MA, Voiculescu V, Boda D, Constantin C, Tanase C, Sifaki M, et al: Neuroendocrine factors: The missing link in non melanoma skin cancer. Oncol Rep 38: 1327-1340, 2017.

58. Grange JD, Duquesne N, Roubyreyrol F, Branisteanu D, Sandon K, Fleury J, Gerard JP, Chauvel F, Pinzaru G, Jean-Louis B and Bievélez B: Double irradiation for macroscopic radioresistance or recurrence of melanomas of the posterior uvea: Clinical, ballistic, therapeutically and prognostic aspects. Series of 19 cases among 462 patients. J Fr Ophtalmol 22: 1054-1063, 1999 (In French).

59. Ancuceanu R, Dnud M, Neag LA, Laszlo FG and Boda D: Development of QSAR machine learning-based models to forecast the effect of substances on malignant melanoma cells. Oncol Lett 17: 4188-4196, 2019.

60. Stefan O, Tudor G, Constantinescu C, Luca C, Boda D, Caruntu C, Cioplea M, Nichita L and Zurac SA: E-cadherin and N-cadherin expression pattern in common melanocytic nevi. Virchows Arch 275, 2022.