Parasol Foundation supported projects
at Sheba Medical Center, Israel

Promoting Women in Leadership Promoting Academic Excellence Improving Cancer Care in Israel

June 2018

Dep. Radiation Oncology
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In the previous report we described how we planned to use funds from the Parasol Foundation to promote critical projects within the Department of Radiation Oncology at the Sheba Medical Center. Each project combines academic excellence with the career development of an outstanding woman. In the current document we provide a progress report on those projects and give the backgrounds of the women and men behind them.

Contents

"by supporting a new generation of women clinicians and researchers, the projects supported by Parasol will have a lasting impact on cancer care in Israel"

Prof Zvi Symon, June 2018
Chairman, Department of Radiation Oncology, Sheba

MRI-based Brachytherapy for Gynecological Malignancies, Dr. Shira Felder

Shira returned home last year after a successful fellowship Shira in the Department of Radiation Oncology at Princess Margaret Cancer Center, Toronto, Canada. Earlier this year Shira was appointed to lead the Radiation-Gynecology service at Sheba.

Varian's fletcher-style applicator with interstitial components.

Shira is deeply immersed in establishing an MRI-brachytherapy service, which will be the first in Israel. An important step was the purchase (with the generous support of Parasol) of MRI-compatible equipment. In parallel the hospital is making the infrastructural changes required for the installment of an MRI simulator.

"My passion is to improve the outcomes amongst women with cervical cancer, not just improving their chance of survival, but also improving their quality of life. MRI-based therapies will help me achieve these twin goals"

Dr Shira Felder

Next month Shira will be participating in the NRG-RTOG scientific meeting in Philadelphia, which will enable her to give her patients the opportunity to participate in international clinical trials.

Shira and her family at Algonquin park, Ontario

New strategies to overcome pancreatic cancer, led by Dr Ariel Sebag

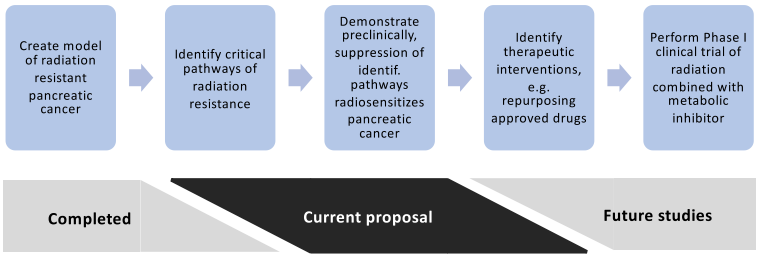
Dr Ariel Shimoni, was born in Nice, France, she made Aliyah following her bachelor degree, subsequently studying for her Masters and Doctoral degrees at the Hebrew University in Jerusalem. Since 2016 she has led a unique project that aims to develop a novel treatment for pancreatic cancer. Ariel lives with her husband and three children in the city of Modiin.

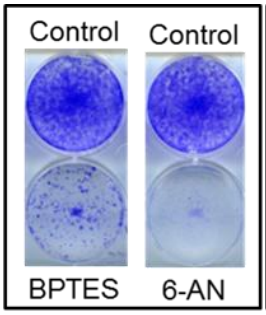
As a direct result of Parasol's funding of Dr Shimoni's work, a new treatment paradigm for patients with pancreatic cancer is in development

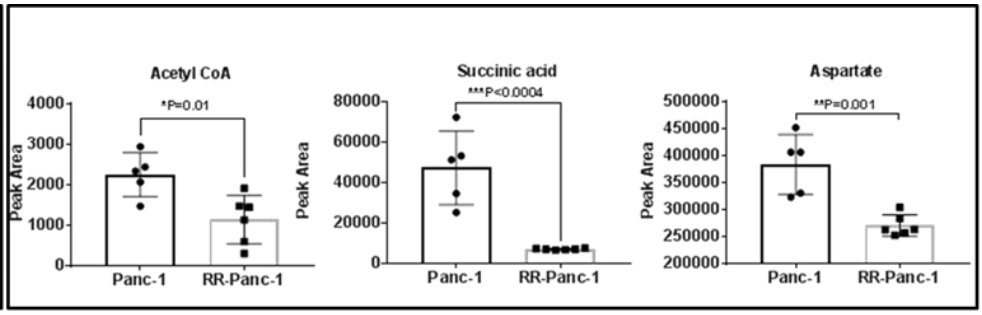
Pancreatic cancer is a frequent cause of death in the Western World. The cancer is characterized by rapid growth and resistance to drug and radiation therapies. The cancer's aggressive nature is related to the tumor's abnormal use of glucose and other nutrients (metabolic reprogramming). Compared to normal cells, nutrients are absorbed at a greater rate, and are processed along different pathways.

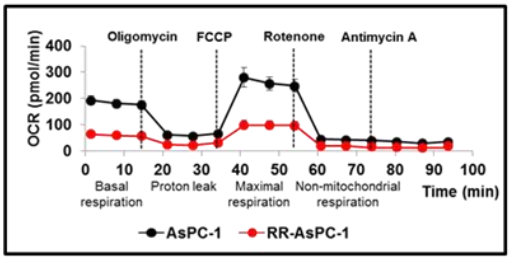
Radiation (X ray) therapy is used in the treatment of 60% of cancer patients. It has an important role in pancreatic cancer in both the locally-advanced and palliative settings. Radiation therapy kills cancer cells by damaging cells' genetic material - DNA. Cells may survive radiation therapy, by either preventing, repairing or ignoring the DNA damage. Compared to normal cells, pancreatic tumors are able to survive surprisingly large doses of radiation therapy, a phenomenon named radioresistance. The mechanisms underlying pancreatic cancer radioresistance are unknown.

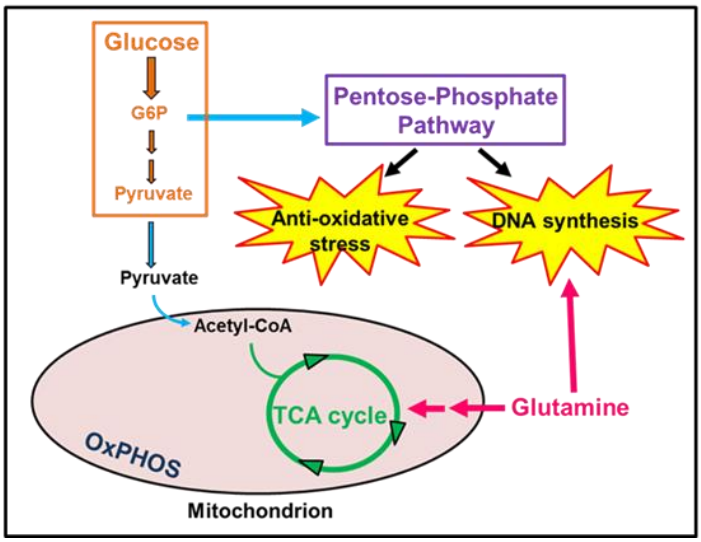
Develop new therapy for pancreatic cancer, overview











In this project, we are investigating the role of metabolic reprogramming and protein-variants in explaining radioresistance, with the longer-term goal of developing new therapeutic strategies.

Ariel has established a novel model of radioresistance and found radioresistant cells are highly sensitive to the metabolic inhibitors BPTES and 6-AN. Moreover, radioresistant cells are dependent on glutamine and shift their metabolism from the TCA cycle and from oxidative phosphorylation, potentially to the pentose-phosphate pathway to generate the precursors for DNA synthesis and anti-oxidative stress molecules. The discovery that radioresistant cells are more sensitive to metabolic inhibitors was unexpected and without precedent. Ongoing experiments are investigating how the metabolic signature of radioresistance may be exploited for therapeutic intent.

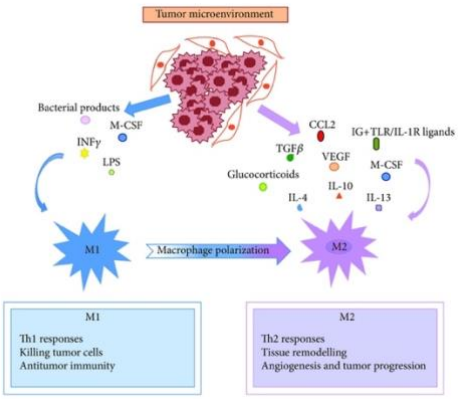
This groundbreaking project is being performed in collaboration with a world-renowned expert in cancer metabolism (Prof Gottlieb). The experimental work at Sheba will be performed by Dr Shimoni- Sebag, an accomplished cancer biologist. This unique team will ensure the successful completion of the project, and facilitate the potential translation of the project's conclusions into a clinical trial for the benefit of pancreatic cancer patients.

Developing new approaches to lung cancer by combining radiation with new immunotherapy agents, led by Dr Tamar Ben-Mordechai

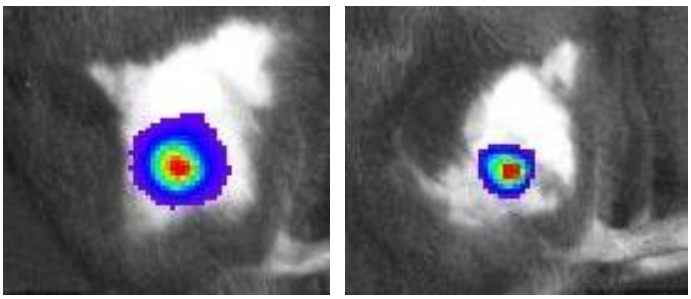
Lung cancer is the leading cause of cancer death in both men and women, causing more than 1.18 million deaths per year. Small cell lung carcinoma accounts for 15% of lung cancer, and the prognosis is poor. Moreover, about 50% patients will finally develop brain metastasis during the course of their disease.

Immunotherapy is a promising strategy to cope with diverse types of cancer. However, only a small subset respond to therapy and it's effects are usually short lived. Therefore there is an unmet need to develop novel therapies to "boost" the immune response to current therapies.

Accumulating evidence proves that macrophages affect cancer initiation and malignancy. Macrophages commonly exist in two distinct subsets: classically activated or M1 macrophages, which are pro-inflammatory and alternatively activated or M2 macrophages, which are anti-inflammatory and immunoregulatory. In a tumor microenvironment, tumor associated macrophages (TAMs) are considered to be of the polarized M2 phenotype that enhances tumor progression and represent a poor prognosis.



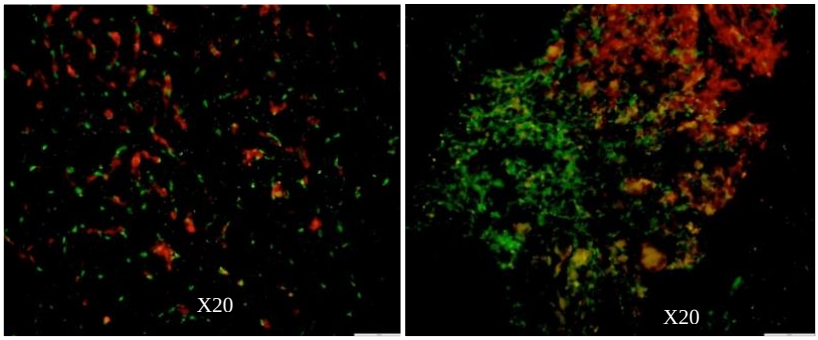
Targeting M2 tumor-associated macrophages as a potential cell therapy.



Left, control not-treated, sub-cutaneous tumor. Right – Targeting tumor associated macrophages as novel cell therapy resulted in tumor growth arrest.

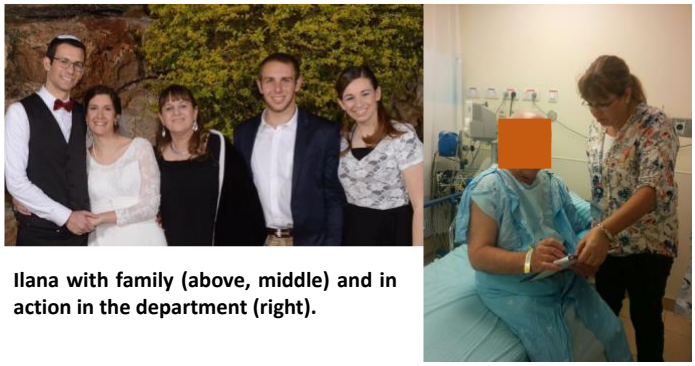
In our research, we aim to develop a novel cell therapy focusing on TAMs manipulation. As preliminary results, sub-cutaneous tumors have shown growth arrest following a vaccine-like treatment targeting TAMs in tumor microenvironment, in a mouse model of lung carcinoma.

One step closer towards a new cancer cure: Tammy's innovative work - Interaction between tumor associated macrophages (green)



Quality of Life amongst prostate cancer patients, Ilana Weiss

Ilana Weiss joined the Radiation Department in 2011 from a background in the social sciences to lead the "Quality of Life after Prostate Cancer" project under Prof. Symon's guidance. Ilana has built a database of several thousand patients, carefully measuring and recording quality of life measures prior to- and following-prostate cancer treatments. This unique database has already led a to a number of publications, with many more in the pipeline.



Ilana with family (above, middle) and in action in the department (right).

Ilana brings warmth and radiance to the department. I has been said that every prostate cancer patient at Sheba becomes a member of Ilana's family

Ilana lives in Moshav Nachlaot with her husband, enjoys spending time with their four children and two grandchildren.

Recently the database has been incorporated into the comprehensive Patient Reported Outcome Measures (PROMS) program being developed at Sheba by Dr Eyal Zimlechman.

Educating the next generation of Radiation Oncology professionals, led by Tamar Katzman

Graduate of the second radiation therapist program, Tamar is sitting, second from left

Tamar Katzman is a radiation therapist, trained in Australia who previously worked at Hadassah Hospital, Jerusalem. In 2012 Tamar launched, and continues to lead the National School of Radiation Therapy. The school serves a national need, as a focus for intradisplenacy radiation education education and testing. The school has hosted Five 4-month courses for the education of radiation therapists, practical testing of physicians and physicists (which prior to the school was not performed). The school recently hosted an international conference on Quality Assurance and Safety on behalf of the International Atomic Energy Agency (IAEA).

As part of the emphasis on training, Sheba has initiated a physicist-residency program. Our first graduate Noam Weizmann is working in Jerusalem, our current resident Yitzchak Darras is being supported by Parasol funding.

Understanding Radiation induced cell death – Dr Liat Hammer

Enhancing radiation-induced cell death and Senescence by perturbations of programmed cell death proteins in lung cancer.

Radiation therapy has a major role in the treatment of Non-small cell lung cancer. Yet, the efficacy of radiation is limited by cancer cell resistance, resulting from mechanisms that are not fully understood. Irradiation of cancer cells can induce multiple death pathways including apoptosis, necrosis, autophagy, mitotic catastrophe and cellular senescence. Senescence is defined as proliferation arrest with preserved metabolic activity and distinct morphology. So far only little is known on the proteins taking part in activating and maintaining senescence.

Liat, one of our outstanding residents is currently taking time out from her clinical responsibilities to pursue a PhD at the Weizmann institute.

In this study performed at Weizmann Institute of Science under the instruction of Prof. Kimchi from the Weizmann Institute and Dr. Lawrence from Sheba Medical Center, we use a model for non-small cell lung cancer: We are working on a lung cancer cell line named NCI-H460 which undergoes senescence as the main cellular response after irradiation, as evident by morphology, biochemical changes and decreased viability. We hypothesized that IR-induced senescence in NCI-H460 is interconnected

with proteins involved in the programmed cell death network, comprising three main signaling modules (apoptosis, autophagy and programmed necrosis). To this end we implied a platform in which we measured the cellular viability following the combination of irradiation and decreased protein levels of 98 different proteins known to be involved in the programmed cell death network. Using this platform we identified a protein which until now was known to take part only in the apoptotic cell death mechanism, but we managed to show it is highly relevant for inducing senescence in lung cancer cells – when the level of this protein is decreased we measured a drop of over 50% in senescence, which implies it takes a major part in inducing senescence. We are currently investigating the function of this protein after irradiation in colon cancer cells as well. Our goal is to substantiate the clinical relevance of this protein in increasing radiation therapy efficiency and elucidate novel mechanisms connecting senescence with different cell death pathways not yet known.

There are striking similarities between the way a leaf wilts and the response of tumors to ionizing radiation, a process named senescence. Liat is investigating these changes, and in the process seeking to develop new cancer treatments.

One of Liat's research projects will be presented at the forthcoming Annual meeting of the American Society for Radiation Oncology (ASTRO), where she will be presented with a Travel Award. Her work will also be featured in the 'Best of ASTRO meetings'.

Yitzchak Darras – Resident in Medical Physics

Yitzchak Darras was born in Ethiopia, and came to Israel in 1985 as part of the Operation Shlomo airlift. After high-school studies Yitzchak served in a combat unit in the Israeli army, subsequently graduated from Beer-Sheba University in Nuclear engineering. Yitzchak is currently a resident physicist at Sheba while in parallel completing his Master's degree.

Next month, after training at Sheba, Yitzchak will be taking up a post to be a senior physicist within the Department of Radiation Oncology at the Hadassah Medical Center

Proposed projects for 2017-2019

Funds will be utilized to promote the people and projects described in this document:

- Dr Shira Felder, Gynecological brachytherapy
- Dr Ariel Sebag, Pancreatic cancer
- Dr. Tamar Ben-Mordechai, Combine radiation with immunotherapy
- Ms Ilana Weiss, Quality of Life amongst prostate cancer patients
- Tamar Katzman, Educating radiation oncology professionals
- Participation in NRG-RTOG network

The Parasol Foundation's support will not only create a new generation of women leadership in the field of Radiation Oncology, but will also lead to long-term improvements in the level of medical treatment and research performed within Israel.

Acknowledgements:

We should like to thank Dr Jeff and Orit Goldstein's contribution to the department, and specifically acknowledge Dr Jeff Goldstein's academic contribution to many of the projects described in this document.

Published articles 2016-7, Department of Radiation Oncology at Sheba.

Does not include in-press articles or meeting abstracts.

Brachytherapy. 2017 Jul 27. pii: S1538-4721(17)30396-3. doi: 10.1016/j.brachy.2017.06.010.
Brachytherapy patient safety events in an academic radiation medicine program.
Felder S1, Morley L2, Ng E2, Chan K2, Ballantyne H2, Di Tomasso A2, Borg J1, Bissonnette JP1, Breen S1, Waldron J1, Rink A1, Milosevic M3.

PURPOSE:

To describe the incidence and type of brachytherapy patient safety events over 10 years in an academic brachytherapy program.
METHODS AND MATERIALS:

Brachytherapy patient safety events reported between January 2007 and August 2016 were retrieved from the incident reporting system and reclassified using the recently developed National System for Incident Reporting in Radiation Treatment taxonomy. A multi-incident analysis was conducted to identify common themes and key learning points.
RESULTS:

During the study period, 3095 patients received 4967 brachytherapy fractions. An additional 179 patients had MR-guided prostate biopsies without treatment as part of an interventional research program. A total of 94 brachytherapy- or biopsy-related safety events (incidents, near misses, or programmatic hazards) were identified, corresponding to a rate of 2.8% of brachytherapy patients, 1.7% of brachytherapy fractions, and 3.4% of patients undergoing MR-guided prostate biopsy. Fifty-one (54%) events were classified as actual incidents, 29 (31%) as near misses, and 14 (15%) as programmatic hazards. Two events were associated with moderate acute medical harm or dosimetric severity, and two were associated with high dosimetric severity. Multi-incident analysis identified five high-risk activities or clinical scenarios as follows: (1) uncommon, low-volume or newly implemented brachytherapy procedures, (2) real-time MR-guided brachytherapy or biopsy procedures, (3) use of in-house devices or software, (4) manual data entry, and (5) patient scheduling and handoffs.
CONCLUSIONS:

Brachytherapy is a safe treatment and associated with a low rate of patient safety events. Effective incident management is a key element of continuous quality improvement and patient safety in brachytherapy.

PMID: 28757402

2.
Isr Med Assoc J. 2017 Jan;19(1):39-43.
Stereotactic Ablative Body Radiation for Stage I Lung Cancer in Israel: A Retrospective Single-Center Report.
Appel S1, Lawrence YR1,2, Goldstein J1, Pfeffer RM3, Weiss I1, Rabin T1, Felder S1, Ben-Ayun M1, Tzvang L1, Alezra D1, Simansky D4, Ben-Nun A4,2, Bar J1,2, Symon Z1,2.

BACKGROUND:

Stereotactic ablative radiation therapy (SABR) is the application of a very high radiation dose to a small treatment volume. It is the new standard of care in medically inoperable early-stage lung cancer.
OBJECTIVES:

To report the outcomes of SABR in stage I lung cancer at Sheba Medical Center since its introduction in 2009.
METHODS:

We conducted a retrospective chart review of patients with stage I lung cancer treated during the period 2009-2015. Survival status was retrieved from the electronic medical records and confirmed with the national registry. Local failure was defined as increased FDG uptake on PETCT scan within a 2 cm radius of the treated region. Toxicity was estimated from medical records and graded according to common toxicity criteria for adverse events (CTCAE) version 4.03. Overall survival and local control were estimated by the Kaplan-Meier method.
RESULTS:

During the study period 114 patients were treated for 122 stage I lung cancer lesions. Median follow-up time was 27 months (range 8.2-69.5 months), median age was 76 years. Eighty-two percent of the tumors were stage IA (size ≤ 3 cm). Median survival was 46 months; estimated 3 year overall survival was 59% (95%CI 47-69%) and local control was 88% (95%CI 78-94%). Toxicity included chest wall pain in 8.4% of patients, rib fracture in 0.9%, grade 1-2 pneumonitis in 12%, grade 3 in 12% and grade 5 (death) in 0.9%.
CONCLUSIONS:

SABR has been successfully implemented at Sheba Medical Center for the treatment of stage I lung cancer in inoperable patients. It is associated with excellent local control, minor toxicity and an acceptable overall survival.

PMID: 28457113

3.
Int J Radiat Oncol Biol Phys. 2017 Jul 1;98(3):506-507. doi: 10.1016/j.ijrobp.2017.03.039. Epub 2017 Mar 31.
Radiation Therapy in the Middle East: Local and Regional Targets.
Corn BW1, Symon Z2.

PMID: 28581392
DOI:
10.1016/j.ijrobp.2017.03.039

4.
Harefuah. 2016 Nov;155(11):672-676.
[STEREOTACTIC ABLATIVE BODY RADIATION -SABR: A NEW THERAPEUTIC OPTION FOR TREATMENT OF STAGE I LUNG CANCER].
[Article in Hebrew]
Appel S1, Symon Z1.

INTRODUCTION:

Stereotactic ablative radiotherapy (SABR) also known as stereotactic body radiation therapy (SBRT) offers a new therapeutic option for stage 1 lung cancer that cannot undergo surgery due to co-morbidities or patient refusal. This treatment evolved in the last decade thanks to technologic advancement of radiation therapy planning and delivery that allow real time imaging of the tumor and real time position correction before every treatment. Ultra high doses of radiation cause ablation of the target with very low collateral scatter dose to surrounding tissue. Numerous phase I/II trials and institutional series have demonstrated efficacy of this treatment with over 90% control of tumors of 3 cm or less and 80-85% for larger tumors, very similar to surgical results. Data from trials have driven guidelines for safe administration, thus, when properly administered, toxicity is minimal. SABR treatment is administered routinely at the Chaim Sheba Medical Center and in other radiation centers in Israel.

PMID: 28530067

5.
Isr Med Assoc J. 2017 Jan;19(1):19-24.
Salvage Radiation Therapy for Biochemical Failure Following Radical Prostatectomy.
Spieler B1,2, Goldstein J3, Lawrence YR3, Saad A3, Berger R4, Ramon J5, Dotan Z5, Laufer M5, Weiss I3, Tzvang L3, Poortmans P6, Symon Z3.

BACKGROUND:

Radiotherapy to the prostate bed is used to eradicate residual microscopic disease following radical prostatectomy for prostate cancer. Recommendations are based on historical series.
OBJECTIVES:

To determine outcomes and toxicity of contemporary salvage radiation therapy (SRT) to the prostate bed.
METHODS:

We reviewed a prospective ethics committee-approved database of 229 patients referred for SRT. Median pre-radiation prostate-specific antigen (PSA) was 0.5 ng/ml and median follow-up was 50.4 months (range 13.7-128). Treatment was planned and delivered using modern three-dimensional radiation techniques. Mean bioequivalent dose was 71 Gy (range 64-83 Gy). Progression was defined as two consecutive increases in PSA level > 0.2 ng/ml, metastases on follow-up imaging, commencement of anti-androgen treatment for any reason, or death from prostate cancer. Kaplan-Meier survival estimates and multivariate analysis was performed using STATA.
RESULTS:

Five year progression-free survival was 68% (95%CI 59.8-74.8%), and stratified by PSA was 87%, 70% and 47% for PSA < 0.3, 0.3-0.7, and > 0.7 ng/ml (P < 0.001). Metastasis-free survival was 92.5%, prostate cancer-specific survival 96.4%, and overall survival 94.9%. Low pre-radiation PSA value was the most important predictor of progression-free survival (HR 2.76, P < 0.001). Daily image guidance was associated with reduced risk of gastrointestinal and genitourinary toxicity (P < 0.005).
CONCLUSIONS:

Contemporary SRT is associated with favorable outcomes. Early initiation of SRT at PSA < 0.3 ng/ml improves progression-free survival. Daily image guidance with online correction is associated with a decreased incidence of late toxicity.

PMID: 28457109

6.
Radiat Oncol. 2017 Jan 6;12(1):5. doi: 10.1186/s13014-016-0743-2.
Classifying high-risk versus very high-risk prostate cancer: is it relevant to outcomes of

conformal radiotherapy and androgen deprivation?
Saad A1, Goldstein J1, Lawrence YR1, Spieler B1, Leibowitz-Amit R2, Berger R2, Davidson T3, Urban D2, Tsang L1, Alezra D1, Weiss I1, Symon Z4.

OBJECTIVE:

To evaluate outcomes in prostate cancer patients classified as high-risk (HR) or very high-risk (VHR) who were treated with conformal radiation therapy (CRT) and androgen deprivation therapy (ADT).
METHODS:

Between 11/2001 and 3/2012, 203 patients with HR disease received CRT to the prostate (78-82 Gy) and pelvic lymph nodes (46-50 Gy) with ADT (6 m-2 years). Median follow-up was 50 months (12 m-142 m). Biochemical failure was defined according to Phoenix definition. Imaging studies were used to identify local, regional or metastatic failure. Four different VHR/HR groupings were formed using the 2014 and revised 2015 NCCN guidelines. Differences were examined using Kaplan Meier (KM) estimates with log rank test and uni- and multivariate Cox regression analysis (MVA).
RESULTS:

Failure occurred in 30/203 patients (15%). Median time to failure was 30 m (4 m-76 m). KM estimate of 4 year biochemical disease free survival (b-DFS) for the entire cohort was 87% (95%CI: 82-92%). Four year KM survival estimates for b-DFS, PCSS and OS were comparable for each NCCN subgroup. On univariate analysis, the NCCN subgroups were not predictive of b-DFS at 4 years, however, DMFS was worse for both VHR subgroups ($p = .03$and .01) respectively. Cox univariate analysis was also significant for: PSA $\geq$40 ng/ml $p = 0.001$; clinical stages T2c $p = .004$, T3b $p = .02$ and > 4 cores with Gleason score 8-10 $p < .03$. On MVA, only PSA ≥ 40 ng/ml was predictive for b-DFS or MFS at 4 years (HR: 3.75 and 3.25, $p < 0.005$).
CONCLUSION:

Patients with HR and VHR disease treated with CRT and ADT had good outcomes. Stratification into HR and VHR sub-groups provided no predictive value. Only PSA $\geq$40 ng/ml predicted poor outcomes on MVA. Distant failure was dominant and local recurrence rare, suggesting that improved systemic treatment rather than intensification of local therapy is needed. Patients with high-risk prostate cancer are most often treated with conformal dose escalated radiation therapy with androgen deprivation. Stratification into high versus very high-risk subgroups using 2014 or revised 2015 National Comprehensive Cancer Network (NCCN) criteria did not impact treatment outcomes. Only Prostate Serum Antigen (PSA) $\geq$40 ng/ml was predictive of poor prognosis. Distant failure was dominant and local recurrence uncommon which challenges the notion that intensification of local therapy will further improve outcomes in patients with high-risk disease.

PMID: 28061904

7.
Am J Clin Oncol. 2016 Oct;39(5):479-483.
A Retrospective Feasibility Study of Salvage Pelvic Nodal Radiation in 6 Patients With Biochemical Failure Following Prostate Fossa Radiation: An Alternative to Androgen Deprivation Therapy (ADT).
Symon Z1, Ben-Bezalel G, Spieler B, Tsvang L, Alezra D, Berger R, Dotan Z, Lawrence YR, Goldstein J.

PURPOSE:

To evaluate salvage pelvic nodal radiation as an alternative to androgen deprivation therapy (ADT) in patients with biochemical failure and lymph node recurrence following salvage prostate fossa radiation.
METHODS:

Six patients with biochemical failure and lymph node recurrence following prostate fossa radiation were treated with salvage pelvic nodal radiation therapy. A gross target volume was contoured using Choline PET/CT, CT, or MRI imaging. The clinical target volume included pelvic nodes. Avoidance structures were created using isodose lines from previous prostate fossa radiation plans. Radiation was delivered using IMRT or VMAT techniques. Failure was defined as a confirmed rise of prostate-specific antigen (PSA) over 0.2 ng/mL.
RESULTS:

Four patients had presalvage PSA values <1 and 2 patients had PSAs >1. Dose to the clinical target volume was 54 to 60 Gy. The gross target volume dose was 60 to 73.6 Gy. One of the 2 patients with a high PSA received 6 months of concomitant ADT. Mean follow-up after RT for all patients was 24.9 months (range, 18.1 to 33.0 mo). All 5 patients with no ADT had significant PSA responses. PSA reduction was 80% (62% to 100%) of pre-RT PSA. At last follow-up, 2 patients with initial PSA<1 ng/mL remain free of biochemical progression at 33 and 20 months. Four patients have had PSA rise and meet criteria for failure. This included both patients with initial PSA values > 1. Duration of response before failure was 18.1 to

30.7 months. ADT for failure has been started in 1 patient. There was no grade ≥2 GI or GU toxicity.
CONCLUSIONS:

Salvage lymph node irradiation for patients with early biochemical recurrence and radiologic evidence of pelvic nodal metastases is well tolerated and associated with a durable biochemical response and may be an alternative to or may delay the need for ADT in some patients.

PMID: 27655099

8.
Isr Med Assoc J. 2016 Jan;18(1):49-53.
Impact of Androgen Deprivation Therapy on Sexual and Hormonal Function in Patients Receiving Radiation Therapy for Prostate Cancer.
Kushnir T, Gofrit ON, Elkayam R, Paluch-Shimon S, Lawrence YR, Weiss L, Symon Z.
BACKGROUND:

Androgen deprivation therapy (ADT) added to radiation therapy (RT) in intermediate to high risk prostate cancer negatively impacts quality of life.
OBJECTIVES:

To compare health-related quality of life (HR-QOL) in patients receiving combined RT with and without ADT METHODS: The study population comprised patients treated with definitive RT for prostate cancer who completed the Expanded Prostate Cancer Index Composite-26 form between 3 and 24 months after completing RT. Covariance and a stepwise backward logistic regression model was used.
RESULTS:

Data were available for 143 patients who received RT+ADT and 70 who received RT alone. The sexual function and hormonal vitality scores of patients receiving RT+ADT were significantly lower than those receiving RT alone ($P < 0.0001$). Patients with only compulsory school education had significantly lower sexual function scores than patients with university level education ($P \leq 0.005$). Patients with depression had significantly lower hormonal vitality scores than those without depression ($P \leq 0.0001$).
CONCLUSIONS:

The addition of ADT to RT is responsible for decrements in quality of life in the sexual and hormonal vitality domains, which is further compounded by depression and lack of education. This underlines the need to improve education, identify and treat depression, and develop strategies to improve the quality of life of patients receiving combination therapy.

PMID: 26964281

9.
Int J Comput Assist Radiol Surg. 2016 Jun;11(6):1015-23. doi: 10.1007/s11548-016-1380-9. Epub 2016 Mar 26.
Deformable registration of trans-rectal ultrasound (TRUS) and magnetic resonance imaging (MRI) for focal prostate brachytherapy.
Mayer A1,2, Zholkover A3, Portnoy O3,4, Raviv G4,5, Konen E3,4, Symon Z4,6.

PURPOSE:

Focal therapy in low-risk prostate cancer may provide the best balance between cancer control and quality of life preservation. As a minimally invasive approach performed under TRUS guidance, brachytherapy is an appealing framework for focal therapy. However, the contrast in TRUS images is generally insufficient to distinguish the target lesion from normal prostate tissue. MRI usually offers a much better contrast between the lesion and surrounding tissues. Registration between TRUS and MRI may therefore significantly improve lesion targeting capability in focal prostate brachytherapy. In this paper, we present a deformable registration framework for the accurate fusion of TRUS and MRI prostate volumes under large deformations arising from dissimilarities in diameter, shape and orientation between endorectal coils and TRUS probes.
METHODS:

Following pose correction by a RANSAC implementation of the ICP algorithm, TRUS and MRI Prostate contour points are represented by a 3D extension of the shape-context descriptor and matched by the Hungarian algorithm. Eventually, a smooth free-form warping is computed by fitting a 3D B-spline mesh to the set of matched points.
RESULTS:

Quantitative validation of the registration accuracy is provided on a retrospective set of ten real cases, using as landmarks either brachytherapy seeds (six cases) or external beam radiotherapy fiducials (four cases) implanted and visible in both modalities. The average registration error between the landmarks was 2.49 and 3.20 mm, for the brachytherapy and external beam sets, respectively, that is less than the MRI voxels' long axis length ([Formula: see text]). The overall average registration error (for brachytherapy and external beam datasets together) was 2.56 mm.
CONCLUSIONS:

The proposed method provides a promising framework for TRUS-MRI registration in focal prostate brachytherapy.
KEYWORDS:

Brachytherapy; Deformable image registration; Focal therapy; Image-guided prostate surgery; TRUS–MRI fusion

PMID: 27017500

Select item 28740882
10.
Adv Radiat Oncol. 2016 Mar 24;1(2):136-140. doi: 10.1016/j.adro.2016.03.002. eCollection 2016 Apr-Jun.
Reexpansion of atelectasis caused by use of continuous positive airway pressure (CPAP) before radiation therapy (RT).
Appel S1, Weizman N1, Davidson T2, Urban D3, Lawrence YR1, Symon Z1, Goldstein J1.

INTRODUCTION:

Although radiation therapy (RT) is an effective treatment for malignant atelectasis, its accurate delivery is challenging because of difficulty differentiating between tumor and atelectatic lung. Furthermore, reexpansion of lung during treatment repositions tumor and normal structures necessitating replanning to ensure treatment accuracy. Facilitating lung reexpansion before initiation of RT may improve RT treatment accuracy, spare normal tissue, and reduce obstructive symptoms. We report a case of reexpansion of right upper lobe (RUL) atelectasis caused by use of continuous positive airway pressure (CPAP) before RT.
CASE REPORT:

A 52-year-old woman presented with dyspnea and cough. Imaging studies showed an RUL mass with atelectasis. Bronchoscopy showed extrinsic compression of the RUL and middle lobe bronchi. Biopsy showed small cell lung cancer. Staging with positron emission tomography-computed tomography (CT) and contrast enhanced CT of brain showed no other disease. Following 4 cycles of platinum-based chemotherapy, CT imaging showed a decrease in tumor volume, but persistent RUL atelectasis. She agreed to participate in an institutional study to evaluate the use of CPAP to reduce respiratory motion and immobilize tumors during RT. During CPAP training, she complained of vertigo, headache, and weakness and refused simulation. The next day she reported less dyspnea and completed training and CT simulation without difficulty. CT simulation with CPAP showed reexpansion of the RUL. Lung volume increased from 2170 to 3767 mL (74 %). Gross tumor volume, clinical volume, and planning volume decreased 46%, 45%, and 38%, respectively. Mean lung dose and mean heart dose decreased 20% and 51%, respectively. CPAP was used daily for 1 hour before and during treatment. Cone beam CT scans showed that the RUL remained inflated throughout treatment.
CONCLUSION:

This is the first reported use of CPAP for reexpansion of atelectasis before RT planning and treatment. Reexpansion of atelectasis improved RT planning, decreased dose to uninvolved lung, and removed the need for replanning. Further study of CPAP as an initial intervention to improve RT delivery in patients with malignant atelectasis is warranted.

PMID: 28740882

11.
J Med Radiat Sci. 2015 Dec;62(4):261-6. doi: 10.1002/jmrs.122. Epub 2015 Jul 29.
Transperineal implantation of gold fiducial markers (gold seeds) for prostate image-guided radiation therapy: a feasible technique associated with a low risk of complications.
Saad A1, Goldstein J1, Lawrence YR2, Weiss I1, Saad R1, Spieler B1, Symon Z2.

INTRODUCTION:

The purpose is to describe the method, safety and efficacy of transperineal gold seed placement for image-guided radiation therapy.
METHODS:

An ethics committee approved database was used to review records of consecutive patients from October 2008 through December 2013, who underwent transperineal implantation of three gold markers into the prostate using staged local anaesthesia and transrectal ultrasound. Seeds were counted on radiographs from CT simulation, first treatment and last treatment. Retention and use of at least three markers for kV/kV matching was considered a successful implant. A visual analogue scale (VAS) pain assessment was performed. SAS was used for data analysis.
RESULTS:

Fiducial marker placement was successful for kV/kV matching in 556/581 patients (95.7%). The procedure was aborted due to pain in two patients. Additional sedation during the procedure was required in two patients. Complications include urinary infections (2 patients, <0.5%) and transient haematuria (2 patients, <0.5%). There were no recorded calls requesting additional pain

medication or delays in radiation due to complications. The number of seeds identified at simulation: 4 (2 patients), 3 (554 patients), 2 (21 patients), 1 (1 patient), 0 (1 patient). One patient with three seeds and two patients with <2 seeds had cone beam CT instead of kV/kV imaging for image guidance. No seeds were lost after simulation. The mean visual analogue pain score associated with transperineal gold seed insertion met patients' expectations (respectively 4.1 vs. 4.4 P = 0.19). CONCLUSION:

Outpatient transperineal insertion of fiducials avoids the rectum, is effective, convenient, well tolerated and has few side effects.
KEYWORDS:

Gold fiducial markers; image-guided radiation; prostate cancer; transperineal implant

PMID: 27512572

12.
J Natl Compr Canc Netw. 2017 Aug;15(8):1022-1027. doi: 10.6004/jnccn.2017.0138.
Short- and Long-Term Survival in Metastatic Pancreatic Adenocarcinoma, 1993-2013.
Golan T1,1, Sella T1,1,1, Margalit O1,1, Amit U1,1, Halpern N1, Aderka D1,1, Shacham-Shmueli E1,1, Urban D1,1, Lawrence YR1,1.

Background: During the past 2 decades, numerous clinical trials have focused on improving outcomes in patients with metastatic pancreatic cancer (mPDAC). The efficacy of new treatments has been demonstrated among highly selected patients in randomized phase III trials; hence, it is not clear to what extent these advances are reflected within the broader mPDAC population. Materials and Methods: Survival statistics were extracted from the SEER database for patients diagnosed with mPDAC between 1993 and 2013. Survival was analyzed using the Kaplan-Meier method and proportional hazard models. Results: The study population consisted of 57,263 patients diagnosed with mPDAC between 1993 and 2013; 52% were male, with a median age of 69 years (range, 15-104). Superior prognosis correlated with younger age, being married, tumor located within the head of the pancreas, lower grade disease, and more recent year of diagnosis. Median overall survival (OS) remained stable at 2 months between 1993 and 2013. Improvements in OS were seen for younger patients (age <50 years) and those with a more recent year of diagnosis (2009-2013). The percentage of patients who died within 2 months of initial diagnosis decreased between 1993 and 2013 (from 63.5% to 50.6%; P<.0001). The percentage of patients surviving ≥12 months improved from 4.9% in 1993 to 12.7% in 2013 (P<.0001). Conclusions: In recent years a modest improvement in OS has been seen among younger patients with mPDAC. The percentage of patients living beyond 1 year has significantly increased over time; however, the percentage of those dying within 2 months remains substantial.

PMID: 28784864

13.
PLoS One. 2016 May 19;11(5):e0155711. doi: 10.1371/journal.pone.0155711. eCollection 2016.
Overcoming Resistance of Cancer Cells to PARP-1 Inhibitors with Three Different Drug Combinations.
Yalon M1,2, Tuval-Kochen L2,3, Castel D4, Moshe I1, Mazal I2, Cohen O5, Avivi C6, Rosenblatt K6, Aviel-Ronen S6, Schiby G6, Yahalom J7, Amariglio N2, Pfeffer R2, Lawrence Y2, Toren A1,2, Rechavi G2, Paglin S2.

Inhibitors of poly[ADP-ribose] polymerase 1 (PARPis) show promise for treatment of cancers which lack capacity for homologous recombination repair (HRR). However, new therapeutic strategies are required in order to overcome innate and acquired resistance to these drugs and thus expand the array of cancers that could benefit from them. We show that human cancer cell lines which respond poorly to ABT-888 (a PARPi), become sensitive to it when co-treated with vorinostat (a histone deacetylase inhibitor (HDACi)). Vorinostat also sensitized PARPis insensitive cancer cell lines to 6-thioguanine (6-TG)-a drug that targets PARPis sensitive cells. The sensitizing effect of vorinostat was associated with increased phosphorylation of eukaryotic initiation factor (eIF) 2α which in and of itself increases the sensitivity of cancer cells to ABT-888. Importantly, these drug combinations did not affect survival of normal fibroblasts and breast cells, and significantly increased the inhibition of xenograft tumor growth relative to each drug alone, without affecting the mice weight or their liver and kidney function. Our results show that combination of vorinostat and ABT-888 could potentially prove useful for treatment of cancer with innate resistance to PARPis due to active HRR machinery, while the combination of vorinostat and 6-TG could potentially overcome innate or acquired resistance to PARPis due to secondary or reversal BRCA mutations, to decreased PARP-1 level or to increased expression of multiple drug resistant proteins. Importantly, drugs which increase phosphorylation of eIF2α may mimic the sensitizing effect of vorinostat on

cellular response to PARPis or to 6-TG, without activating all of its downstream effectors.

PMID: 27196668

14.
JAMA Oncol. 2016 Mar;2(3):390-1. doi: 10.1001/jamaoncol.2015.4833.
Quality and Reporting Accuracy of Phase 1 Drug Radiation Clinical Trials.
Kim H1, Dan TD1, Palmer JD1, Leiby BE2, Lawrence YR3, Dicker AP1.

PMID: 26841256

15.
J Neurooncol. 2016 May;127(3):535-9. doi: 10.1007/s11060-016-2059-3. Epub 2016 Jan 29.
Phase I trial of panobinostat and fractionated stereotactic re-irradiation therapy for recurrent high grade gliomas.
Shi W1, Palmer JD2, Werner-Wasik M2, Andrews DW3, Evans JJ3, Glass J3, Kim L3, Bar-Ad V2, Judy K3, Farrell C3, Simone N2, Liu H2, Dicker AP2, Lawrence YR2,4.

Panobinostat is an oral HDAC inhibitor with radiosensitizing activity. We investigated the safety, tolerability and preliminary efficacy of panobinostat combined with fractionated stereotactic re-irradiation therapy (FSRT) for recurrent high grade gliomas. Patients with recurrent high grade gliomas were enrolled in a 3 + 3 dose escalation study to determine dose limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, tolerability, and preliminary efficacy. FSRT was prescribed to 30-35 Gy delivered in 10 fractions. Panobinostat was administrated concurrently with radiotherapy. Of 12 evaluable patients, 8 had recurrent GBM, and 4 had recurrent anaplastic astrocytoma. There were three grade 3 or higher toxicities in each the 10 and 30 mg cohorts. In the 30 mg cohort, there was one DLT; grade 4 neutropenia. One patient developed late grade 3 radionecrosis. The median follow up was 18.8 months. The PFS6 was 67, 33, and 83 % for 10, 20, and 30 mg cohorts, respectively. The median OS was 7.8, 6.1 and 16.1 months for the 10, 20 and 30 mg cohorts, respectively. Panobinostat administrated with FSRT is well tolerated at 30 mg. A phase II trial is warranted to assess the efficacy of panobinostat plus FSRT for recurrent glioma.
KEYWORDS:

HDAC inhibitor; Panobinostat; Phase I trial; Radiotherapy; Recurrent high grade glioma

PMID: 26821711

16.
Neurosurg Focus. 2017 Jan;42(1):E3. doi: 10.3171/2016.9.FOCUS16332.
Spine radiosurgery: lessons learned from the first 100 treatment sessions.
Harel R1,2,3, Pfeffer R4, Levin D4, Shekel E4, Epstein D4, Tsvang L5, Ben Ayun M5, Alezra D5, Zach L3,5.

OBJECTIVE Local therapy to spine tumors has been shown to be effective in selected cases. Spinal radiosurgery (SRS) is an evolving radiotherapy regimen allowing for noninvasive, highly efficacious local treatment. The learning curve can compromise the results of any newly employed technology and should be studied to minimize its effects. In this paper the first 100 SRSs performed at several medical centers are presented and analyzed for the effects of the learning curve on outcome. METHODS A retrospective analysis was undertaken to evaluate data from patients treated with SRS at Sheba Medical Center and Assuta Medical Centers in the period from September 2011 to February 2016. Medical history, clinical and neurological findings, pathological diagnoses, SRS variables, complications, and follow-up data were collected and analyzed. Local control rates were calculated, and local treatment failure cases were qualitatively studied. RESULTS One hundred treatment sessions were performed for 118 lesions at 179 spinal levels in 80 patients. The complication rate was low and did not correlate with a learning curve. Mean follow-up time was 302 days, and the overall local control rate was 95%. The local control rate was dose dependent and increased from 87% (among 35 patients receiving a dose of 16 Gy) to 97% (among 65 patients receiving a dose of 18 Gy). The 6 treatment failure cases are discussed in detail. CONCLUSIONS Spinal radiosurgery is a safe and effective treatment. Comprehensive education of the treating team and continuous communication are essential to limit the effects of the learning curve on outcome.
KEYWORDS:

ATRT = atypical teratoid/rhabdoid tumor; CBCT = cone-beam CT; CTV = clinical target volume; Dmax = maximum cord point dose; IMRT = intensity-modulated radiotherapy; NST = nerve sheath tumor; SRS = spinal radiosurgery; VMAT = volumetric modulated arc therapy; learning curve; spine radiosurgery; spine tumors

PMID: 28041321

17.
Biomed Res Int. 2016;2016:6805979. doi: 10.1155/2016/6805979. Epub 2016 Jan 13.

Volumetric Modulated Arc Therapy for Spine Radiosurgery: Superior Treatment Planning and Delivery Compared to Static Beam Intensity Modulated Radiotherapy.
Zach L1, Tsvang L1, Alezra D1, Ben Ayun M2, Harel R3.

PURPOSE:

Spine stereotactic radiosurgery (SRS) delivers an accurate and efficient high radiation dose to vertebral metastases in 1-5 fractions. We aimed to compare volumetric modulated arc therapy (VMAT) to static beam intensity modulated radiotherapy (IMRT) for spine SRS.
METHODS AND MATERIALS:

Ten spine lesions of previously treated SRS patients were planned retrospectively using both IMRT and VMAT with a prescribed dose of 16 Gy to 100% of the planning target volume (PTV). The plans were compared for conformity, homogeneity, treatment delivery time, and safety (spinal cord dose).
RESULTS:

All evaluated parameters favored the VMAT plan over the IMRT plans. D min in the IMRT was significantly lower than in the VMAT plan (7.65 Gy/10.88 Gy, $p < 0.001$), the Dice Similarity Coefficient (DSC) was found to be significantly better for the VMAT plans compared to the IMRT plans (0.77/0.58, resp., p value < 0.01), and an almost 50% reduction in the net treatment time was calculated for the VMAT compared to the IMRT plans (6.73 min/12.96 min, $p < 0.001$).
CONCLUSIONS:

In our report, VMAT provides better conformity, homogeneity, and safety profile. The shorter treatment time is a major advantage and not only provides convenience to the painful patient but also contributes to the precision of this high dose radiation therapy.

PMID: 26885513

18.
J Clin Neurosci. 2016 Apr;26:46-9. doi: 10.1016/j.jocn.2015.05.068. Epub 2015 Dec 8.
Durable brain response with pulse-dose crizotinib and ceritinib in ALK-positive non-small cell lung cancer compared with brain radiotherapy.
Dudnik E1, Siegal T2, Zach L3, Allen AM4, Flex D4, Yust-Katz S2, Limon D5, Hirsch FR6, Peled N7.

Crizotinib achieves excellent systemic control in anaplastic lymphoma kinase-rearranged (ALK+) non-small cell lung cancer (NSCLC); however, central nervous system (CNS) metastases frequently occur as an early event. Whole brain irradiation, the standard treatment, results in neurocognitive impairment. We present a case series of three ALK+ NSCLC patients with progressing CNS metastases who were treated with pulse-dose crizotinib followed by ceritinib. Three ALK+ NSCLC patients treated between 2011 and 2014 (two males, two never smokers, age range 20-54years, all echinoderm microtubule-associated protein-like 4/ALK rearrangement), were diagnosed with progressing cerebral disease while receiving crizotinib. Clinico-pathological characteristics, treatments, and outcomes were analyzed. In two patients the progression was limited to the CNS, and radiological evidence of leptomeningeal spread was present in one patient. Sequential use of crizotinib 500mg administered once daily (pulse-dose) followed by ceritinib on progression achieved control of the disease in the CNS for over 18 months and over 7 months in Patient 1 and Patient 2, respectively. This strategy provided durable CNS control after whole-brain radiotherapy failure in Patient 1, and allowed the whole-brain radiotherapy to be deferred in Patient 2. Limited CNS progression was documented in Patient 3 while he was on standard-dose/pulse-dose crizotinib for 15months; durable (over 7 months) complete remission was achieved with stereotactic radiotherapy and ceritinib. Manipulating the crizotinib schedule in ALK+ NSCLC patients with CNS metastases and using a novel ALK-inhibitor at the time of further progression may provide durable CNS control and allow brain radiotherapy to be deferred.

PMID: 26677785

19.
Support Care Cancer. 2017 Jun 26. doi: 10.1007/s00520-017-3795-4. [Epub ahead of print]
From will to live to will to die: oncologists, nurses, and social workers identification of suicidality in cancer patients.
Granek L1, Nakash O2, Ariad S3, Chen W4, Birenstock-Cohen S5, Shapira S6, Ben-David M7.

PURPOSE:

The purpose of this research was to examine how oncologists, nurses, and social workers identify suicidality in cancer patients.
METHODS:

Sixty-one healthcare professionals (23 oncologists, 18 social workers, and 20 nurses) at two academic cancer centers were interviewed using an in-depth interview guide. This was a qualitative study based on grounded theory methodology. Analysis

involved line-by-line coding, with categories and themes emerging from participants' narratives.
RESULTS:

Suicidality in cancer patients exists on a wide spectrum that ranges from an active will to live to an active will to die. Four phases were identified that included: (A) a strong will to live expressed in themes of active treatments, seeking second opinions, overtreatment, and alternative treatments; (B) a decreasing will to live indicated in themes of mental health distress and physical pain and suffering; (C) a readiness to die expressed in themes of mental health distress, previous mental health diagnoses, physical pain, avoiding more suffering, preserving quality of life in old age, nearing end of life, lack of social support, and maintaining a sense of control; and (D) a will to die indicated in themes of euthanasia and active suicidality.
CONCLUSIONS:

Suicidality in cancer patients exists on a continuum. Cancer patients fluctuate on this spectrum depending on circumstances such as degree of suffering, their personalities and life circumstances, and whether they are nearing the end of life. Results of the study emphasize the need to collect more context specific data on suicidality among cancer patients and the importance of early integration of psychosocial and palliative care in the cancer treatment trajectory.

PMID: 28653106

20.
Psychooncology. 2017 Jun 21. doi: 10.1002/pon.4481. [Epub ahead of print]
Oncologists', nurses', and social workers' strategies and barriers to identifying suicide risk in cancer patients.
Granek L1, Nakash O2, Ben-David M3,4, Shapira S5, Ariad S6.

OBJECTIVE:

To identify oncologists', nurses', and social workers' strategies and barriers in identifying suicide risk in cancer patients.
METHODS:

Sixty-one oncology healthcare professionals (HCPs) at 2 cancer centers were interviewed. We used the grounded theory method (GT) of data collection and analysis. Analysis involved line-by-line coding, and was inductive, with codes and categories emerging from participants' narratives.
RESULTS:

The majority of oncologists and nurses reported that they had encountered at least 1 patient who had committed suicide during their careers (56% and 55%, respectively) and/or had suicidal ideation (65% and 75%, respectively). Social workers reported having fewer suicides in their practices (22%), but similar rates of suicidal ideation among patients (66%). Strategies to identifying suicide risk included paying attention to patients' verbal indicators, explicit actions, and mental health distress. In addition HCPs reported that mental health disorders and other patient characteristics increased their likelihood to assess suicidality among patients. Reported barriers to identification included patient factors such as patients giving no warning, patients concealing suicidality, and patients failing to come in. HCP barriers to identification included lack of training and awareness, difficulty in differentiating suicidality from mental health distress, lack of time with patients, fear of asking about suicidality, and lack of coping resources to deal with suicidal patients.
CONCLUSIONS:

HCPs reports of their lack of training and awareness on identifying suicide risk is alarming given the higher risk of suicide among cancer patients. Training programs should incorporate the successful strategies used by HCPs and overcome barriers to identifying suicide risk.

PMID: 28635073

21.
J Altern Complement Med. 2017 Apr 25. doi: 10.1089/acm.2017.0023. [Epub ahead of print]
The Effect of Reflexology on the Pain-Insomnia-Fatigue Disturbance Cluster of Breast Cancer Patients During Adjuvant Radiation Therapy.
Tarrasch R1, Carmel-Neiderman NN2, Ben-Ami S3, Kaufman B3, Pfeffer R4, Ben-David M4,5, Gamus D2.

OBJECTIVE:

To evaluate the effects of reflexology treatment on quality of life, sleep disturbances, and fatigue in breast cancer patients during radiation therapy.
METHODS/SUBJECTS:

A total of 72 women with breast cancer (stages 1-3) scheduled for radiation therapy were recruited.
DESIGN:

Women were allocated upon their preference either to the group receiving reflexology treatments once a week concurrently with radiotherapy and continued for 10 weeks or to the control group (usual care).
OUTCOME MEASURES:

The Lee Fatigue Scale, General Sleep Disturbance Scale, and Multidimensional Quality of Life Scale Cancer were completed by each patient in both arms at the beginning of the radiation treatment, after 5 weeks, and after 10 weeks of reflexology treatment.
RESULTS:

The final analysis included 58 women. The reflexology treated group demonstrated statistically significant lower levels of fatigue after 5 weeks of radiation therapy ($p < 0.001$), compared to the control group. It was also detected that although the quality of life in the control group deteriorated after 5 and 10 weeks of radiation therapy ($p < 0.01$ and $p < 0.05$, respectively), it was preserved in the reflexology group, which also demonstrated a significant improvement in the quality of sleep after 10 weeks of radiation treatment ($p < 0.05$). Similar patterns were obtained in the assessment of the pain levels experienced by the patients.
CONCLUSIONS:

The results of the present study indicate that reflexology may have a positive effect on fatigue, quality of sleep, pain, and quality of life in breast cancer patients during radiation therapy. Reflexology prevented the decline in quality of life and significantly ameliorated the fatigue and quality of sleep of these patients. An encouraging trend was also noted in amelioration of pain levels.
KEYWORDS:

breast cancer; fatigue; radiation therapy; reflexology

PMID: 28440664

22.
J Oncol Pract. 2017 Jan;13(1):e1-e10. doi: 10.1200/JOP.2016.014746. Epub 2016 Oct 31.
Mixed-Methods Study of the Impact of Chronic Patient Death on Oncologists' Personal and Professional Lives.
Granek L1, Ariad S1, Nakash O1, Cohen M1, Bar-Sela G1, Ben-David M1.

PURPOSE:

Although some research has found that health care professionals experience grief when their patients die, within the oncology context, few studies have examined the impact of this loss on oncology personnel. Given the paucity of empirical studies on this topic, this research explored the impact of patient death on oncologists. Methods and Materials This study used a mixed-methods design. The qualitative component used the grounded theory method of data collection and analysis. Twenty-two oncologists were recruited from three adult oncology centers. Purposive sampling was used to gain maximum variation in the sample. The quantitative component involved a convenience sample of 79 oncologists recruited through oncologist collaborators.
RESULTS:

The qualitative study indicated that frequent patient death has both personal and professional impacts on oncologists. Personal impacts included changes to their personality, gaining of perspective on their lives, and a strain to their social relationships. Professional impacts included exhaustion and burnout, learning from each patient death, and decision making. The frequency analysis indicated that oncologists experienced both positive and negative impacts of patient death. A majority reported that exposure to patient death gave them a better perspective on life (78.5%) and motivated them to improve patient care (66.7%). Negative consequences included exhaustion (62%) and burnout (75.9%) as well as compartmentalization of feelings at work and at home (69.6%).
CONCLUSION:

Frequent patient death has an impact on oncologists' lives, some of which negatively affect the quality of life for oncologists, their families, and their patients.

PMID: 28084882

23.
Support Care Cancer. 2017 May;25(5):1607-1614. doi: 10.1007/s00520-016-3562-y. Epub 2017 Jan 13.
Oncologists' negative attitudes towards expressing emotion over patient death and burnout.
Granek L1, Ben-David M2, Nakash O3, Cohen M3, Barbera L4, Ariad S5, Krzyzanowska MK6.

PURPOSE:

The aims of this study were to examine the relationship between negative attitudes towards expressing emotion following patient death and burnout in oncologists and to explore oncologists' preferences for institutional interventions to deal with patient death.
METHODS:

The participants included a convenience sample of 177 oncologists from Israel and Canada. Oncologists completed a questionnaire package that included a sociodemographic survey, a burnout measure, a survey assessing negative attitudes towards expressing emotion, and a survey assessing desired interventions to cope with patient death. To

examine the association between burnout and negative attitudes while controlling for the effect of sociodemographic variables, a hierarchical linear regression was computed.
RESULTS:

Higher burnout scores were related to higher negative attitudes towards perceived expressed emotion (partial $r = .25$, $p < .01$) of those who viewed this affect as a weakness and as a sign of unprofessionalism. Approximately half of the oncologists found each of the five categories of institutional interventions (pedagogical strategies, emotional support, group/peer support, taking time off, and research and training) helpful in coping with patient death.
CONCLUSIONS:

Our findings suggest that high burnout scores are associated with negative attitudes towards expressing emotion and that there is a wide variation in oncologist preferences in coping with patient death. Institutions should promote interventions that are varied and that focus on the needs of oncologists in order to reduce burnout. Interventions that legitimize expression of emotion about patient death may be useful. Another way to reduce stigma would be to require oncologists to "opt out" rather than "opt in" to accessing a selection of social and/or individual interventions.
KEYWORDS:

PMID: 28084531

24.
Psychooncology. 2016 Oct 4. doi: 10.1002/pon.4289. [Epub ahead of print]
Oncologists' communication about end of life: the relationship among secondary traumatic stress, compassion satisfaction, and approach and avoidance communication.
Granek L1, Nakash O2, Cohen M2, Ben-David M3, Ariad S4.

BACKGROUND:

Oncologists must communicate effectively with patients and their families about end of life (EOL). Despite the importance of communicating on this topic, many oncologists avoid these conversations. The objective of this study was to examine the associations between secondary traumatic stress and compassion satisfaction and approach and avoidant communication about EOL with cancer patients.
METHODS:

A convenience sample of 79 oncologists (n = 27 men, n = 52 women) participated in the study. Oncologists completed a survey that included a sociodemographic and clinical information questionnaire, the Professional Quality of Life Scale, and Communication about End of Life Survey. To examine the effect of secondary traumatic stress and compassion satisfaction on approach and avoidant communication, while controlling for gender and age, 2 hierarchical linear regression analyses were computed.
RESULTS:

Oncologists reported high levels of secondary traumatic stress and high compassion satisfaction. Scores on the approach and avoidant communication scales were in the mid-range of the scale. Lower reports of secondary traumatic stress and higher compassion satisfaction were associated with higher approach communication strategies: however, only higher secondary traumatic stress was associated with higher avoidant communication strategies.
CONCLUSIONS:

Our findings indicate that there is an association between emotional factors and approach communication. The findings have clinical implications in designing effective communication skills training. Further research and training should take secondary traumatic stress and compassion satisfaction into consideration to be able to ensure that terminal patients and their families receive the best quality EOL care.

PMID: 27699908

25.
Cancer. 2016 Dec 1;122(23):3705-3714. doi: 10.1002/cncr.30236. Epub 2016 Aug 10.
Gender differences in the effect of grief reactions and burnout on emotional distress among clinical oncologists.
Granek L1, Krzyzanowska MK2, Nakash O3, Cohen M3, Ariad S4, Barbera L5, Levy R6, Ben-David M7.

BACKGROUND:

The current study was conducted to examine gender differences in the effect of grief reactions and burnout on emotional distress among clinical oncologists.
METHODS:

The participants included a convenience sample of 178 oncologists from Israel (52 of whom were women) and Canada (48 of whom were women). Oncologists completed a questionnaire package that included a sociodemographic survey, the General Health Questionnaire, a burnout measure, and the Adult Oncologists Grief Questionnaire. To examine the effect of grief reactions and burnout on emotional distress while controlling for country

and past depression within each gender, 2 hierarchical linear regression analyses were computed.
RESULTS:

Female oncologists reported significantly more grief responses to patient death (mean, 47.72 [standard deviation (SD), 8.71] and mean, 44.53 [SD, 9.19], respectively), more emotional distress (mean, 12.41 [SD, 4.36] and mean, 10.64 [SD, 3.99], respectively), and more burnout (mean, 2.59 [SD, 1.69] and mean, 1.84 [SD, 1.5], respectively). For both genders, higher levels of grief reactions were associated with greater emotional distress among those who reported high levels of burnout (P<.001). However, for men, the association between grief reactions and emotional distress also was documented at moderate levels of burnout (P<.001).
CONCLUSIONS:

Patient death is a regular part of clinical oncology. It is essential that oncologists be able to cope effectively with this aspect of their work. The findings of the current study highlight the need to take into account the cumulative stressors that oncologists contend with when designing supportive interventions. Gender differences in burnout, reactions to patient death, and emotional distress need to be addressed to ensure the best quality of life for oncologists and the best quality of care for their patients. Cancer 2016;122:3705-14.

KEYWORDS:

burnout; emotional distress; gender differences; grief reactions; oncologists; oncology; patient death

PMID:
27509210
DOI:
10.1002/cncr.30236

[Indexed for MEDLINE]

Icon for Wiley
MeSH terms

Select item 27228641
26.
Isr Med Assoc J. 2016 Mar-Apr;18(3-4):188-92.
Melatonin for Prevention of Breast Radiation Dermatitis: A Phase II, Prospective, Double-Blind Randomized Trial.
Ben-David MA, Elkayam R, Gelernter I, Pfeffer RM.
BACKGROUND:

Radiation-induced dermatitis is commonly seen during radiotherapy for breast cancer. Melatonin-based creams have shown a protective effect against ultraviolet-induced erythema and a radioprotective effect in rats.
OBJECTIVES:

To evaluate the efficacy of melatonin-containing cream in minimizing acute radiation dermatitis.
METHODS:

In this phase II, prospective, randomized, placebo-controlled double-blind study, patients who underwent breast-conserving surgery for stage 0-2 breast cancer were randomly allocated to melatonin emulsion (26 women) or placebo (21 women) for twice daily use during radiation treatment and 2 weeks following the end of radiotherapy. All women received 50 Gy whole breast radiation therapy with 2 Gy/fx using computed tomography-based 3D planning. Patients were examined and completed a detailed questionnaire weekly and 2 weeks following the end of treatment.
RESULTS:

The occurrence of grade 1/2 acute radiation dermatitis was significantly lower (59% vs. 90%, P = 0.038) in the melatonin group. Women older than 50 had significantly less dermatitis than younger patients (56% vs. 100%, P = 0.021). The maximal radiation dermatitis in the study group was grade 2 in 15% of the treated patients.
CONCLUSIONS:

Patients treated with melatonin-containing emulsion experienced significantly reduced radiation dermatitis compared to patients receiving placebo.

PMID: 27228641

27.
Support Care Cancer. 2016 Oct;24(10):4219-27. doi: 10.1007/s00520-016-3249-4. Epub 2016 May 5.
Barriers and facilitators in coping with patient death in clinical oncology.
Granek L1, Ariad S2, Shapira S3, Bar-Sela G4, Ben-David M5,6.

PURPOSE:

The purpose of this study was to explore barriers and facilitators in coping with patient death in the oncology context.
METHODS:

The grounded theory method was used to collect and analyze the data. Twenty-two oncologists were

interviewed between March 2013 and June 2014 from three adult oncology centers. Oncologists were at different stages of their careers and varied in their sub-specialties, gender, and personal and professional backgrounds.
RESULTS:

The analysis revealed that facilitators to coping with patient death included cognitive, behavioral, relational, professional, and spiritual coping strategies. Behavioral coping strategies included sports, hobbies, entertainment, and taking vacations. Cognitive strategies included accepting and normalizing death and focusing on the positive, and on successes in the practice of oncology. Relational coping strategies included accessing social support from family, friends, and colleagues. Professional coping strategies included focusing on work, withdrawing from patients at end of life, and compartmentalization. Spiritual coping strategies included turning to faith and religious coping. Oncologists also reported a number of challenges and barriers in coping effectively with patient deaths. These included challenges in accessing social support, challenges that were related to gender and expression of emotion, and challenges in maintaining emotional boundaries when patients died.
CONCLUSIONS:

Oncologists turn to a number of diverse coping strategies in dealing with patient death, but many obstacles to accessing this support were reported. Targeted interventions for managing and coping with grief related to patient death need to be developed to support oncologists in their emotionally difficult work.
KEYWORDS:

Cancer; Coping; Grief; Oncology; Patient death

PMID: 27146494

28.
Med Dosim. 2016 Summer;41(2):142-7. doi: 10.1016/j.meddos.2015.11.002. Epub 2016 Feb 26.
Immediate breast reconstruction with anatomical implants following mastectomy: The radiation perspective.
Ben-David M1, Granot H2, Gelernter I3, Scheflan M4.

Immediate implant-based breast reconstruction followed by postmastectomy radiation therapy (PMRT) is controversial because of the risk of compromised treatment plans and concerns regarding cosmetic outcomes. We evaluated the effects of immediate direct-to-implant breast reconstruction with anatomical implants on the quality of PMRT delivered by 3-dimensional conformal radiotherapy (3D-CRT). In this retrospective, single-institution study, patients who had undergone reconstruction with direct anatomic implant, performed by a single surgeon, received 3D-CRT between 2008 and 2013. For each patient, 2 plans (including or excluding internal mammary nodes [IMN]) were created and calculated. The primary end point was the dose distribution among reconstructed breasts, heart, lungs, and IMNs, and between right and left breasts. Of 29 consecutive patients, 11 received right-sided and 18 received left-sided PMRT to a total dose of 50Gy. For plans excluding IMN coverage, mean Dmean for right and left reconstructed breasts was 49.09Gy (98.2% of the prescribed dose) and 48.51Gy (97.0%), respectively. For plans including IMNs, mean Dmean was 49.15Gy (98.3%) for right and 48.46Gy (96.9%) for left reconstructed breasts; the mean IMN Dmean was 47.27Gy (right) and 47.89Gy (left). Heart Dmean was below 1.56Gy for all plans. Mean total lung volume receiving a dose of ≥ 20Gy was 13.80% to 19.47%. PMRT can be delivered effectively and safely by 3D-CRT after direct-to-implant breast reconstruction with anatomical implants, even if patients require IMN treatment.

PMID: 26923467

30.
Clin Case Rep. 2016 Jan 20;4(3):247-9. doi: 10.1002/ccr3.417. eCollection 2016 Mar.
Viable triplet pregnancy coexisting with a complete molar pregnancy.
Polonsky A1, Olteanu I1, Ben-David M1, Mamet J1, Agranat A1, Fridman E1.

This case is extraordinary because it was never before described in English literature. The case describes a long-standing debate about the safety of carrying this pregnancy to term. Some authors are for and some are against. The risks and benefits should be thoroughly reviewed before a decision is made.

PMID: 27014444

31.
Psychooncology. 2017 Jul;26(7):960-966. doi: 10.1002/pon.4118. Epub 2016 Mar 14.
Grief symptoms and difficult patient loss for oncologists in response to patient death.
Granek L1, Ben-David M2,3, Shapira S4, Bar-Sela G5, Ariad S6.

OBJECTIVE:

The study aimed to explore oncologist's grief symptoms over patient death and to identify why and which losses are particularly challenging when patients die.
METHODS:

The grounded theory method was used to collect and analyze the data. Twenty-two oncologists were interviewed between March 2013 and June 2014 from three adult oncology centers in the north, center, and south of Israel. Oncologists were at different stages of their careers and varied in their sub-specialties, gender, and personal and professional backgrounds.
RESULTS:

Grief begun when the patient died, in anticipation of the patient's death, many days after the death, or when the patient received a poor prognosis. The phenomenological experience of grief for oncologists included behavioral, cognitive, physical, and emotional symptoms in response to patient death. Behavioral symptoms included crying and difficulties sleeping. Cognitive symptoms included self-doubt and rumination about the patient and the care the patient had received before death. Physical symptoms included chest pain, fatigue, and general physical discomfort. Emotional symptoms included sadness, anxiety, helplessness, guilt, relief, irritability, and loss. Difficult patient loss was caused by patient-related factors, family-related factors, and disease-related factors.
CONCLUSIONS:

Patient deaths result in behavioral, cognitive, physical, and emotional symptoms of grief in oncologists. These symptoms become particularly intense in the context of patient, family, and disease-related factors. Educational and supportive interventions for managing grief related to patient death are needed in order to support oncologists in their emotionally and mentally taxing work.

PMID: 26988940

32.
Am J Hypertens. 2017 Aug 29. doi: 10.1093/ajh/hpx158. [Epub ahead of print]
The Effect of Head and Neck Radiotherapy on Blood Pressure and Orthostatic Hypotension in Patients With Head and Neck Tumors.
Leibowitz A1, Grossman E1, Berkovitch A1, Levartovski M2, Appel S2, Sharabi Y1, Gluck I2.

Background:

Radiotherapy (RT) plays a key role in the management of head and neck cancer (HNC), especially in locally advanced disease. Patients undergoing head and neck RT, especially elderly ones, are suffering from low and labile blood pressure (BP) during the treatment. They complain of weakness and fatigue and are prone to recurrent falls. The aim of this study was to characterized BP changes during RT period.
Methods:

Patients with HNC, recieving radiation to the neck, were recruited from Sheba medical center RT unit. Office BP, orthostatic measurements, 24H ambulatory BP (ABPM), body weight and metabolic parameters were measured at baseline after 30 days and after 90 days from beginning of therapy.
Results:

19 patients (17 males), 64±12 years old were recruited. 9 hypertensive patients continued their antihypertensive treatment during the study. Office systolic BP (SBP) and diastolic BP (DPB) decreased significantly after 30 days (128±4/80±3 to 122±3/74±3 mmHg; $p<0.05$). Average 24H BP values after 30 days of RT decreased from 130±3/76±2 to 123±3/71±2 mm Hg; $P<0.05$. A similar trend was observed for day and night BP levels. Decrease in office and ambulatory BP was sustained for several months after RT completion. No orthostasis was observed during the study period. Patient lost weight significantly during the study period. However, BP changes were independent of weight loss.
Conclusion:

There is a significant and sustained BP reduction after head and neck RT, without orthostatic changes. Clinicians should be aware to this phenomenon and consider treatment adaption accordingly.

PMID: 28985342

33.
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Acquired Hemophilia A in a Patient with Non-Small Cell Lung Carcinoma: A Rare Paraneoplastic Phenomenon.
Ben Haim G1, Manor U2, Appel S3, Lalezari S4, Margalit-Yehuda R1, Steinlauf S1,5.

Manuscript Update: June 2018

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PMID:29311597

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Spieler B, Goldstein J, Lawrence YR, Saad A, Berger R, Ramon J, Dotan Z, Laufer M, Weiss I, Tzvang L, Poortmans P, Symon Z.

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