Artigo

Radioterapia hemitorácica oligofracionada seguida de cirurgia radical - novo paradigma no tratamento do mesothelioma pleural

Oligofractionated hemithoracic radiation followed by radical surgery – a new treatment paradigm for malignant pleural mesothelioma

Marc de Perrot

Resumo

O papel da cirurgia no mesotelioma pleural maligno é controverso devido à incapacidade de fazer uma ressecção completa (R0). O papel da quimioterapia e da radiação em combinação com a cirurgia radical permanece um campo de investigação. As diretrizes atuais recomendam a ressecção completa macroscópica (MCR) para pacientes selecionados com doença em estágio inicial em combinação com outras terapias. A MCR pode ser realizada com pleurectomia-decorticação (DP), DP estendida ou pneumonectomia extrapleural (PPE). A pneumonectomia extrapleural (PPE) e a pleurectomia-decorticação estendida (PPE) são procedimentos radicais com o objetivo de obter a ressecção macroscópica completa do tumor. Avanços recentes na seleção de pacientes, técnicas cirúrgicas, anestesia e manejos pós-operatórios diminuíram a taxa de mortalidade para menos de 5% em centros experientes para ambos os procedimentos. A escolha da cirurgia radical entre EPD e EPP permanece um debate aberto e a maioria dos centros escolherá as opções cirúrgicas com base em sua experiência, estado do paciente e achados radiológicos. Nossa análise preliminar da abordagem SMART com 90 pacientes mostrou resultados encorajadores com uma sobrevida média de 28,3 meses como uma análise por intenção de tratar. Esta sobrevida média dobrou em relação à nossa abordagem anterior com quimioterapia de indução seguida por EPP e radiação hemitorácica.

Descritores: mesotelioma pleural, tratamento multimodal, smart trial, pneumonectomia extrapleural, pleurectomia/descorticação.

Abstract

The role of surgery in malignant pleural mesothelioma is controversial due to the inability to do a complete resection (R0). The role of chemotherapy and radiation in combination with radical surgery remains a field of investigation. Current guidelines recommend macroscopic complete resection (MCR) for selected patients with early stage disease in combination with other therapies. MCR can be performed with pleurectomy-decortication (PD), extended PD, or extrapleural pneumonectomy (EPP). Extrapleural pneumonectomy (EPP) and extended pleurectomy-decortication (EPD) are both radical procedures aiming to achieve complete macroscopic resection of the tumor. Recent advances in patient selection, surgical techniques, anesthesia, and postoperative managements have decreased the mortality rate to less than 5% in experienced centers for both of these procedures. The choice of radical surgery between EPD and EPP remains an open debate and most centers will choose the surgical options based on their experience, the patient's status and radiological findings. Our preliminary analysis of the SMART approach with 90 patients has shown encouraging results with a median survival of 28.3 months as an intention-to-treat analysis. This median survival has doubled from our previous approach with induction chemotherapy followed by EPP and hemithoracic radiation.

Keywords: Pleural mesothelioma, Multimodal treatment, Smart Trial, Extrapleural pneumonectomy, Pleurectomy/Decortication.

Toronto General Hospital and Princess Margaret Cancer Centre, University Health Network, Toronto, Canada
Marc de Perrot, MD, MSc, FRCSC - Director, Mesothelioma Program, UHN - Division of Thoracic Surgery - Toronto General Hospital, 9N-961 - 200 Elizabeth Street - Toronto, Ontario M5G 2C4, Canada
Tel: 416 340-5549 - Fax: 416 340-5549

Introduction

Malignant pleural mesothelioma (MPM) continues to be a worldwide health concern due to industrial and environmental exposure to asbestos[1]. MPM are characterized by alterations in tumor suppressor genes, poor prognosis, and standard-of-care limited to chemotherapy with cisplatin-pemetrexed±bevacizumab[1,2,3]. The role of surgery is controversial due to the inability to do a complete resection (R0) in the context of disseminated tumor in the pleural cavity[4]. Current guidelines recommend macroscopic complete resection (MCR) for selected patients with early stage disease in combination with other therapies[5]. MCR can be performed with pleurectomy-decortication (PD), extended PD, or extrapleural pneumonectomy (EPP). The prognosis remains poor despite multimodality therapy with median survivals ranging between 13 and 20 months in the intention-to-treat analysis of large prospective trials[6,7,8]. Single agent immunotherapy so far had limited benefit in mesothelioma[9]. Double agent immunotherapy offers more promising results, but randomized clinical trials are still ongoing[10,11]. Pre-clinical work demonstrates that combining immunotherapy with conventional therapy such as chemotherapy or radiation therapy could provide the best approach to treat mesothelioma[12,13,14].

Current therapy

The treatment of mesothelioma is broad, from palliative therapy to aggressive curative-intent therapy using a multimodality approach with surgery, chemotherapy and radiotherapy. Currently, chemotherapy and radiation therapy are recognized for palliation in MPM. Two randomized trials have shown the benefit of cisplatin combined with an anti-folate agent (pemetrexed or raltitrexed) on survival with a benefit of about 3 months[1,2]. More recently, the addition of bevacizumab, a VEGF-specific angiogenesis inhibitor, to cisplatin and pemetrexed was shown to provide additional benefit in a large randomized trial in France[3]. The survival improved from 16.1 months in patients receiving cisplatin-pemetrexed to 18.8 months in those receiving bevacizumab combined with cisplatin-pemetrexed[3].

Radiation therapy is occasionally used for palliation of chest pain when a specific site of tumor invasion is seen[6]. A retrospective study on palliative radiation using 36 Gy in 12 fractions from a single center in the United Kingdom has shown that palliative radiation could provide clinical benefit with reduction of chest pain in up to 57% of the patients[4]. More recently, a prospective multicenter phase II study has confirmed these findings with an effective pain relief in 35% of the patients at five weeks after radiation using 20 Gy in 5 fractions[5]. Noteworthy, in 12.5% of patients a complete analgesic response was observed. The impact of radiation on the tumor activity was also shown on 18F--FDG PET/CT scan performed before and after palliative radiotherapy in a study looking at metabolic changes in total glycolytic volume[6]. The optimal dosage for palliative radiation is not yet defined and most centers currently use 20 Gy in 5 fractions.

Prophylactic radiation with 21 Gy in 3 fractions as recommended by Boutin and colleagues in 1995 to prevent tumor metastasis to the port sites has been mostly abandoned since two large randomized trials have been negative[15,16,17]. Of importance, however, was the differences in response to this short course of radiation between epithelioid and non-epithelioid mesothelioma[38]. Although the trials reported by Clive and colleagues was statistically negative, there was a clear trend in favor of radiation in the epithelioid group suggesting that the response to short courses of radiation may differ between the subtypes of mesothelioma[16].

Multimodality therapy

The role of chemotherapy and radiation in combination with radical surgery remains a field of investigation. Extrapleural pneumonectomy (EPP) and extended pleurectomy-decortication (EPD) are both radical procedures aiming to achieve complete macroscopic resection of the tumor. Recent advances in patient selection, surgical techniques, anesthesia, and postoperative managements have decreased the mortality rate to less than 5% in experienced centers for both of these procedures[7,8]. In the absence of adequately powered clinical trials to assess the role of surgery, a propensity score analysis was performed using data from the National Cancer Database[18]. The analysis demonstrated that radical surgery provided significant benefit on median survival ranging from 2.2 months in sarcomatoid MPM to 4.7 months in epithelioid tumors on average[18]. The study also demonstrated that combination therapy provided better outcome than single therapy and trimodality therapy achieved the best survival. The median survival was extended from 11.2 months to 20.8 months in patients who completed the trimodality therapy[18].

The choice of radical surgery between EPD and EPP remains an open debate and most centers will choose the surgical options based on their experience, the patient's status and radiological findings. EPP or EPD are generally associated with chemotherapy in the induction or adjuvant setting. The results of EPP have been well documented as part of prospective clinical trials. In contrast, the experience with EPD have generally been reported as part of retrospective studies. The results of EPD have been variable with median survivals ranging between 7 and 32 months, and a disease free survival ranging between 10 and 12 months on average[19]. Local recurrence in the ipsilateral hemithorax is frequent and can be seen in up to 89% of the patients[20]. Several centers have been administering adjuvant hemithoracic intensity modulated radiation therapy (IMRT) to decrease the rate of local recurrence after EPD[21,22]. The risk of severe radiation pneumonitis of the underlying lung

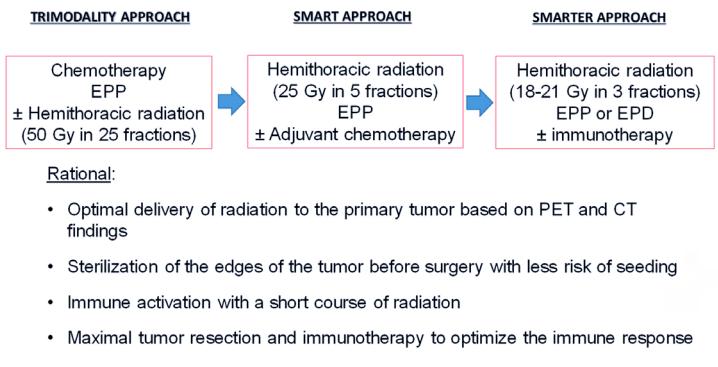
has decreased with experience from 20% in the initial experience to less than 10% in more recent publications[22,23]. In the largest series, the rate of local recurrence was 64% with a median disease free survival of 10 months[22]. The rate of local failure was more important in the presence of gross disease, emphasizing the importance of achieving an R1 resection even if adjuvant IMRT is given after EPD[22].

SMART approach

In Toronto, we developed a first-in-man concept focusing on Surgery for Mesothelioma After Radiation Therapy (SMART). This approach entails the administration of a radiation dose of 25 Gy to the whole hemithorax in 5 fractions over one week with a concomitant boost of 5 Gy to the gross disease on PET-CT scan[24]. The doses of 25 Gy in five fractions with boost of 5 Gy to areas at high risk are based on previous experience in neoadjuvant accelerated radiation for colorectal cancer. The fractionation, although shorter and lower in dose compared to the adjuvant setting (50 Gy/25 fractions over 5 weeks), is comparable in radiobiological potency in sterilizing residual microscopic disease. The surgery consists in an EPP performed within a week after the end of radiation. The pneumonectomy is required to prevent the risk of pneumonitis of the underlying lung due to the high dose of radiation. We demonstrated that this approach was safe with all patients completing the intended radiation and surgery with a 90-day mortality of less than 5%[25].

The advantages of the SMART protocol are: 1) the higher proportion of patients successfully completing the treatment protocol due to improved compliance, 2) boosting tumor area at high risk determined by high SUV on PET scan or area of infiltration and/or bulkiness on CT scan, 3) tumoricidal action of radiation potentially decreasing the risk of viable tumor spillage during the surgery, and 4) a shorter overall treatment duration which improves convenience and reduces risk of disease progression since the radiation is delivered over 5 days and the surgery is performed approximately one week after the end of the radiation (Figure 1).

Figura 1. Evolution of multimodality therapy for mesothelioma in Toronto



Our preliminary analysis of the SMART approach with 90 patients has shown encouraging results with a median survival of 28.3 months as an intention-to-treat analysis[6]. This median survival has doubled from our previous approach with induction chemotherapy followed by EPP and hemithoracic radiation[26]. Patient characteristics, pathological stage and postoperative complication rates were similar between both cohorts of patients[27]. The 30-day mortality has been less than 2% and rate of grade 4 complications around 10% after SMART[25].

The SMART approach demonstrated particularly encouraging results in patients with epithelioid mesothelioma with a median survival of 36 months[8]. Further analysis showed that the median survival reached 47 months in epithelioid mesothelioma in the absence of metastatic lymph nodes, and 51 months in tumors less than 500cc3 volume[8,28]. However, despite prolonged survival, the vast majority of patients still developed recurrence, even beyond 5 years[8].

An analysis of the tumor microenvironment in our initial cohort of 69 consecutive patients undergoing the SMART approach was recently completed[29]. We observed that an increased infiltration of CD8+ T cells at the time of surgery after radiation was an independent predictor of improved survival (p=0.02, HR 0.47, 95%CI 0.25-0.89). Epithelioid histology (p=0.0004, HR 0.3, 95%CI 0.16-0.59) and metastatic nodal disease were other independent predictors of survival (p=0.03, HR 1.92, 95%CI 1.05-3.51). Further analysis in the same cohort of patients demonstrated that expression of PD-L1 on tumor cells was associated with better survival in epithelioid mesothelioma and worse survival in biphasic disease compared to PD-L1 negative tumors. This observation supports previous work demonstrating that epithelioid and non-epithelioid mesothelioma have different tumor immune microenvironment and that tumor cells may have different mechanisms of resistance to radiation[30,31,32].

SMARTER: a platform for immunotherapy

Over the past decade, clinical and pre-clinical evidence have demonstrated that oligofractionated radiation characterized by a short course (2-5 fractions) of hypofractionated radiation can boost an antitumor immune response through the induction of type I interferon[33,34]. This effect has gained increasing interest over the past few years with the introduction of immune checkpoint inhibitors in clinical practice. The benefit of combining oligofractionated radiation with immune checkpoints has been particularly relevant in the context of metastatic disease. Although the response rate has been variable, these studies have demonstrated that the combination of radiation and immunotherapy offers great potential[35,36]. One of the advantages of this new treatment paradigm is the ability to generate

an immune activation by delivering a non-ablative dose of radiation, thus limiting its toxicity. Increasing evidence suggests that the antigen load is a key determinant of clinical response and that even robust immune response may be clinically ineffective if the tumor burden is high[37,38]. Hence, the combination of a short course of radiation to generate a specific antitumoral immune response followed by radical surgery to reduce the tumor antigen load to a minimal appears very promising.

Considering our results with the SMART approach and the increasing knowledge on the impact of radiation on the immune system, the concept of oligofractionated radiation followed by surgery could offer an ideal platform for immunotherapy in mesothelioma. We have therefore designed a new clinical trial (SMARTER) to exploit the whole benefit of this new treatment paradigm (Figure 1). The optimal distribution of radiation to generate an immunogenic cell death will correspond to the density of mesothelioma cells with greater boost given to macroscopic disease and less dose given to microscopic disease. Based on our pre-clinical experience and the literature, we estimate that a dose of radiation of at least 21Gy in 3 fractions to the gross (macroscopic) disease will be optimal in activating the immune system and generate a potential abscopal effect that will target the sites of microscopic disease. The radiation will be followed by surgery, either EPD or EPP, which will reduce the tumor burden once the immune system is activated to optimize the benefit of radiation. This new concept raises key questions related to safety, efficacy and the importance of radiating microscopic pleural disease to improve the abscopal effect that will be addressed in the SMARTER trial.

Conclusions

Mesothelioma remains associated with poor outcome. New developments in immunotherapy and better understanding of the effect of radiation and chemotherapy on the immune system is offering new treatment paradigms that will hopefully achieve long term remission in this disease. The combination of a short course of radiation associated with macroscopic complete resection could provide an optimal platform for immunotherapy. The SMARTER trial is designed to answer this question.

Referências

1. Carbone M, Adusumilli PS, Alexander HR Jr, Baas P, Bardelli F, Bononi A, Bueno R, Felley-Bosco E, Galateau-Salle F, Jablons D, Mansfield AS, Minaai M, de Perrot M, Pesavento P, Rusch V, Severson DT, Taioli E, Tsao A, Woodard G, Yang H, Zauderer MG, Pass HI. Mesothelioma: Scientific clues for prevention, diagnosis, and therapy. CA Cancer J Clin. 2019 Jul 8.
2. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, Niyikiza C, Paoletti P. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003 Jul 15;21(14):2636-44.
3. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, Molinier O, Corre R, Monnet I, Gounant V, Rivière F, Janicot H, Gervais R, Locher C, Milleron B, Tran Q, Lebitasy MP, Morin F, Creveuil C, Parienti JJ, Scherpereel A; French Cooperative Thoracic Intergroup (IFCT). Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet. 2016 Apr 2;387(10026):1405-1414.
4. Weder W, Stahel RA, Baas P, Dafni U, de Perrot M, McCaughan BC, Nakano T, Pass HI, Robinson BW, Rusch VW, Sugarbaker DJ, van Zandwijk N. The MARS feasibility trial: conclusions not supported by data. Lancet Oncol. 2011 Nov;12(12):1093-4.
5. Kindler HL, Ismaila N, Armato SG 3rd, Bueno R, Hesdorffer M, Jahan T, Jones CM, Miettinen M, Pass H, Rimner A, Rusch V, Sterman D, Thomas A, Hassan R. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018 May 1;36(13):1343-1373.
6. de Perrot M, Wu L, Wu M, Cho BCJ. Radiotherapy for the treatment of malignant pleural mesothelioma. Lancet Oncol 2017;18:e532-42.
7. Tilleman TR, Richards WG, Zellos L, Johnson BE, Jaklitsch MT, Mueller J, Yeap BY, Mujoomdar AA, Ducko CT, Bueno R, Sugarbaker DJ. Extrapleural pneumonectomy followed by intracavitary intraoperative hyperthermic cisplatin with pharmacologic cytoprotection for treatment of malignant pleural mesothelioma: a phase II prospective study. J Thorac Cardiovasc Surg. 2009 Aug;138(2):405-11.
8. Burt BM, Richards WG, Lee HS, Bartel S, Dasilva MC, Gill RR, Jaklitsch MT, Johnson BE, Swanson SJ, Bueno R, Sugarbaker DJ. A Phase I Trial of Surgical Resection and Intraoperative Hyperthermic Cisplatin and Gemcitabine for Pleural Mesothelioma. J Thorac Oncol. 2018 Sep;13(9):1400-1409.
9. Maio M, Scherpereel A, Calabrò L, Aerts J, Cedres Perez S, Bearz A, Nackaerts K, Fennell DA, Kowalski D, Tsao AS, Taylor P, Grosso F, Antonia SJ, Nowak AK, Taboada M, Puglisi M, Stockman PK, Kindler HL. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. Lancet Oncol. 2017 Sep;18(9):1261-1273.
10. Scherpereel A, Mazieres J, Greillier L, Lantuejoul S, Dô P, Bylicki O, Monnet I, Corre R, Audigier-Valette C, Locatelli-Sanchez M, Molinier O, Guisier F, Urban T, Ligeza-Poisson C, Planchard D, Amour E, Morin F, Moro-Sibilot D, Zalcman G; French Cooperative Thoracic Intergroup. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. Lancet Oncol. 2019 Feb;20(2):239-253.
11. Calabrò L, Morra A, Giannarelli D, Amato G, D'Incecco A, Covre A, Lewis A, Rebelatto MC, Danielli R, Altomonte M, Di Giacomo AM, Maio M. Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study. Lancet Respir Med. 2018 Jun;6(6):451-460.
12. Anraku M, Tagawa T, Wu L, Yun Z, Keshavjee S, Zhang L, Johnston MR, de Perrot M. Synergistic anti-tumor effects of regulatory T cell blockade combined with pemetrexed in murine malignant mesothelioma. J Immunol 2010;185:956-66.
13. Wu L, Yun Z, Tagawa T, De la Maza L, Wu M, Yu J, Zhao Y, de Perrot M. Activation of CD1d-restricted natural killer T cells can inhibit cancer cell proliferation during chemotherapy by promoting the immune responses in murine mesothelioma. Cancer Immunol Immunother 2014;63:1285-96.
14. Lesterhuis WJ, Salmons J, Nowak AK, Rozali EN, Khong A, Dick IM, Harken JA, Robinson BW, Lake RA. Synergistic effect of CTLA-4 blockade and cancer chemotherapy in the induction of anti-tumor immunity. PLoS One. 2013 Apr 23;8(4):e61895.

15. Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. Chest. 1995 Sep;108(3):754-8.
16. Clive AO, Taylor H, Dobson L, Wilson P, de Winton E, Panakis N, Pepperell J, Howell T, Stewart SA, Penz E, Jordan N, Morley AJ, Zahan-Evans N, Smith S, Batchelor TJP, Marchbank A, Bishop L, Ionescu AA, Bayne M, Cooper S, Kerry A, Jenkins P, Toy E, Vigneswaran V, Gildersleve J, Ahmed M, McDonald F, Button M, Lewanski C, Comins C, Dakshinamoorthy M, Lee YCG, Rahman NM, Maskell NA. Prophylactic radiotherapy for the prevention of procedure--tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open--label, phase 3, randomised controlled trial. Lancet Oncol. 2016 Aug;17(8):1094-1104.
17. Bayman N, Appel W, Ashcroft L, Baldwin DR, Bates A, Darlison L, Edwards JG, Ezhil V, Gilligan D, Hatton M, Jegannathen A, Mansy T, Peake MD, Pemberton L, Rintoul RC, Snee M, Ryder WD, Taylor P, Faivre-Finn C. Prophylactic Irradiation of Tracts in Patients With Malignant Pleural Mesothelioma: An Open-Label, Multicenter, Phase III Randomized Trial. J Clin Oncol. 2019 May 10;37(14):1200-1208.
18. Nelson DB, Rice DC, Niu J, Atay S, Vaporciyan AA, Antonoff M, Hofstetter WL, Walsh GL, Swisher SG, Roth JA, Tsao A, Gomez D, Giordano SH, Mehran R, Sepesi B. Long-Term Survival Outcomes of Cancer-Directed Surgery for Malignant Pleural Mesothelioma: Propensity Score Matching Analysis. J Clin Oncol. 2017 Oct 10;35(29):3354-3362.
19. Cao C, Tian DH, Pataky KA, Yan TD. Systematic review of pleurectomy in the treatment of malignant pleural mesothelioma. Lung Cancer 2013;81:319-27.
20. Lang-Lazdunski L, Bille A, Papa S, et al J. Pleurectomy/decortication, hyperthermic pleural lavage with povidone-iodine, prophylactic radiotherapy, and systemic chemotherapy in patients with malignant pleural mesothelioma: a 10-year experience. J Thorac Cardiovasc Surg 2015;149:558-66.
21. Chance WW, Rice DC, Allen PK, et al. Hemithoracic intensity modulated radiation after pleurectomy/decortication for malignant pleural mesothelioma: toxicity, patterns of failure, and a matched survival analysis. Int J Radiation Oncol Biol Phys 2015;91:149-56.
22. Rimner A, Spratt DE, Zauderer MG, et al. Failure patterns after hemithoracic pleural intensity modulated radiation therapy for malignant pleural mesothelioma. Int J Radiation Oncol Biol Phys 2014;90:394-401.
23. Rosenzweig KE, Zauderer MG, Laser B, et al. Pleural intensity--modulated radiotherapy for malignant pleural mesothelioma. Int J Radiation Oncol Biol Phys 2012;83:1278-83.
24. Cho BCJ, Feld R, Leighl N, Opitz I, Anraku M, Tsao MS, Hwang DM, Hope A, de Perrot M. A Feasibility Study Evaluating Surgery for Mesothelioma After Radiation Therapy: The "SMART" Approach for Resectable Malignant Pleural Mesothelioma. J Thorac Oncol 2014;9:397-402.
25. de Perrot M, Feld R, Leighl NB, Hope A, Waddell TK, Keshavjee S, Cho BC. Accelerated hemithoracic radiation followed by extrapleural pneumonectomy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2016;151:468-73.
26. de Perrot M, Feld R, Cho BC, Bezjak A, Anraku M, Burkes R, Roberts H, Tsao MS, Leighl N, Keshavjee S, Johnston MR. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Clin Oncol. 2009 Mar 20;27(9):1413-8.
27. Mordant P, McRae K, Cho J, Keshavjee S, Waddell TK, Feld R, de Perrot M. Impact of induction therapy on postoperative outcome after extrapleural pneumonectomy for malignant pleural mesothelioma: does induction-accelerated hemithoracic radiation increase the surgical risk? Eur J Cardiothorac Surg. 2016 Sep;50(3):433-8.
28. de Perrot M, Dong Z, Bradbury P, Patsios D, Keshavjee S, Leighl NB, Hope A, Feld R, Cho J. Impact of tumour thickness on survival after radical radiation and surgery in malignant pleural mesothelioma. Eur Respir J. 2017 Mar 15;49(3). pii: 1601428.
29. de Perrot M, Wu L, Cabanero M, Perentes JY, McKee TD, Donahoe L, Bradbury P, Kohno M, Chan ML, Murakami J, Keshavjee S, Tsao MS, Cho BCJ. Prognostic Impact of Tumor Microenvironment after Hypofractionated Radiation and Surgery for Mesothelioma. J Thorac Cardiovasc Surg 2019 (in press).
30. Lee HS, Jang HJ, Choi JM, Zhang J, de Rosen VL, Wheeler TM, Lee JS, Tu T, Jindra PT, Kerman RH, Jung SY, Kheradmand F, Sugarbaker DJ, Burt BM. Comprehensive immunoproteogenomic analyses of malignant pleural mesothelioma. JCI Insight 2018;3:98575.
31. Hmeljak J, Sanchez-Vega F, Hoadley KA, Shih J, Stewart C, Heiman D, Tarpey P, Danilova L, Drill E, Gibb EA, Bowlby R, Kanchi R, Osmanbeyoglu HU, Sekido Y, Takeshita J, Newton Y, Graim K, Gupta M, Gay CM, Diao L, Gibbs DL, Thorsson V, Iype L, Kantheti H, Severson DT, Ravegnini G, Desmeules P, Jungbluth AA, Travis WD, Dacic S, Chirieac LR, Galateau-Sallé F, Fujimoto J, Husain AN, Silveira HC, Rusch VW, Rintoul RC, Pass H, Kindler H, Zauderer MG, Kwiatkowski DJ, Bueno R, Tsao AS, Creaney J, Lichtenberg T, Leraas K, Bowen J; TCGA Research Network, Felau I, Zenklusen JC, Akbani R, Cherniack AD, Byers LA, Noble MS, Fletcher JA, Robertson AG, Shen R, Aburatani H, Robinson BW, Campbell P, Ladanyi M. Integrative Molecular Characterization of Malignant Pleural Mesothelioma. Cancer Discov. 2018 Dec;8(12):1548-1565.
32. Chee SJ, Lopez M, Mellows T, Gankande S, Moutasim KA, Harris S, Clarke J, Vijayanand P, Thomas GJ, Ottensmeier CH. Evaluating the effect of immune cells on the outcome of patients with mesothelioma. Br J Cancer 2017;117:1341-8.
33. De La Maza L, Wu M, Wu L, Yun H, Zhao Y, Cattral M, McCart A, Cho BJ, de Perrot M. In Situ Vaccination after Accelerated Hypofractionated Radiation and Surgery in a Mesothelioma Mouse Model. Clin Cancer Res 2017;23:5502-13.
34. Vanpouille-Box C, Formenti SC, Demaria S. Toward Precision Radiotherapy for Use with Immune Checkpoint Blockers. Clin Cancer Res. 2018 Jan 15;24(2):259-265.
35. Formenti SC, Rudqvist NP, Golden E, Cooper B, Wennerberg E, Lhuillier C, Vanpouille-Box C, Friedman K, Ferrari de Andrade L, Wucherpfennig KW, Heguy A, Imai N, Gnjatic S, Emerson RO, Zhou XK, Zhang T, Chachoua A, Demaria S. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. Nat Med. 2018 Dec;24(12):1845-1851.
36. Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, Benci JL, Xu B, Dada H, Odorizzi PM, Herati RS, Mansfield KD, Patsch D, Amaravadi RK, Schuchter LM, Ishwaran H, Mick R, Pryma DA, Xu X, Feldman MD, Gangadhar TC, Hahn SM, Wherry EJ, Vonderheide RH, Minn AJ. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015 Apr 16;520(7547):373-7.
37. Brooks ED, Chang JY. Time to abandon single-site irradiation for inducing abscopal effects. Nat Rev Clin Oncol. 2019 Feb;16(2):123-135.
38. Huang AC, Postow MA, Orlowski RJ, Mick R, Bengsch B, Manne S, Xu W, Harmon S, Giles JR, Wenz B, Adamow M, Kuk D, Panageas KS, Carrera C, Wong P, Quagliarello F, Wubbenhorst B, D'Andrea K, Pauken KE, Herati RS, Staupe RP, Schenkel JM, McGettigan S, Kothari S, George SM, Vonderheide RH, Amaravadi RK, Karakousis GC, Schuchter LM, Xu X, Nathanson KL, Wolchok JD, Gangadhar TC, Wherry EJ. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. Nature. 2017 May 4;545(7652):60-65.