



Narrative review of theoretical considerations regarding HITHOC between past and future

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Abstract: Hippocrates constructed the medicines-surgery-energy triangle which includes all therapeutical modalities. Hyperthermic intraoperative chemotherapy (HITHOC) is a synergy-based single stage multimodality treatment encompassing the locoregional manifestation of the systemic malignant process. Pleural space, thermal effect, lavage/irrigation and chemotherapy represent the basic science ports of the network hub: HITHOC. The malignant transformation and process of the pleural surface (and underlying lung) challenges space management and tissue control. Thermotherapy without local chemotherapy is insufficient, similar to the normothermic local irrigation aligned with anticancer agents. The local administration of combined heat-transfer fluid and chemotherapy with or without subsequent surgical removal offers reasonable outcome in extensive primary pleural neoplasms (malignant mesothelioma), advanced (> Stage IIIA) NSCLC, functionally inoperable lung cancer and pleural carcinosis from extrathoracic malignancies. Measured by symptom-free survival and the quality of life, HITHOC in its present form, offers a modest yet fully substantiated solution. HITHOC in combination with the local application of targeted therapy and/or immunotherapy administered in the pleural space are currently under investigation. Additional development including new acting substances, their solvents and the means regarding surgical delivery and anesthesiology techniques are sign posts up ahead. Level 2 evidence are required in order to stepping up the recommendation levels, rewriting protocols and guidelines, in which HITHOC earns its revered position in the decision making process it deserves.

Keywords: Intrapleural hyperthermy; pleurodesis; video-assisted thoracoscopic surgery (VATS)

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Introduction

Unearthing the philosophical roots of a therapeutical modality may seemingly be an outdated approach used to explore core issues during the search for a hidden path leading to the promised land of increased efficacy, better survival not to mention cost-benefit optimization. The Greek philosopher Empedocles (490-430 BC) laid down the concept of the four elements representing constituents

of the World: earth, fire, water and air (1). This concept, further developed by Aristoteles inevitably found its way into the medical teachings of Asclepius and Hippocrates (2). Causes of diseases and treatment modalities were implemented into this quadrangular theorem in which temperature and fluid-content (humidity) served as the independent variables. Hippocrates while educating us, his very late disciples, while referencing to the complete horizon of medical interventions wrote: “*Those diseases*

which medicines do not cure, iron cures; those which iron cannot cure, fire cures; and those which fire cannot cure, are to be reckoned wholly incurable." (3). Decoding the particular modalities one by one, from the hierarchy applicable to present day cancer treatment ushers in a unique transformation, one evolving into a tripod schematic. Medicine is to chemotherapy added by targeted and/or immunotherapy. Surgery is the direct descendant of the iron in the text of Hippocrates, and refers to the scalpel. Fire as a per sé caloric treatment, originally in the form of heated oils or a blazing scarlet-red metal rod, yet astonishingly, present day hyperthermy matches and synchronizes to the expression. Radiotherapy also encapsulates the very same notion. Hyperthermic Intraoperative Chemotherapy (HITHOC) is an exquisite example regarding the modern transformation of the antiquated holistic concept turning all arms against the malignant processes. The scope of the present review is limited to intrapleural HITHOC (pHITHOC), excluding focused hyperthermy (tumor ablation). However, being voluntarily self-quarantined into the thoracic cage facilitates a closer focused look at the context of loosely related issues in their supportive role passim. Three basic science approaches leading to our main target: HITHOC of the pleural surface will be circumnavigated. Anatomical, physical and (bio)chemical aspects of hyperthermy are investigated in order to create a take-off platform for ideas leading to further developments.

Annotating a trajectory representing the future of the pHITHOC, is much like a task in putting jigsaw puzzle pieces together. The various pieces are positioned according to shape (strength) and potential (efficacy, toxicity) future union (interaction) with its partner(s). And so it is with the particular notions regarding pleural space, thermal effect, lavage/irrigation and chemotherapy, our primary actors.

We present the following article in accordance with the Narrative Review reporting checklist (<http://dx.doi.org/10.21037/atm-20-5855>).

Anatomy: the pleural space and its walls

The healthy pleural surface features the unique function in securing a frictionless movement between the parietal and visceral envelopes. A minimum amount of hyponcotic fluid is responsible for "oiling" the apparatus. Average intrapleural fluid turnover is estimated at or about 0.1–0.3 (0.02–2.0) mL/kg/h. Visceral pleura produces majority of pleural fluid, while the reabsorption is accomplished by parietal pleural lymphatics. There is an apicobasal

distribution among the production/absorption, in which the diaphragmatic mediastinal surfaces are responsible for the latter (4). The rate of flow seen in pleural lymphatics can lead to increases in response to an increase in pleural fluid filtration. The oncotic pressure is dependent on the macromolecular contents of the pleural fluid (5). Any potential mismatch between the production and absorption volume/capacity and/or change in the colloid/capillary oncotic and hydrostatic pressures of the fluid will likely result in the accumulation of the intrapleural fluid and subsequent compression on the underlying lung parenchyma. Apposition and the mesothel reaction of the two opposing layers resulting in symphysis leads to the elimination of the virtual space. While such a reaction is a dreaded consequence of tissue trauma in the abdominal cavity leading to the adhesions causing mechanical ileus (6), pleurodesis (7) is a much desired phenomenon in thoracic medicina and surgery. Assisted pleural adhesions in form of chemical pleurodesis is a well established method in coping with malignant pleural effusions (MPF) (8). The telling lack of mentioning pHITHOC in the combined European MPF guideline (9) as a viable therapeutical option is clear proof, the modality is out of focus in spite of its evidence-based applications (10). The hope of achieving local antitumor activity while performing pleurodesis by chemotherapeutical agents remains to be as of yet unfulfilled (11), and the results presented thus far are unconvincing (12). One of the most striking features regarding the contour of the pleural envelope affected by pathologic processes and malignant deposits are their diffuse and wildly irregular shape. This bizarre geometry and the extension of the malignant process typically excludes the "iron/blade" component of the hypocratean triangle. Irrigation overcomes the disadvantages regarding the static "filling up the cavity" as the turbulent streams reach the outermost recesses. The idea of irrigating the space surrounded by tumorous infiltration originates from the local treatment of abscesses and stage II thoracic empyaema (13). The concept of inflammatory process control by diluted substances has been transplanted into the field of topical anticancer treatment. Historical substances intended for wound treatment with acidificating agents such as wine (14) are distant reminders how the oncotic/hydrostatic pressure and pH are interrelated (15) during pHITHOC. Systematic drug delivery targeting malignant cells on or below the pleural surface bears a theoretical alternative in direct contact by flooding the cave with fluid (16) with or without continuous irrigation.

Medication in the classic hypocratean meaning of the therapeutical modality implies systemic chemotherapy. Synchron or adjuvant irrigation of an empty thoracic space created by (pleuro)pneumonectomy for malignancy with normothermic chemotherapeutics emerged in the 1990s (17). Armed with the advent of targeted therapy and immunotherapy the pleural space was plausibly offered. While the concept of topical application of anti-VEGF and anti-EGFR (18) sounds reasonable, the method is still confined to the wetlabs. Experiences with locally administered immunotherapy agents are promising to a certain degree, yet are far from earning a consolidated position in clinical practice (19). The third option offered by Hippocrates is fire, which can be translated either to hyperthermic therapy or radiotherapy.

Physics: the heat

There is a citation causing more harm than benefit to HITHOC circulating within the commonly referred to, alternative/complementary medicine domain, “give me the power to produce fever and I’ll cure all disease” supposed words credited to Parmenides, the presocratean philosopher (540?-460?BC). Giving medical credit to his cosmology whose fragments (20) are strewn over time is like stating there is a hidden recipe in the form of a mysterious panacea for all maladies. When more specific pathologies are in question, the picture is not so hazy. Systemic and sudden heating in the form of a provoked fever is a dated concept regarding the treatment of mental diseases (21). It was around 100 years ago in which Jauregg treated paralysis as a result of advanced syphilis with malaria reportedly achieving a response rate of 30% (22). Psychiatry is the territory of wide grey zones in which definitions are concerned, therefore outcomes hard to standardize. Malignant tumor responses to fevers alone are more objective, and the literature in this aspect is considerably transparent (23). Heat as a trigger of the immune system (24), a sort of biological therapy is a more recently evolving concept (25), however the cause-consequence question as of yet remains unanswered.

Opposed by focused heat directed at the solid tumor mass in any form of tumor ablation which is an established palliative method (26,27) local fluid hyperthermy with no added substance via irrigation appears to be a suboptimal solution (28). Seemingly, the concept appeared plausible and the application simple, yet the results lacked conviction (29).

Chemotherapeutics and other anticancer agents

A lengthy debate regarding the potential survival benefit of intrapleurally administered and irrigated normothermic chemotherapeutics concluded in 1995 with negative results (30). Drugs and times changed, yet no fundamentally contradictory observations followed (31,32).

The magic bullet of the cisplatin of the 1990s (33) and subsequent other drugs including bleomycin, etoposid and later the taxanes (34), all failed to achieve a measurable antitumor effect in the pleural space. Capillary leakage syndrome, toxic pulmonary injury, unpredictable absorption rate/depth were responsible for the unfavourable outcomes of the normothermic tests associated with these drugs (35,36). Encouraging experiences with bladder irrigation and other compartmental administrations, including intrathecal therapies (37) missed the pleural space. The jury is still out regarding the question of the efficacy of antigen triggered antitumor immunological response (38). Recently, intrapleural immunotherapy ushers new indications (19). Monoclonal antibodies such as bevacizumab and similar actors, cope with the metastasizing tumor causing MPE offers a logical bifocal action (39). To make a complicated picture more confusing, there is an accumulating number of observations in reference to beneficial alterations regarding therapy resistance in both directions of immunotherapies and chemotherapies as seen in pulmonary malignancies. Since we are focusing on the local application of these agents, the question is beyond our present interest.

Crossroad

Systemic cisplatin based chemotherapies and the taxanes radically improved median survivals from the mid-1990s, and many patients survived long enough to develop MPE, a treatment challenge. Vascular endothel growth factor (VEGF) promoting blood vessel permeability was a iatrogenic cause in the drastic increase of MPE. Intrapleurally administered chemotherapies failed to fulfill the promise in keeping the process at bay. Paradigm changes in oncotherapies regarding extrathoracic malignancies, especially breast cancer (40), and large bowel malignancies (41) produced many long survivors and very late relapses and more importantly pleural metastases. Combined anticancer treatment results had to be interpreted in a matrix in which many shades of a grey zone replaced the former black and white division line between the categories of curative and palliative

treatments. Mesothelioma thus far as a neglected emerging entity posed as the third element (42) The four main factors, and several others not independent from one another, all in the context of the pleural space and underlying lung were in need of an efficient therapeutical solution. One of the answers was HITHOC.

Dawning from the early 1990s an emerging number of cases were treated using hyperthermy and results have been published (43) covering the NSCLC (44), the mesothelioma (45) and the metastatic pleural malignancies domains reached the present state of art. Different pHITHOC methodologies are investigated, hyperthermic chemotherapy with or without surgery, synchron or adjuvant setting are presented, including a variation regarding delivery teactics (46-49).

Currently the distribution regarding the origin of the publications show the method is center-of-experience linked, scattered throughout Italy, Germany (50) and France with a seemingly similar pattern when compared with the early stage of the evolving technique of video-assisted thoracoscopic surgery (VATS) in Europe around the turn of the new milleneum. Dedicated centers in Turkey and USA collected vast experiences, while Chinese authors (10,29) are accumulating and publishing encouragingly positive mass experiences and basic research.

Presently, the journal covers the state of art regarding HITHOC, and there is no need to discuss the recent evidences in their full depth nor to detail the existing controversies. What is the most pressing issue is, where to go from here? A notion pro futuro.

The next steps

Nanotechnology is one of the fields exalting promise in which a high definition delivery of the antitumor agents is the key element. Exploiting the interaction of the components is the modern equivalent of the hypocratean category representing fire: hyperthermy and irradiation, the potentials of the heat radiosensitivation are perhaps worth exploring. Magnetic-nanoparticle-mediated intracellular hyperthermia aims at the localized tumor heating with minimal or no collateral damage (51). The temperature threshold is a tor about 43 °C. Heat-shock protein expression causing tumor-specific immune response may be an added value. Another nanotechnical method is to optimize the chemotherapeutic agent delivery (52-54). Temperature dependence regarding the chemical reaction rate and diffusion coefficients is one of the basic rules,

HITHOC handsomely applies (55). Differences in heat sensitivity among particular cell types and tissues are paramount regarding selective effects and reactions. The same time-temperature relationship has been observed regarding heat inactivation in proteins, The combination of HITHOC with ipsilateral lung perfusion (56) used in cancer control is a theoretical option.

There are two more questions to discuss, more specifically surgical issues. The first topic is the oncotic pressure of the intracavitary fluid and the interdependence with the pH. The standard medium for chemotherapeutics use implies pHITHOC is the isotonic solution. The pharmacokinetics of the drugs are optimized for their original intravenous application, in which vascular wall protection is a priority. However, the pleural surface is more resilient than the vascular endothel, therefore a more relaxed attitude is permitted. The pharmacodynamics of the given acting substance, not the solvent itself serves as the decisive factor. Intraoperative irrigation using isotonic salt in order to protect the serosal cell layers of intraabdominal organs is a generally established preventive maneuver. The release of a freed tumor cell by the intracavitary maneuvers in oncosurgery is a well documented phenomenon in the abdomen (57) and also the thorax (58). Turnbull's no-touch precept (59), once a universal cancer surgery command is not yet entirely cancelled. The intraabdominal/thoracic organ trauma during extensive video controlled procedures do not seem to confirm the validity regarding the 50 years old teaching, or at least the published results do not reflect it. Only a few publications are available referencing the clinical practice of using sterile water or hyponcotic (hypotonic) fluid in order to cause malignant cell cytolysis, or osmotic death. The hypotonic shock (60) kills the freed tumor cell by the osmotic imbalance when excess water is diffused into the cell through the cell membrane or through the aquaporins, the selective membrane channels. Reaching the membrane capacity, the malignant tumor cell bursts. Many of us, who have been following the same practice for ages did not consider this protocol worth of a publication. Chloride ion channel blockers have been proven to increase the efficacy of cellular hypotonic shock during pancreas surgery (61). Oncocytolytic maneuvers are reported during gastric (62), and colorectal (63) surgeries. Surprisingly, published papers are scarce regarding the thoracic cavity (64), a place where pleural surface pH protection is not a priority. Urologists, pioneers of intracavitary immunotherapy decades before the monoclonal antibodies became available, investigated the

tumor cell killing capacity of sterile water (65). The acting mechanism theories regarding how water induces autocrine stimulation leading to cell death by apoptosis are indeed numerous (66). There is indirect evidence referencing the effect, in which there is increased oncotic pressure in solid tumors (67). The question emerging here, “Will the use of hyponcotic solvents for the intrapleurally administered anticancer drugs during pHITHOC increase therapeutical efficacy?”—begs for consideration.

Minimal access delivery of pHITHOC via VATS (68) is yet another field witnessing development, especially the issue of anesthesia. The application of experiences gained during noninvasive ventilation (NIV) regarding lung cancer surgery is promising territory (69). Anesthesia for HITHOC is a delicate subject for excessive systemic response to treatment (70). Recent modifications securing airways without positive end pressure bears the added value of beneficial pressure conditions on the lung parenchyma (71).

Conclusions

Extensive primary pleural neoplasms (malignant mesothelioma), advanced (> Stage IIIA) NSCLC, functionally inoperable lung cancer and pleural carcinosis due to extrathoracic malignancies (i.e., breast cancer and colonic cancer, etc.) are the main targets regarding the pHITHOC, a synergy-based single stage multimodality treatment. In the foreseeable future cancer medicine cannot cancel the methods of physically destroying the tumor mass, the locoregional manifestation of a systemic disease (72). The combination of the systemic treatment and local control of a malignant pleural process are the key elements characteristic of pHITHOC, a chimera, and a hybrid approach for a disease which is symbolically best described as Cancer. One might argue that abundance of Greek philosophy surreptitiously infiltrated this review, but without understanding the basic principles of our art no Artificial Intelligence Wonder Algorithm can help us orientate throughout the labyrinth regarding pneumopleural malignancies.

Symptom free survival and quality of life are the two goals of oncosurgery. Measuring using these two parameters, pHITHOC in present form offers a modest yet well established solution. To become a standard procedure in the field pHITHOC must follow the pattern of emerging modalities regarding focused energy tumor ablation including high frequency and radiotherapy. The

prospective studies presented thus far and cited here provide solid level III evidence is support regarding the efficacy of HITHOC treatment. Randomized studies are needed in stepping up the recommendation levels, rewriting protocols and guidelines, in which HITHOC is awarded its position in the decision making process it righteously deserves.

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