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Utilisation des plasmas gazeux en oncologie : Une revue systématique

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A mes parents

Vous m'avez toujours soutenu, soyez assurés de ma grande reconnaissance.
Je vous dédie ce travail en témoignage de mon amour.

A ma sœur et mon frère

Merci pour nos moments complices.

A toute ma famille

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Xavier et JB, merci pour les bons moments passés à discuter.

A notre Président de thèse,

Madame le Professeur NABET Cathy

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- Lauréate de l'Université Paul Sabatier,
- Lauréate de l'Académie Nationale de Chirurgie Dentaire

Vous nous faites le très grand honneur de présider ce jury de thèse.

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Nous vous remercions et vous prions de bien vouloir trouver ici l'expression de notre gratitude et de nôtre profond respect.

A notre directeur de thèse,

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- Docteur de l'Université Paul Sabatier,
- Ancienne Interne des Hôpitaux de Toulouse,
- Lauréate de l'Université Paul Sabatier.

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Veuillez trouver ici l'expression de notre profonde reconnaissance.

A notre jury de thèse,

Madame le Docteur Laurencin Sara

- Maître de Conférences des Universités, Praticien Hospitalier d'Odontologie,
- Docteur en Chirurgie Dentaire,
- Docteur de l'Université Paul Sabatier,
- Diplôme Universitaire de Parodontologie

Nous vous remercions d'avoir accepté de juger ce travail et de siéger parmi les membres du Jury. Veuillez croire en l'expression de notre sincère et profonde gratitude.

A notre jury de thèse,

Monsieur le Docteur Paul Monsarrat

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- Docteur de l'Université Paul Sabatier - Spécialité Physiopathologie,
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- CES Biomatériaux en Odontologie.

Vous nous faites l'honneur de juger ce travail. Nous vous remercions pour cela et les précieux conseils que vous nous avez si gentiment donnés.

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Introduction

Ce travail de thèse s'inscrit dans la thématique « applications biomédicales des plasmas ». Ce champ de recherche est relativement jeune (une vingtaine d'années environ). Il présente aujourd'hui un rayonnement national et international certain et croissant.

Les « applications biomédicales des plasmas » regroupent 3 sous-thématiques :

-Stérilisation et décontamination par les espèces produites par plasma

-Traitements des surfaces pour une application médicale : Biomatériaux, élaboration de nouveaux tissus, matériaux bioactifs

-Plasmas thérapeutiques pour la médecine

Nous avons axé notre recherche sur les plasmas thérapeutiques pour la médecine et en particulier dans le domaine de l'oncologie. Notre objectif est de dresser un état des lieux des connaissances dans ce domaine.

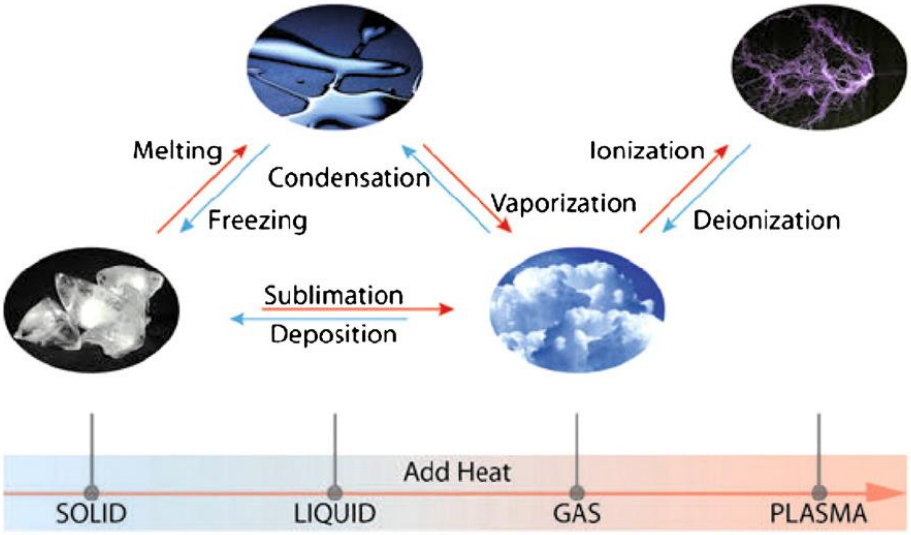
Dans une première partie, nous introduirons la notion de « plasmas thérapeutiques pour la médecine » ainsi que les principaux résultats dans l'application à l'oncologie.

Dans une deuxième partie, nous présenterons une revue systématique de la littérature selon les critères PRISMA. Cette partie sera rédigée sous la forme d'un article, soumis dans une revue internationale et indexée PubMed.

1. A propos des plasmas gazeux

1.1. Généralités [1,2]

Le plasma est défini comme étant le 4éme état de la matière. Il a été découvert par le physicien britannique Sir William Crookes en 1879 mais c'est le chimiste américain Irving Longmuir qui lui donna l'appellation de « Plasma » en 1929.L'univers visible est composé à 99% de plasmas.



Les quatre états de la matière [1]

Un plasma est un milieu gazeux ionisé, comportant des électrons, des ions et des espèces neutres, atomes ou radicaux. Il existe deux types de plasmas : les plasmas froids qui possèdent un degré d'ionisation assez faible (le rapport des densités des particules chargées sur celles des espèces neutres est compris entre 10^{-7} et 10^{-4}) et les plasmas chauds qui concernent la fusion thermonucléaire contrôlée, dont le degré d'ionisation est voisin de 1. Seuls les plasmas froids sont utilisés pour les applications biomédicales.

Les plasmas froids sont des milieux ionisés dans lesquels la température des atomes et des molécules neutres (T0) est froide, comprise entre 30°C environ et plus de 700°C. Les électrons, en revanche, captent l'énergie fournie par l'alimentation électrique qui permet de créer le plasma. Leur température (Te) est très élevée, de 1 à 10 eV (1 eV est équivalent à plus de 11000°C). Ce sont les électrons qui, par collisions sur le gaz neutre, vont donner leurs propriétés réactives aux plasmas froids.

Nous nous intéressons dans notre thèse aux plasmas froids hors équilibre thermodynamique, Te>>T0. Ce sont des plasmas de décharges. Grâce aux avancées récentes dans la compréhension des mécanismes physico-chimiques permettant de générer un plasma « froid », à pression atmosphérique, et grâce aux progrès techniques de miniaturisation des dispositifs électriques nécessaires à la génération de ces plasmas, une nouvelle thématique est née : les applications biomédicales des plasmas.

Plusieurs méthodes existent aujourd'hui afin de produire un plasma atmosphérique froid. Nombreux sont les gaz utilisables pour générer un plasma, ainsi on retrouvera : l'Hélium, l'Argon, l'Azote, l'Oxygène, l'Air, ou même des mélanges de ces gaz.

1.2 Plasma médecine [3–8]

Les applications biomédicales des plasmas atmosphériques froids sont très vastes et constituent un champ médical à part entière nommé : Plasma médecine.
L'utilisation actuelle de ces plasmas atmosphériques froids (CAPs pour « Cold Atmospheric Plasmas ») est essentiellement retrouvée au niveau industriel pour la production de biomatériaux et repose sur des applications indirectes du plasma. Les recherches actuelles ouvrent la voie vers des applications directes du plasma sur les tissus vivants, notamment en médecine humaine.

Les CAPs trouvent leur utilité dans la décontamination et la stérilisation de certains dispositifs médicaux et implantables, ainsi que dans l'optimisation des biomatériaux. L'une des applications cliniques les plus étudiées aujourd'hui est la cicatrisation des plaies chroniques [6]. L'action cicatrisante des CAPs semble être médiée par une action de décontamination (y compris en présence de SARM [7]), par une action anti-inflammatoire et par une action pro-angiogénique. D'autres champs d'application sont également à l'étude tel que l'ingénierie tissulaire, le traitement de certaines pathologies dermatologiques (dont le psoriasis), la parodontologie [8], les blanchiments dentaires ou encore le traitement des cellules tumorales [1].
En effet, les CAPs sont sources d'espèces réactives de l'oxygène et de l'azote. Les radicaux libres ainsi générés sont à l'origine du stress oxydatif au sein des tissus et cellules vivantes, ou bien de l'activité antimicrobienne.

D'autres applications cliniques des CAPs concernent la coagulation et la découpe de tissus vivants (bistouri de coagulation par plasma d'Argon à radiofréquence)

De telles applications des CAPs sont un véritable challenge d'un point de vue médical mais également d'un point de vu physique, de par la nécessité de la mise au point de sources de plasma adéquates au milieu biomédical, tout en garantissant un haut niveau de sécurité.

1.3 Production des Plasmas [1,3,9]

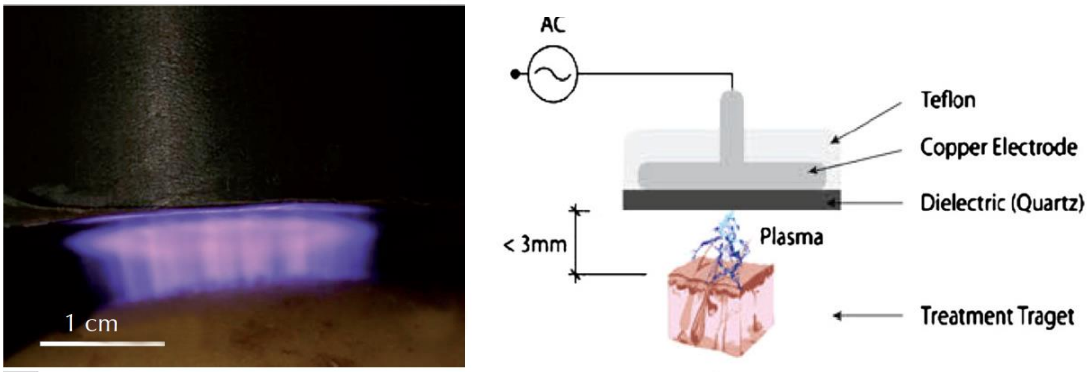
Les systèmes produisant les CAPs peuvent être classés en trois grandes catégories en fonction de leur application sur les zones cibles. Ainsi on retrouve :

- Les systèmes directs
- Les Systèmes indirects
- Les systèmes hybrides

1.3.1. Les Systèmes directs

Dans un système direct, la zone cible constitue une électrode auxiliaire. La principale technologie est le système de décharge à barrières diélectriques (DBD) à électrode flottante. Un système direct permet la formation d'un plasma homogène et à haute concentration en espèces réactives.

Il est parfaitement adapté au traitement des srfaces et ne génère pas d'UV-C. Le milieu plasmagène est l'air ambiant. Cependant, il nécessite une distance constante entre la surface traitée et l'électrode, le courant généré doit traverser les tissus et doit donc faire l'objet d'une surveillance stricte.



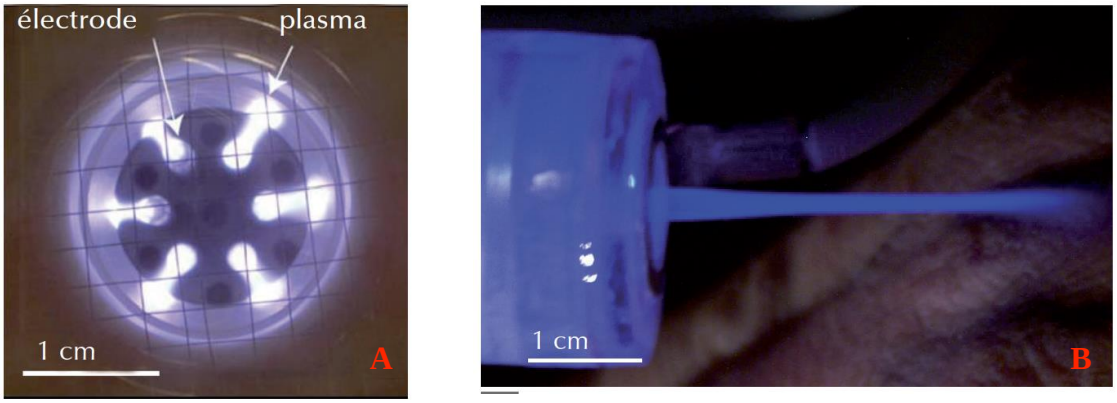
Système de décharge à barrières diélectriques à électrode flottante.
A. Application clinique (3). B. Schéma de composition [1]

1.3.2. Les systèmes Indirects

Les systèmes indirects n'utilisent pas la zone cible comme électrode auxiliaire. Le plasma est généré entre deux électrodes qui font partie intégrante de l'appareil. Ce plasma est transporté vers la zone cible au moyen d'un gaz. La composition du plasma peut alors être modifiée par le choix du gaz utilisé. Les systèmes indirects sont des jets de plasmas à pression atmosphérique et génèrent un « plume plasma » dont la taille peut varier de celle d'une aiguille à celle d'une torche.

De nombreux paramètres influencent la longueur de la « plume plasma » et la quantité d'espèces réactives, tels que le débit du gaz entrant.

Les jets de plasma peuvent êtres initiés par radiofréquence ou micro-ondes ou par des DBDs annulaires. Dans le cas des jets de plasma radiofréquence, la température de sortie du plasma et de l'ordre de 70 à 80 °C et doit donc être maintenu à distance de la zone cible.



A. Jet de Plasma par radiofréquence. B. Jet de plasma par système de décharge à barrières diélectriques annulaires [3]

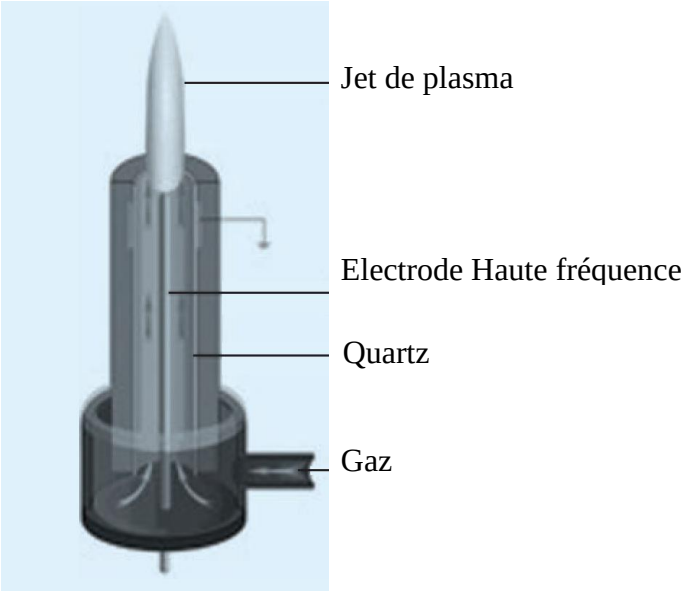
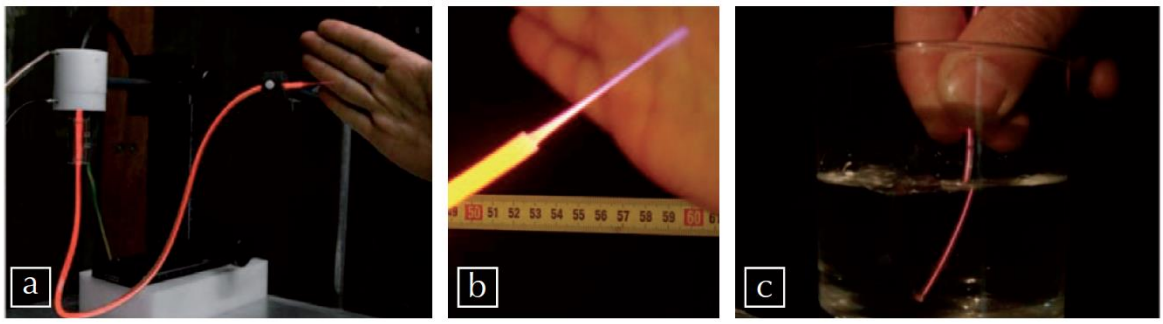


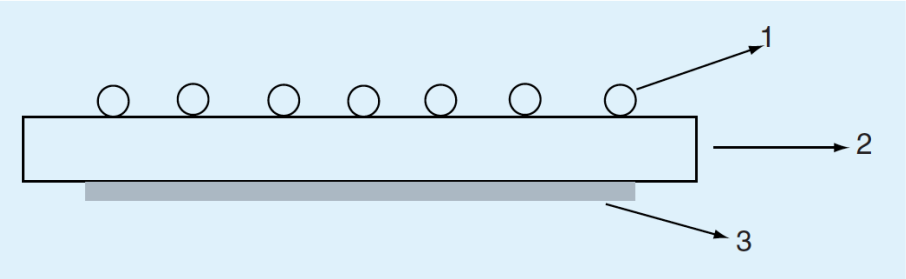
Schéma d'un jet de plasma à pression atmosphérique kINPen09® ((INP Greifswald/neoplas GmbH, Greifswald, Germany) [9]



Système Plasma Gun mis au point par le Groupe de Recherches sur l'Énergétique des Milieux Ionisés (CNRS/Université d'Orléans). A. Vue générale B. Plume plasma générée C. Plume plasma débouchant dans l'eau. [3]

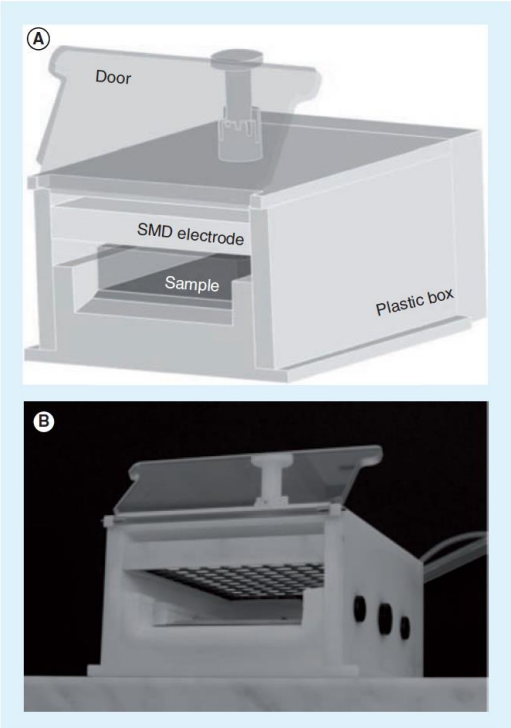
1.3.3. Les Systèmes hybrides

Enfin, les systèmes les plus récemment mis au point sont les systèmes hybrides. Ils combinent les bénéfices des systèmes directs et indirects. La génération du plasma est réalisée via des micro ou nano décharges sur une électrode terre. Le courant ne passe pas au travers de la cible. Des décharges homogènes peuvent facilement être produites même dans l'air ambiant. Le système est facilement adaptable à des zones cibles réduites ou larges par le remplacement des électrodes.



Structure d'une électrode Surface micro discharge (SMD). [9]

1.Electrode à maillage. 2. Plaque diélectrique flottante. 3. Electrode plane à alimentation

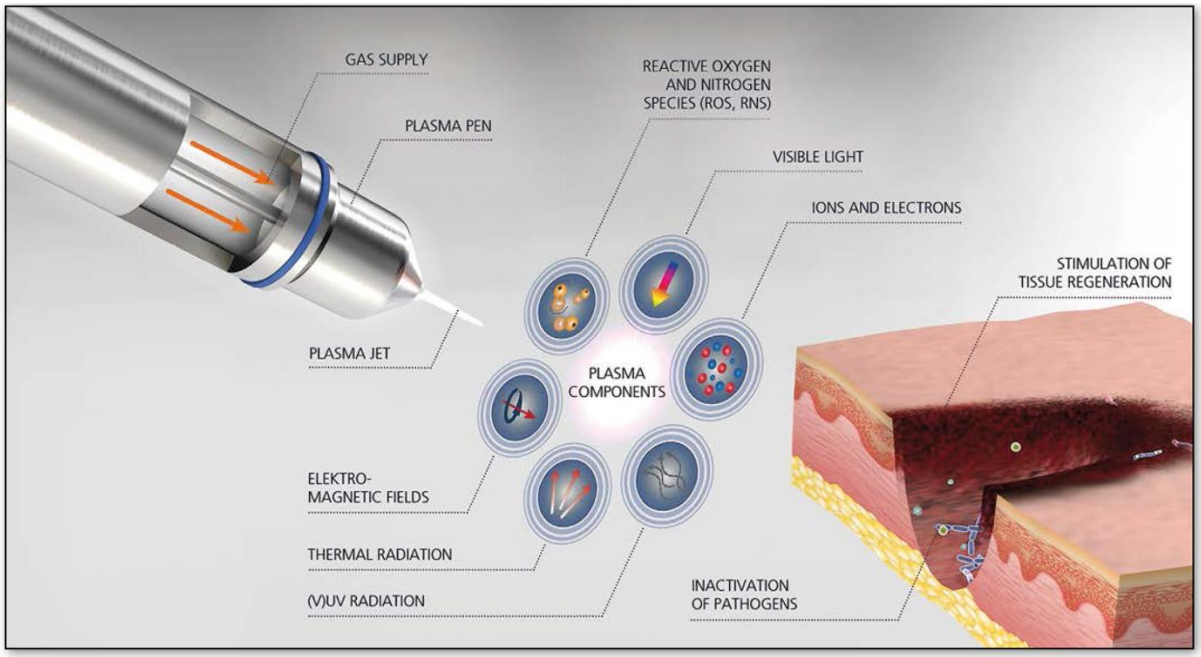


Système FlatPlaSter® (Adtec Plasma Technologies Co. Ltd, London, UK). [9]

A. Schéma du système. B. Photo du système en utilisation

1.4 Interaction des décharges à pression atmosphériques avec le vivant [10]

Les plasmas peuvent être considérés comme des convertisseurs énergétiques, utilisant l'énergie électrique ou électromagnétique, pour interagir avec un milieu (liquide notamment).



Composition des CAPs : Espèces réactives de l'oxygène, lumière visible, ions, électrons, champs électromagnétique, radiation thermique, radiation UV. [10]

Comme présenté dans le schéma précédent, les CAPs sont susceptibles d'interagir avec les tissus biologiques via des interactions physiques et chimiques impliquant : ultraviolets, chaleur, champs électromagnétiques et de nombreuses espèces réactives. Les effets physiques sont négligeables alors que le rôle espèces réactives semble majeur [10].

1.5. Intérêts des CAPs en oncologie. [1,11–18]

1.5.1. Exposition des systèmes biologiques au CAPs.

L'effet de ces espèces réactives sur les cellules cancéreuses a été étudié au cours des dernières décennies et est à la base des traitements par radiothérapie et certaines chimiothérapies [11]. Les plasmas atmosphériques froids via la production d'espèces réactives de l'oxygène et de l'azote sont donc des outils particulièrement intéressants pour traiter les cellules tumorales.

L'application de ces plasmas sur les tissus ou cellules repose sur un processus en plusieurs phases [12]. Une première phase d'initiation et d'état d'équilibre du noyau de plasma est suivie d'une phase de plasma post rayonnement. Cette dernière aboutit à la formation d'une interface de diffusion au sein d'un environnement liquide (milieu de culture ou fluides physiologiques entourant la tumeur). Cet environnement liquide modifié interagit, alors avec les cellules et tissus à proximité.

Les réactions chimiques au sein du noyau de plasma sont extrêmement complexes. On dénombre plus de 60 espèces différentes impliquées dans 1000 réactions [12]. Les espèces réactives de l'oxygène et de l'azote extracellulaires mais aussi intracellulaires jouent un rôle dans l'initiation des effets sur la cellule mais aussi dans la réponse à ces effets. Par ailleurs, de nombreux facteurs influencent les interactions tels que les mélanges de gaz ou bien les flux des différents espèces réactives à la surface des tissus.

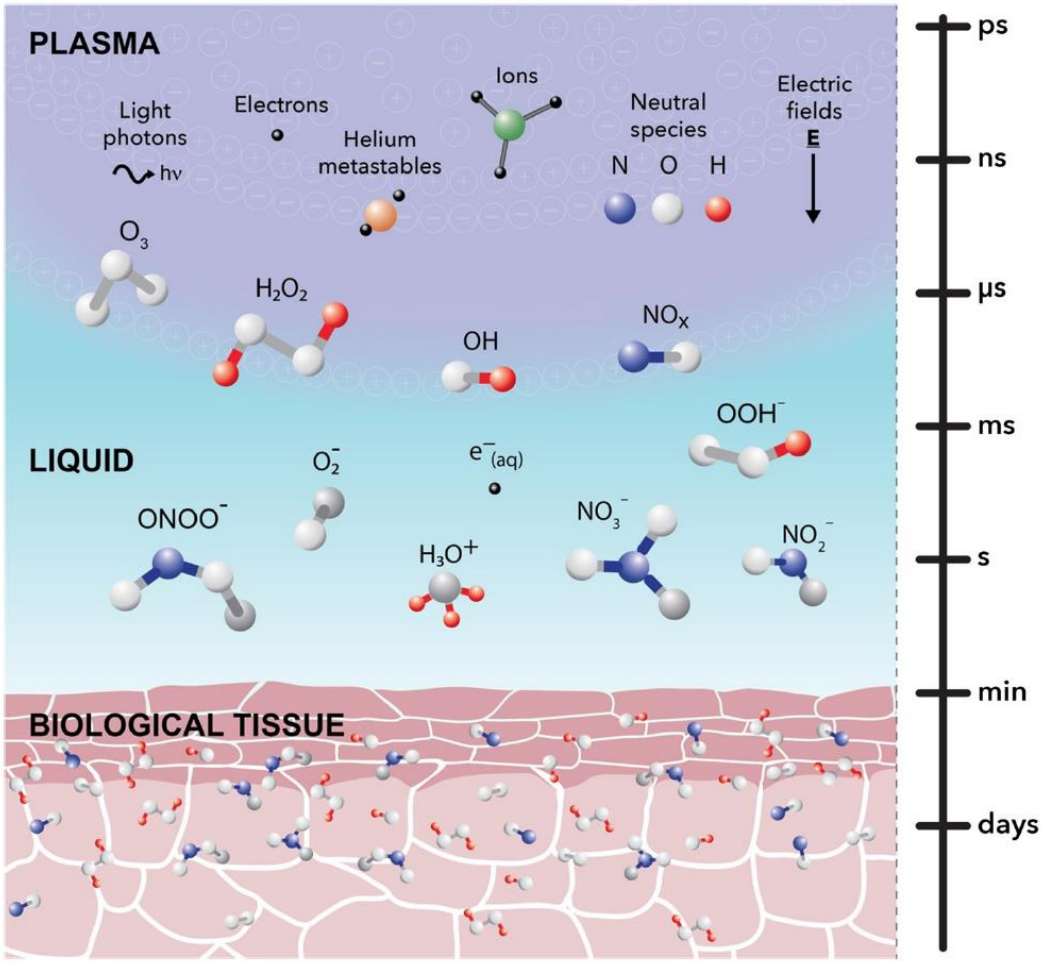


Schéma du processus d'interaction entre le plasma atmosphérique froid et les tissus biologiques. [12].

Les principaux constituants du plasma, que sont les photons, électrons, ions ou espèces neutres, conduisent à la formation au sein de l'environnement liquidien de nombreuses espèces réactives. Ces dernières se propagent ensuite dans les tissus. Les effets biologiques peuvent prendre plusieurs minutes à plusieurs jours par comparaison à la production des espèces réactives qui est constatée en quelques micro secondes à secondes et à la génération du flux de plasma en nanosecondes.

1.5.2. Stratégies d'utilisation du plasma atmosphérique froid [13]

Deux stratégies ont été mises au point pour traiter les cellules ou tissus :

- application directe du Jet de plasma ou de la DBD sur les cellules en culture ou les tumeurs in vivo (tumeurs sous-cutanées)

- application du plasma sur une solution secondairement utilisée comme milieu de culture ou bien injectée dans les tumeurs in vivo (tueurs sous-cutanées)

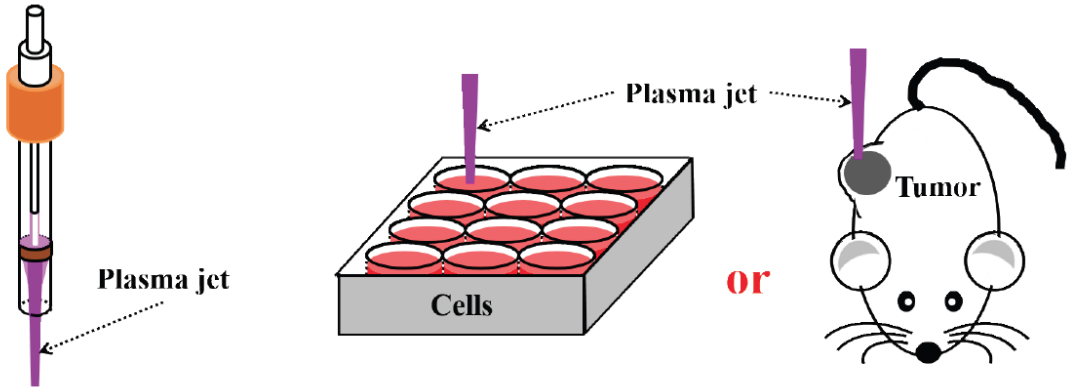


Illustration d'un traitement direct. [13]

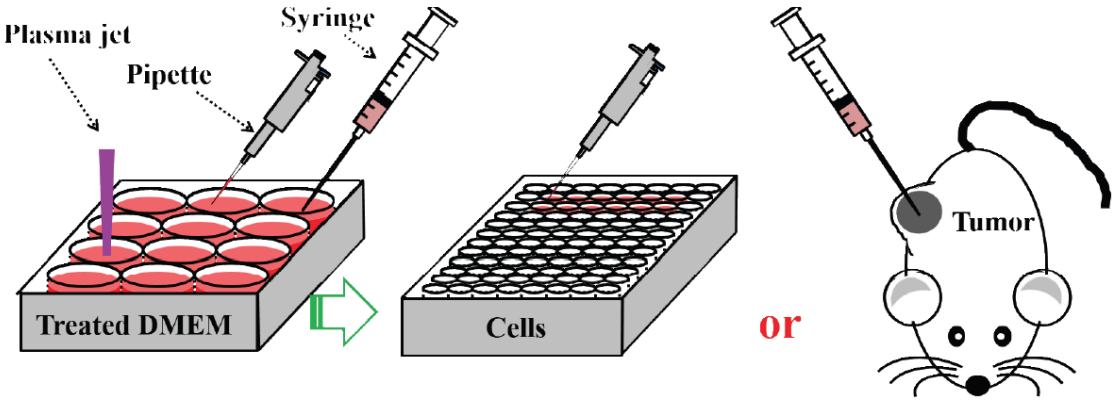


Illustration d'un traitement indirect [13]

1.5.3. Effets *in vivo* et *in vitro* bénéfiques en oncologie

De nombreuses études ont observé l'effet du plasma atmosphérique froid sur des tumeurs xénogénes sous cutanées greffées chez la souris. Plusieurs études *in vivo* ont été réalisées. Les résultats sont similaires et montrent une réduction significative de la taille de la tumeur après application du plasma atmosphérique froid [13,15]. D'autre part les taux de survie des souris traitées sont augmentés.

Pour autant, les mécanismes à l'origine de ces résultats ne sont pas encore élucidés. Une hypothèse avancée, implique le passage à travers la peau des espèces réactives et entrainerait une réponse immunitaire conduisant à la mort cellulaire. Une récente étude, menée sur un modèle de mélanome, a montré que la présence d'H_2O_2 était insuffisante pour éliminer la tumeur. L'efficacité du plasma serait alors liée à la production de nombreuses espèces réactives et pas uniquement H_2O_2 [14]. Enfin, cette même étude conclut à un effet négligeable des facteurs physiques (chaleur, UV, champs électromagnétique).

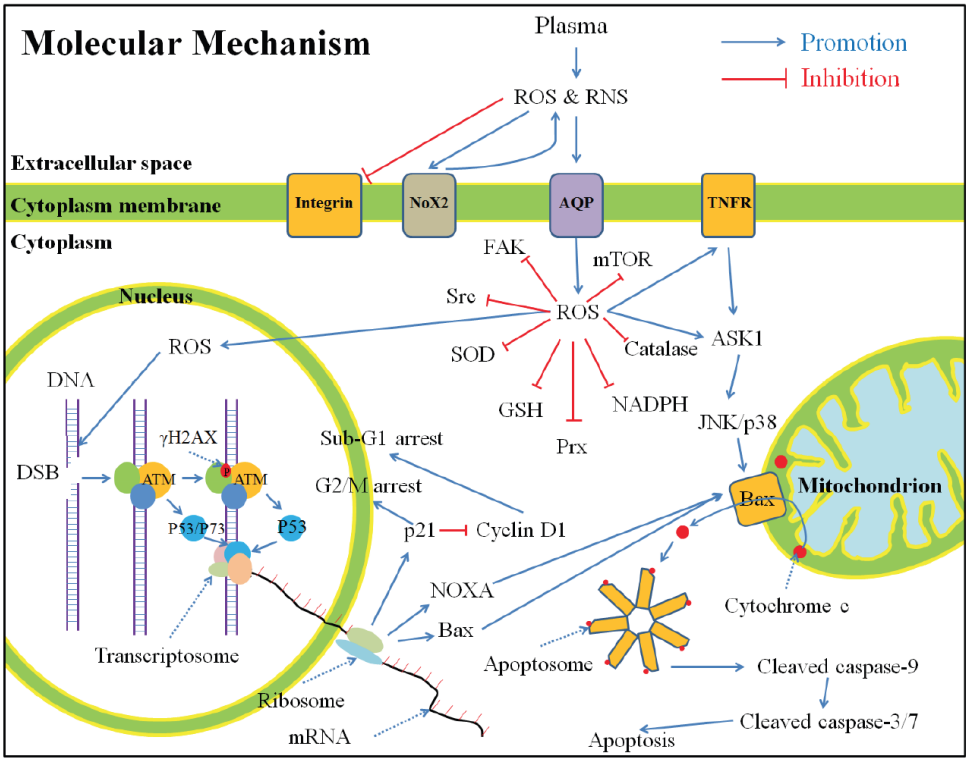
Après l'application directe ou indirecte du plasma, les espèces réactives de l'oxygène et de l'azote entrent en contact avec la membrane cytoplasmique. Un changement de morphologie est alors observé suite au traitement. Les cellules ont alors une forme étalée et perdent la polarisation et les protubérances cytoplasmiques. Ces changements morphologiques sont accompagnés d'une perte de l'adhésion et de la migration cellulaire. [11] La baisse de l'expression de certaines protéines telles que les intégrines ou les protéines kinases liées à l'adhésion (FAK) est constatée.

Le traitement par plasma atmosphérique froid entraine également une augmentation intracellulaire des espèces réactives et une modification de la balance redox. Cette augmentation pourrait être liée à la diffusion directe à travers la membrane cytoplasmique des espèces réactives produites par le plasma ou bien encore liée à l'activation de protéines membranaires qui secondairement induisent la production intracellulaire d'espèces réactives de l'oxygène. La perturbation de la balance redox au sein du cytoplasme de la cellule est inhibée par les substances anti-oxydantes telles que la N-acétyl-cystéine. Le stress oxydatif, induit par le plasma, a donc un rôle essentiel.

Par ailleurs, le traitement par le plasma entraine également des dommages de l'ADN et une activation des voies de signalisation de l'apoptose.[11,13,16] De nombreuses cassures double brin de l'ADN ont été observées après le traitement par plasma atmosphérique froid.

En effet, suite à l'apparition d'une cassure double brin, la protéine ATM (ataxia telangectasia mutated) est responsable de la phosphorylation de la sérine 139 de l'histone H2AX (γ-H2AX). Or, il a été observé une augmentation significative du taux de protéine ATM et γ-H2AX suite à l'application du plasma.

La protéine ATM peut également phosphoryler p53. La protéine p53 joue un rôle essentiel de maintien de l'intégrité cellulaire et peut induire l'apoptose. Cette protéine peut activer p21 et entrainer l'arrêt du cycle cellulaire en inhibant la cycline D1 ou bien activer l'expression de nombreux facteurs pro-apoptotiques (BAX, NOXA…). Ces facteurs pro-apoptotiques sont responsable de la libération du cytochrome C et d'autres protéines mitochondriales dans le cytosol. Le cytochrome C peut alors se fixer sur Apaf-1 activant par clivage la caspase 9 puis la caspase 3/7 qui finalement entraine le clivage de la polymérase poly ADP-ribose (PARP), marqueur important de l'apoptose. [13]



Mécanismes d'action du plasma atmosphérique froid *in vitro :* [13]

Enfin, le ciblage sélectif des cellules tumorales est un paramètre essentiel. De très nombreuses études ont mis en évidence une action du plasma atmosphérique froid sur les cellules cancéreuses tout en préservant les cellules bénignes [17]. Plusieurs hypothèses sont avancées pour expliquer ce phénomène.

La première repose sur le niveau intracellulaire basal en espèces réactives de l'oxygène. En effet, dans les cellules cancéreuses, le métabolisme est augmenté et par conséquent le niveau basal en espèces réactives aussi. L'ajout d'un stress supplémentaire par les espèces réactives produites par le plasma dépasse la limite de survie cellulaire plus facilement que dans les cellules saines. Cependant, cette hypothèse n'explique pas l'augmentation sélective en espèces réactives dans les cellules cancéreuses.

La deuxième hypothèse [17] expliquerait la sélectivité par la présence en nombre important des aquaporines sur la membrane des cellules cancéreuses. Ces aquaporines sont responsables du passage d'H_2O_2 dans la cellule. La diffusion des molécules d'H_2O_2 serait donc significativement plus rapide que dans une cellule saine.

Enfin, plus récemment [18], la diffusion des espèces réactives de l'oxygène a été associée à la fraction de cholestérol de la membrane. La membrane des cellules cancéreuses contient moins de cholestérol que la membrane des cellules saines. Ce cholestérol est responsable de la rigidité mais également de la perméabilité des membranes cellulaires. La peroxydation des lipides membranaires aboutit à la formation de pores et entraine une diffusion des espèces réactives, du milieu extracellulaire vers le milieu intracellulaire. Une fraction en cholestérol plus faible rendrait la cellule moins résistante à la peroxydation, à la diffusion d'espèces réactives et au stress oxydatif.

2. Revue systématique.

PLOS Medicine

Use of cold atmospheric plasma in oncology: a concise systematic review

--Manuscript Draft--

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	devices may be used directly at the bedside, others open the way for the development of new pharmaceutical products that can be generated at an industrial scale. The clinical use of this innovative therapy strongly needs the development of standardized reliable protocols. More studies are needed to determine the more efficient type of plasma for each type of cancer, probably to be combined with conventional treatments.
Suggested Reviewers:	
Opposed Reviewers:	
Additional Information:	
Question	**Response**
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Competing Interests You are responsible for recognizing and disclosing on behalf of all authors any competing interest that could be perceived to bias their work, acknowledging all financial support and any other relevant financial or non-financial competing interests. Do any authors of this manuscript have competing interests (as described in the PLOS Policy on Declaration and	The authors have declared that no competing interests exist.

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Please describe where your data may be found, writing in full sentences. **Your answers should be entered into the box below and will be published in the form you provide them, if your manuscript is accepted.** If you are copying our sample text below, please ensure you replace any instances of XXX with the appropriate details.	Data are available from S1 Table.

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Additional data availability information:	

Paul Sabatier University

Dear Editor,

We would like to submit a manuscript entitled “Use of cold atmospheric plasma in oncology: a concise systematic review” in PLOS Medecine.

The content of this manuscript has not been published or submitted for publication elsewhere. All of the named authors were involved in the paper, and have read it before it is submitted for publication.

Plasma is the 4th state of matter, an ionized gas that can be produced at low temperature and at atmospheric pressure. Already used in plasma medicine for sterilization and treatment of chronic wounds, its effects may also be beneficial for oncology. **Cold Atmospheric Plasma exposure** on eukaryotic cells induces chemical species that may be responsible for **beneficial effects regarding cancer cells**. *In-vivo* studies confirm these anti-cancer effects by decreasing the tumor volume and improving the survival rate.
Through this article, we are keen to provide an **overview** of this constantly evolving and promising field of the use of plasma in oncology. This is the first systematic review performed, in accordance with the PRISMA guidelines. The protocol of this systematic review has not been previously published or registered.

Our aims in the present work were to:

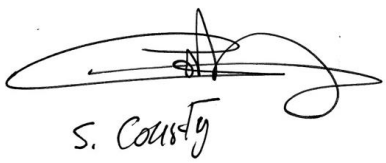
1) ***Provide a mapping of the use of plasma in oncology,***
2) ***Highlight the different methodologies of plasma production and application (cell targets, physical parameters, direct or indirect therapies).***

Taken together, all results reflect a **multiplicity of means of production and clinical applications** of the cold atmospheric plasma in the field of oncology. Among the different promising biological effects, plasma can **induce apoptosis of cancer cells resistant to conventional chemotherapy** treatments and may be used in combination with current treatments to obtain a **synergistic and complementary** action. The clinical use of this innovative therapy strongly needs the development of **standardized reliable protocols**. More studies are needed to determine the more efficient type of plasma for each type of cancer.
While plasma jets (indirect plasma sources) find their indication in a direct approach, Dielectric barrier Discharge (direct plasma sources) open the way for the development of **new pharmaceutical products** that can be generated at an industrial scale.

We have chosen to submit our manuscript to your prestigious journal in order to share our thoughts with the medical community and hope that these additional elements will contribute to cancer treatment.
We look forward to hearing from you.

DUBUC Antoine

COUSTY Sarah



Use of cold atmospheric plasma in oncology: a concise systematic review

Short title: Use of cold atmospheric plasma in oncology

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Abstract

Background: Cold atmospheric plasma (CAP) is an ionized gas that can be produced at an atmospheric pressure. CAP treatment induces the production of reactive species and therefore biological responses on human cells (e.g. apoptosis), which can be put at the service of oncology.

Objective: The aim of this systematic review is to map the use of CAP in oncology and the different methodologies implemented so far (cell targets, physical parameters, direct or indirect therapies).

Methods: Pubmed, ICTRP and Google Scholar were explored until 2017/01/17. All original reports regarding the use of plasma treatment for oncology were included (*in-vitro*, *in-vivo* studies, clinical trials). Were considered the countries of publication, the methodology, the type of plasma used, the gas used for its production, the application protocol (direct or indirect treatment) and the type of tumor cells.

Results: 152 original articles were included. USA and South-Korea published respectively 25.5% and 25.0% of the included citations. Plasma jets are the most used production systems 74.3%. Helium alone was the most used gas 34.7%, followed by air 27.6% and argon 19.7%. Most of the included studies were *in-vitro* (84.6%). Direct plasma treatments concerned 77.3% of studies. The most targeted cancer cell lines are human cell lines (82.2%), in particular brain cancer (15.0%).

Conclusions: This study highlights the multiplicity of means of production and clinical applications of the cold atmospheric plasma in the field of oncology. While some devices may be used directly at the bedside, others open the way for the development of new pharmaceutical products that can be generated at an industrial scale. The clinical use of this innovative therapy strongly needs the development of standardized reliable protocols. More

studies are needed to determine the more efficient type of plasma for each type of cancer, probably to be combined with conventional treatments.

Keywords: Non-Thermal Atmospheric Pressure Plasma; Neoplasms; Review; Plasma Jet

Abbreviations: CAP, Cold Atmospheric Plasma; DBD, Dielectric Barrier Discharge; FE-DBD, Floating Electrode DBD; PAM, Plasma Activated Medium; RONS Reactive Nitrogen and Oxygen Species; ROS Reactive Oxygen Species.

Introduction

Plasma is described as the fourth state of the matter. There are various biomedical applications of nonthermal plasma, such as sterilization [1,2] but its production at an atmospheric pressure (cold atmospheric plasma, or CAP) made possible the use for other medical applications (wound healing, blood coagulation, antibacterial treatment, proliferation of endothelial cells, …). Some devices are already used clinically [3], others are still on the bench side. Two predominant types of plasma devices can be distinguished: direct or indirect devices. Direct plasma sources (*e.g.* Dielectric barrier Discharge (DBD)) use the target area as a counter electrode. The produced plasma is homogeneous with a composition that can be controlled more easily. The major disadvantage of this technique is the application distance (between the electrodes) which must remain constant and limits its use for small areas. Indirect sources (*e.g.* Plasma jet) produce the plasma between two electrodes included inside the device, and a carrier gas then brings the plasma to the target. The composition in reactive oxygen and nitrogen species (RONS) is less homogeneous than using direct sources and the generated plasma is less controllable. However, the use of some specific carrier gases makes it possible to obtain changes about the plasma composition [4]. Two ways of applying plasma are also described: direct treatment and indirect treatment using plasma activated medium (PAM).

In-vitro plasma exposure on eukaryotic cells demonstrates several effects such as cell detachment, alteration of cell migration, apoptosis or necrosis according to the type of tested cells and the exposure parameters (power, time of exposure) [2]. Similar effects have been obtained with cancer cell lines, inducing apoptosis [5] and decreasing cell migration [6,7]. Studies suggest that cancer cells are more sensitive to CAP treatment than normal cells [8–12].

CAP induces both physical effects (production of ultraviolet, heat and electromagnetic fields) as well as chemical effects (production of RONS). Whereas the physical effects seem to have a negligible cellular impact [13,14], RONS may induce alterations of the membrane integrity, an increase in intracellular reactive oxygen species (ROS), a decrease of the antioxidant potential and DNA double strand brakes, and subsequent apoptosis [9].

We are keen to provide an overview of this constantly evolving and promising field of the use of plasma in oncology. The aim of this systematic review is to map the use of plasma in oncology and the different methodologies implemented so far (cell targets, physical parameters, direct or indirect therapies).

Methods and Materials

This systematic review was performed in accordance with the PRISMA guidelines (S1 Appendix) [15].

Sources of data and search strategy

Two major electronic databases were searched: PubMed and Google Scholar. Clinical Trials were also identified through the ICTRP search portal (available at http://apps.who.int/trialsearch/).

The search strategy (S1 Table) combines both keywords related to plasma (e.g. "plasma discharge" or "atmospheric plasma") and keywords related to medical fields (e.g. tumor, oncology).

This strategy was then slightly adapted to meet requirements of each database. Reference lists of query studies were inspected to identify any additional relevant published or unpublished data. The last search was conducted on 2017/01/17.

Inclusion criteria

All original reports regarding the use of plasma treatment for oncology were included in this systematic review. *In-vitro*, *in-vivo* studies, and clinical trials were considered. Language of publication was restricted to English and French.

Outcomes

The following outcomes were considered: the countries of author's affiliations (each authors' nationality was recorded, a study could be related to several countries), the type of methodology (*in-vivo*, *in-vitro*, clinical trial), the type of plasma used (DBD or Plasma jet), the gas used to produce the plasma (helium, air, argon w/wo adjuvant), the application

protocol (direct or indirect treatment), and when applicable, type of tumor cells (type of cancer or origin of the tumor cell line).

Study Selection and data extraction

All results were screened based on titles and abstracts. Full-texts of the potential selected records were obtained for definitive inclusion. Reviews and conference proceedings were not excluded but were considered apart. A standardized extraction form was created to collect data according to outcomes detailed above (S2 Table). Data extraction was performed twice by one author (AD) at one-month interval.

Results

We identified 3324 results, corresponding to 3187 unique citations. Final, 180 results were included: 152 original articles (84.4%), 20 reviews (11.1%), 7 conference proceedings and one ongoing clinical trial. Three studies, 1 in Chinese, 1 in Korean and 1 in German were excluded [16–18]. Flow diagram was available (S1 Figure). Details for each study are presented in S2 Table.

From 2005, the number of original articles has grown exponentially (Fig. 1A) while the proportion of reviews is variable from year to year (Fig. 1B). The world map (Fig. 1C) reveals that USA and South-Korea published respectively 25.5% and 25% of the citations.

Plasma production

The two methods of plasma production were found (Fig. 2), although more studies used the Plasma jet compared to the DBD (74.3% and 25.7%, respectively). One study did not specify the type of plasma production [19]. Helium alone was the most used carrier gas (32.7%), followed by air (25.9%) and argon (18.5%) (Table 1).

Table 1. Gas used in non-review articles (N=152). A study could be considered into several categories.

	Helium	Air	Argon	Helium + Oxygen	Nitrogen	Argon + Oxygen	Nitrogen + Oxygen	Argon + Nitrogen	Helium + Oxygen + Nitrogen
Number of studies	52	42	30	20	8	5	2	1	1
Proportion of studies	34.2%	27.6%	19.7%	13.1%	5.2%	3.2%	1.3%	0.6%	0.6%

Three studies did not specify the gas used to produce the plasma [19–21]. The use of argon seemed to be on the rise since 2015 while the use of Helium remained stable since 2014 (Fig. 3).

Plasma application

Fig. 4 reveals most of the studies were *in-vitro* (143, 84.6%). The proportion of studies with *in-vivo* results remained low (22, 13.0%). Few clinical trials (4, 2.4%) have been found [3,22,23] and only one is ongoing [24]. Fig. 5 highlights the predominant use of direct plasma treatments (129, 77.3%) compared to indirect treatments (38, 22.7%). However, in recent years, the number of studies using an indirect plasma treatment has importantly increased (Fig. 5).

Type of neoplasms

The various cancers studied are presented in Table 2. The most commonly reported human cancers (125, 82.2% of total studies) were brain cancer (23, 15%), followed by lungs cancer (20, 13.0%) and blood cancer (19, 12.4%). Murine cancer cell lines are less studied (19, 12.5% of total studies), mainly melanomas (13, 8.5%).

Table 2. Cancer and tumor cell lines studied in non-review-articles (N=152). A study could be considered into several categories.

	Human cancer cells	**Murine cancer cells**	**Non-cancer cells**
Brain cancer	23 (15%)	1 (0.6%)	-
Lung cancer	20 (13%)	1 (0.6%)	-
Blood cancer	19 (12.4%)	2 (1.3%)	-
Melanoma	18 (11.7%)	13 (8.5%)	-
Breast cancer	14 (9.1%)	2 (1.3%)	-
Cervical cancer	14 (9.1%)	-	-
Colorectal cancer	14 (9.1%)	-	-
Head and neck cancer	10 (6.5%)	1 (0.6%)	-
Hepatocellular cancer	9 (5.8%)	-	-
Prostatic cancer	6 (3.9%)	-	-
Ovarian cancer	5 (3.2%)	-	-
Bladder cancer	3 (1.9%)	-	-
Gastric cancer	3 (1.9%)	-	-
Osteosarcoma	3 (1.9%)	-	-
Pancreatic cancer	3 (1.9%)	-	-
Thyroid cancer	3 (1.9%)	-	-
Uterine cancer	2 (1.9%)	-	-
Epidermal cancer	1 (1.9%)	-	-
TOTAL	***125 (82.2%)***	***19 (12.5%)***	***52 (34.2%)***

The temporal analysis of the type of cancers derived from either human or murine cell lines are presented in Fig. 6A and 6B, respectively. The main used murine cancer cell line (19, 12.5% of the total studies) is derived from melanoma, and its use significantly increased from 2009. Between 2011 and 2015, six other murine cancer cell lines began to be used. About the human cell lines, before 2008, only cells from breast, melanoma and hepatocellular cancers were found in the studies. The year 2009 marked the use of various cancer cell lines.

Discussion

This systematic review highlights the multiplicity of the means of production and clinical applications of the cold atmospheric plasma in the field of oncology. The clinical use of this innovative therapy strongly needs the development of standardized reliable protocols.

The World Health Organization estimated in 2012 the emergence of more than 14 million new cases of cancer in the world [25]. The search for new complementary or with less side-effect anticancer treatments is therefore in rapid expansion. The implications in research on plasma and oncology seems to be correlated with the incidence of cancer in the world. CAP induces apoptosis of cancer cells [2] and is so a promising treatment. One of its main advantages over conventional therapies is the potential selectivity concerning cancer cells [8,14,26–28]. This is an essential parameter in the era of targeted therapies. Localized treatments also reduce systemic deleterious side-effects. Furthermore, CAP seems to have an effect on resistant cancer cells to current treatments [29–32].

Plasma jet is the predominant system used for plasma production. Direct CAP treatment is more represented but indirect treatment appears to be increasing in recent years.

Concerning the direct application of CAP at the clinical level, two systems stand out today: Plasma jets and Floating Electrode DBD (FE-DBD) [2,33]. When using a FE-DBD, the second electrode is not ground. It is the human tissue or organ that acts as a floating electrode. This system generates plasma in the air and imposes a maximum distance of 3mm between the two electrodes. The use of a plasma jet allows the propagation of plasma in small capillaries. Moreover, the use of a carrier gas makes it possible to modulate the plasma composition [4]. The prospects of clinical application are the deep organs. The development of a device called Plasma gun (which is a plasma jet), allows application of the plasma plume up to 1.5 meters from the source [34]. Such a system allows the application of CAP under

endoscopy and falls within a context of less invasive surgery. CAP may be considered after tumor resection in order to treat the tumor microenvironment and the wound margins. FE-DBD has also demonstrated its anti-cancer properties *in-vitro* and *in-vivo* [33,35]. Otherwise, no study has examined the potential superiority of one system over the other. However, the impact of the electric field in the use of FE-DBD should be evaluated. Indirect treatments can modify the effects of plasma. Indeed, cytotoxic effects depend on the medium and the delay between exposure and change of medium [36]. An indirect treatment allows the injection of PAM, for instance, to treat more superficial tumors by direct approach (skin, oral cavity). Moreover, PAM may be stored at -80°C, keeping its anti-cancer effects [37]. The study of the most stable and effective PAM, opens the way for new pharmaceutical products.

Direct or indirect application does not result in a significant difference in plasma effects on cancer cells [38,39]. Both types of treatment decrease cell viability [40]. The ultimate objective is to be able to bring the benefits of CAP towards the treatment of patients. It is therefore necessary to validate the most reliable therapy for each clinical situation, in terms of efficiency and ergonomics.

We show that helium alone was the most used carrier gas for plasma and that gas mixtures were rarely used. The choice of gas is determinant for the composition of the plasma and the concentration of RONS. According to Kim *et al.* [41], the rate of apoptosis of human breast cancer cells was greater with helium and increases if oxygen was added. The amount of ROS increased using helium compared to argon or nitrogen [42]. The use of nitrogen is responsible for a greater concentration of reactive nitrogen species. The addition of oxygen to a flow of helium was responsible for a higher production of ROS [43]. It is not clear which kind of CAP is more efficient in anticancer application, and more studies are needed to determine the more efficient type of plasma for each type of cancer. Moreover, no resistance to CAPs have been demonstrated till today.

Many cancers may benefit from the use of CAP treatments. The most tested cell lines are derived from brain tumors. Brain and central nervous system cancer account for about 1.8% of new cancers and their incidence and mortality rates are higher in developed regions (Europe, North America, Australia / New Zealand) [25]. The predominant use of glioblastoma cell lines shown in this study may be related to the aggressive nature of this malignant primary brain tumor, whose prognosis is not superior to one year with a very limited long-term survival. This cancer is also highly resistant to chemotherapy, radiotherapy and surgery [44]. Treatment with CAP could become an effective complementary therapy on these cancer cell lines. Murine melanoma cancer cell lines and human melanoma cancer cell lines represented 8.5% and 11.7% of the studies, respectively. Melanoma is the most aggressive skin cancer, and its prevalence is high, representing 1.6% of the new cancers [25]. Melanoma median overall survival is less than 2 years. Melanoma, like brain cancers, is often resistant to acute treatment modalities [40]. Furthermore, due to the anatomical position of the melanomas, a treatment with CAP can be envisaged directly or indirectly. Both approaches have shown their efficiency in reducing the viability of melanoma cells. However, some cancer lines of melanoma are less sensitive to PAM than to direct treatments [40].

Several cancer models have been studied, ranging from 2D cell culture to 3D cell culture or *in-vivo* tumors. Twenty-two *in-vivo* studies have been identified and concluded that there was a significant reduction in tumor size and an increase in survival rate. *In-vivo* interventions were mostly performed on subcutaneous tumor xenograft in mice. Another study based on the use of a tumor chorio-allantoic model was conducted [46]. Although the results corroborate the *in-vitro* studies, the development of models closer to the clinical situation is necessary. Taking into account the tumor microenvironment is essential and can be a target of anti-cancer treatments [47].

The increased interest in the used of CAP for cancer treatment by the medical community is closely related to the need of new therapies.

Only 4 clinical trials or follow-ups have been identified. Two of them studied the application of CAP on patients with head and neck cancers as a palliative treatment or before tumor resection. Such a therapeutic choice can be explained by the ability of CAP to decontaminate [48,49], treat severely infected wounds or ulcerations [50,51] and induce apoptosis in head and neck cancer cell lines [14,52–56].

In addition, the ongoing clinical trial is assessing the effect of CAP on the reduction of lymphocele following pelvic lymph node dissection during robot-assisted radical prostatectomy, which once again shows its potential uses in oncology.

One of the future directions in the field of anti-cancer potential of CAP may be the action on dysplastic cells, in particular extensive lesions in critical areas where surgery could be invasive.

Conclusion

This study highlights the multiplicity of means of production and clinical applications of the cold atmospheric plasma in the field of oncology. Its anti-cancer actions are mainly mediated by the production of reactive species. Among the different promising biological effects, plasma can induce apoptosis of cancer cells resistant to conventional chemotherapy treatments and may be used in combination with current treatments to obtain a synergistic and complementary action. The clinical use of this innovative therapy strongly needs the development of standardized reliable protocols. More studies are needed to determine the more efficient type of plasma for each type of cancer. To obtain comparative results, standardized measures of the effectiveness of the different systems is also necessary. While plasma jets and FE-DBDs find their indication in a direct approach, DBD open the way for the development of new pharmaceutical products that can be generated at an industrial scale.

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References

1. Rossi F, De Mitri R, Bobin S, Eloy R. Plasma Sterilisation: Mechanisms Overview and Influence of Discharge Parameters. In: d'Agostino R, Favia P, Oehr C, Wertheimer MR, editors. Plasma Processes and Polymers. Wiley-VCH Verlag GmbH & Co. KGaA; 2005. pp. 319–331. Available: http://onlinelibrary.wiley.com/doi/10.1002/3527605584.ch24/summary

2. Hoffmann C, Berganza C, Zhang J. Cold Atmospheric Plasma: methods of production and application in dentistry and oncology. Med Gas Res. 2013;3: 21. doi:10.1186/2045-9912-3-21

3. Metelmann H-R, Nedrelow DS, Seebauer C, Schuster M, von Woedtke T, Weltmann K-D, et al. Head and neck cancer treatment and physical plasma. Clin Plasma Med. 2015;3: 17–23. doi:10.1016/j.cpme.2015.02.001

4. Isbary G, Shimizu T, Li Y-F, Stolz W, Thomas HM, Morfill GE, et al. Cold atmospheric plasma devices for medical issues. Expert Rev Med Devices. 2013;10: 367–377. doi:10.1586/erd.13.4

5. Kim JY, Ballato J, Foy P, Hawkins T, Wei Y, Li J, et al. Apoptosis of lung carcinoma cells induced by a flexible optical fiber-based cold microplasma. Biosens Bioelectron. 2011;28: 333–338. doi:10.1016/j.bios.2011.07.039

6. Cheng X, Sherman J, Murphy W, Ratovitski E, Canady J, Keidar M. The Effect of Tuning Cold Plasma Composition on Glioblastoma Cell Viability. PLoS ONE. 2014;9. doi:10.1371/journal.pone.0098652

7. Recek N, Cheng X, Keidar M, Cvelbar U, Vesel A, Mozetic M, et al. Effect of cold plasma on glial cell morphology studied by atomic force microscopy. PloS One. 2015;10: e0119111. doi:10.1371/journal.pone.0119111

8. Yan D, Talbot A, Nourmohammadi N, Sherman JH, Cheng X, Keidar M. Toward understanding the selective anticancer capacity of cold atmospheric plasma--a model based on aquaporins (Review). Biointerphases. 2015;10: 40801. doi:10.1116/1.4938020

9. Yan D, Sherman JH, Keidar M. Cold atmospheric plasma, a novel promising anti-cancer treatment modality. Oncotarget. 2016; doi:10.18632/oncotarget.13304

10. Babington P, Rajjoub K, Canady J, Siu A, Keidar M, Sherman JH. Use of cold atmospheric plasma in the treatment of cancer. Biointerphases. 2015;10: 29403. doi:10.1116/1.4915264

11. Keidar M, Shashurin A, Volotskova O, Stepp MA, Srinivasan P, Sandler A, et al. Cold atmospheric plasma in cancer therapy. Phys Plasmas 1994-Present. 2013;20: 57101. doi:10.1063/1.4801516

12. Ratovitski EA, Cheng X, Yan D, Sherman JH, Canady J, Trink B, et al. Anti-Cancer Therapies of 21st Century: Novel Approach to Treat Human Cancers Using Cold Atmospheric Plasma. Plasma Process Polym. 2014;11: 1128–1137. doi:10.1002/ppap.201400071

13. Panngom K, Baik KY, Nam MK, Han JH, Rhim H, Choi EH. Preferential killing of human lung cancer cell lines with mitochondrial dysfunction by nonthermal dielectric barrier discharge plasma. Cell Death Dis. 2013;4: e642. doi:10.1038/cddis.2013.168

14. GUERRERO-PRESTON R, OGAWA T, UEMURA M, SHUMULINSKY G, VALLE BL, PIRINI F, et al. Cold atmospheric plasma treatment selectively targets head and neck squamous cell carcinoma cells. Int J Mol Med. 2014;34: 941–946. doi:10.3892/ijmm.2014.1849

15. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339: b2535.

16. Huang J, Chen W, Li H, Wang PY, Yang SZ. Inactivation of He la cancer cells by an atmospheric pressure cold plasma jet. 中国科学院机构知识库网格（CAS IR GRID）. 2013;62. Available: http://www.irgrid.ac.cn/handle/1471x/807043

17. Lee J-H, Kim YH, Choi EH, Kim K-N, Kim K-M. Effect of Non-thermal Atmospheric Pressure Plasma Jet for Inducing Oxidative Stress to Oral Squamous Cell Carcinoma. In: 대한치과재료학회 학술대회 [Internet]. Nov 2014 [cited 17 Dec 2016]. Available: http://www.dbpia.co.kr

18. Karrer S, Arndt S. [Plasma medicine in dermatology: Mechanisms of action and clinical applications]. Hautarzt Z Dermatol Venerol Verwandte Geb. 2015;66: 819–828. doi:10.1007/s00105-015-3686-x

19. Omata Y, Iida M, Yajima I, Takeda K, Ohgami N, Hori M, et al. Non-thermal atmospheric pressure plasmas as a novel candidate for preventive therapy of melanoma. Environ Health Prev Med. 2014;19: 367–369. doi:10.1007/s12199-014-0399-1

20. Kumar N, Park JH, Jeon SN, Park BS, Choi EH, Attri P. The action of microsecond-pulsed plasma-activated media on the inactivation of human lung cancer cells. J Phys Appl Phys. 2016;49: 115401. doi:10.1088/0022-3727/49/11/115401

21. Zhu W, Lee S-J, Castro NJ, Yan D, Keidar M, Zhang LG. Synergistic Effect of Cold Atmospheric Plasma and Drug Loaded Core-shell Nanoparticles on Inhibiting Breast Cancer Cell Growth. Sci Rep. 2016;6. doi:10.1038/srep21974

22. Hoffmann M, Bruch H-P, Kujath P, Limmer S. Cold-plasma coagulation in the treatment of malignant pleural mesothelioma: results of a combined approach. Interact Cardiovasc Thorac Surg. 2010;10: 502–505. doi:10.1510/icvts.2009.223768

23. Schuster M, Seebauer C, Rutkowski R, Hauschild A, Podmelle F, Metelmann C, et al. Visible tumor surface response to physical plasma and apoptotic cell kill in head and neck cancer. J Cranio-Maxillo-fac Surg Off Publ Eur Assoc Cranio-Maxillo-fac Surg. 2016;44: 1445–1452. doi:10.1016/j.jcms.2016.07.001

24. ICTRP Search Portal [Internet]. [cited 4 Jul 2017]. Available: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02658851

25. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136: E359-386. doi:10.1002/ijc.29210

26. Van der Paal J, Verheyen C, Neyts EC, Bogaerts A. Hampering Effect of Cholesterol on the Permeation of Reactive Oxygen Species through Phospholipids Bilayer: Possible Explanation for Plasma Cancer Selectivity. Sci Rep. 2017;7. doi:10.1038/srep39526

27. Iseki S, Nakamura K, Hayashi M, Tanaka H, Kondo H, Kajiyama H, et al. Selective killing of ovarian cancer cells through induction of apoptosis by nonequilibrium atmospheric pressure plasma. Appl Phys Lett. 2012;100: 113702. doi:10.1063/1.3694928

28. Keidar M, Walk R, Shashurin A, Srinivasan P, Sandler A, Dasgupta S, et al. Cold plasma selectivity and the possibility of a paradigm shift in cancer therapy. Br J Cancer. 2011;105: 1295–1301. doi:10.1038/bjc.2011.386

29. Conway GE, Casey A, Milosavljevic V, Liu Y, Howe O, Cullen PJ, et al. Non-thermal atmospheric plasma induces ROS-independent cell death in U373MG glioma cells and augments the cytotoxicity of temozolomide. Br J Cancer. 2016;114: 435–443. doi:10.1038/bjc.2016.12

30. Chang JW, Kang SU, Shin YS, Seo SJ, Kim YS, Yang SS, et al. Combination of NTP with cetuximab inhibited invasion/migration of cetuximab-resistant OSCC cells: Involvement of NF-κB signaling. Sci Rep. 2015;5: 18208. doi:10.1038/srep18208

31. Köritzer J, Boxhammer V, Schäfer A, Shimizu T, Klämpfl TG, Li Y-F, et al. Restoration of Sensitivity in Chemo — Resistant Glioma Cells by Cold Atmospheric Plasma. PLoS ONE. 2013;8. doi:10.1371/journal.pone.0064498

32. Utsumi F, Kajiyama H, Nakamura K, Tanaka H, Mizuno M, Ishikawa K, et al. Effect of Indirect Nonequilibrium Atmospheric Pressure Plasma on Anti-Proliferative Activity against Chronic Chemo-Resistant Ovarian Cancer Cells In Vitro and In Vivo. PLoS ONE. 2013;8. doi:10.1371/journal.pone.0081576

33. Fridman G, Shereshevsky A, Jost MM, Brooks AD, Fridman A, Gutsol A, et al. Floating Electrode Dielectric Barrier Discharge Plasma in Air Promoting Apoptotic Behavior in Melanoma Skin Cancer Cell Lines. Plasma Chem Plasma Process. 2007;27: 163–176. doi:10.1007/s11090-007-9048-4

34. Pouvesle J-M, Robert É. Applications thérapeutiques des plasmas froids atmosphériques. Reflets Phys. 2013; 17–22. doi:10.1051/refdp/201333017

394
395 35. Vandamme M, Robert E, Lerondel S, Sarron V, Ries D, Dozias S, et al. ROS
396 implication in a new antitumor strategy based on non-thermal plasma. Int J Cancer. 2012;130:
397 2185–2194. doi:10.1002/ijc.26252
398
399 36. Boehm D, Heslin C, Cullen PJ, Bourke P. Cytotoxic and mutagenic potential of
400 solutions exposed to cold atmospheric plasma. Sci Rep. 2016;6. doi:10.1038/srep21464
401
402 37. Adachi T, Tanaka H, Nonomura S, Hara H, Kondo S, Hori M. Plasma-activated
403 medium induces A549 cell injury via a spiral apoptotic cascade involving the mitochondrial-
404 nuclear network. Free Radic Biol Med. 2015;79: 28–44.
405 doi:10.1016/j.freeradbiomed.2014.11.014
406
407 38. Gherardi M, Turrini E, Laurita R, De Gianni E, Ferruzzi L, Liguori A, et al.
408 Atmospheric Non-Equilibrium Plasma Promotes Cell Death and Cell-Cycle Arrest in a
409 Lymphoma Cell Line. Plasma Process Polym. 2015;12: 1354–1363.
410 doi:10.1002/ppap.201500033
411
412 39. Mohades S, Laroussi M, Sears J, Barekzi N, Razavi H. Evaluation of the effects of a
413 plasma activated medium on cancer cells. Phys Plasmas. 2015;22: 122001.
414 doi:10.1063/1.4933367
415
416 40. Vermeylen S, De Waele J, Vanuytsel S, De Backer J, Van der Paal J, Ramakers M, et
417 al. Cold atmospheric plasma treatment of melanoma and glioblastoma cancer cells. Plasma
418 Process Polym. 2016;13: 1195–1205. doi:10.1002/ppap.201600116
419
420 41. Kim J, WEI Y, Li J, Kim S. 15-μm-sized single-cellular-level and cell-manipulatable
421 microplasma jet in cancer therapies. Biosens Bioelectron. 2010;26: 555–559.
422 doi:10.1016/j.bios.2010.07.043
423
424 42. Joh HM, Kim SJ, Chung TH, Leem SH. Comparison of the characteristics of
425 atmospheric pressure plasma jets using different working gases and applications to plasma-
426 cancer cell interactions. AIP Adv. 2013;3: 92128. doi:10.1063/1.4823484
427
428 43. Joh HM, Choi JY, Kim SJ, Chung TH, Kang T-H. Effect of additive oxygen gas on
429 cellular response of lung cancer cells induced by atmospheric pressure helium plasma jet. Sci
430 Rep. 2014;4. doi:10.1038/srep06638
431
432 44. Johnson DR, O'Neill BP. Glioblastoma survival in the United States before and during
433 the temozolomide era. J Neurooncol. 2012;107: 359–364. doi:10.1007/s11060-011-0749-4
434
435 45. Calugaru A, Cremer L, Herold A, Lupu A, Szegli G, Lungu C, et al. The effect of the
436 plasma needle on tumoral cell lines apoptosis. Roum Arch Microbiol Immunol. 2005;64: 57–
437 64.
438
439 46. Partecke LI, Evert K, Haugk J, Doering F, Normann L, Diedrich S, et al. Tissue
440 Tolerable Plasma (TTP) induces apoptosis in pancreatic cancer cells in vitro and in vivo.
441 BMC Cancer. 2012;12: 473. doi:10.1186/1471-2407-12-473
442
443 47. Sounni NE, Noel A. Targeting the Tumor Microenvironment for Cancer Therapy. Clin

Chem. 2013;59: 85–93. doi:10.1373/clinchem.2012.185363

48. Daeschlein G, Scholz S, Emmert S, von Podewils S, Haase H, von Woedtke T, et al. Plasma Medicine in Dermatology: Basic Antimicrobial Efficacy Testing as Prerequisite to Clinical Plasma Therapy. Plasma Med. 2012;2: 33–69. doi:10.1615/PlasmaMed.2014006217

49. Yang B, Chen J, Yu Q, Li H, Lin M, Mustapha A, et al. Oral Bacterial Deactivation Using a Low-Temperature Atmospheric Argon Plasma Brush. J Dent. 2011;39: 48–56. doi:10.1016/j.jdent.2010.10.002

50. Daeschlein G, Napp M, Lutze S, Arnold A, von Podewils S, Guembel D, et al. Skin and wound decontamination of multidrug-resistant bacteria by cold atmospheric plasma coagulation. J Dtsch Dermatol Ges J Ger Soc Dermatol JDDG. 2015;13: 143–150. doi:10.1111/ddg.12559

51. Daeschlein G, Lutze S, Arnold A, von Podewils S, Jünger M. [Importance of modern treatment procedures for infected and colonized wounds in dermatology]. Hautarzt Z Dermatol Venerol Verwandte Geb. 2014;65: 949–959. doi:10.1007/s00105-014-3526-4

52. Kang SU, Cho J-H, Chang JW, Shin YS, Kim KI, Park JK, et al. Nonthermal plasma induces head and neck cancer cell death: the potential involvement of mitogen-activated protein kinase-dependent mitochondrial reactive oxygen species. Cell Death Dis. 2014;5: e1056. doi:10.1038/cddis.2014.33

53. Kim S-Y, Kim H-J, Kang SU, Kim YE, Park JK, Shin YS, et al. Non-thermal plasma induces AKT degradation through turn-on the MUL1 E3 ligase in head and neck cancer. Oncotarget. 2015;6: 33382–33396. doi:10.18632/oncotarget.5407

54. Lee J-H, Om J-Y, Kim Y-H, Kim K-M, Choi E-H, Kim K-N. Selective Killing Effects of Cold Atmospheric Pressure Plasma with NO Induced Dysfunction of Epidermal Growth Factor Receptor in Oral Squamous Cell Carcinoma. PloS One. 2016;11: e0150279. doi:10.1371/journal.pone.0150279

55. Lee JK, Kim MS, Byun JH, Kim KT, Kim GC, Park GY. Biomedical Applications of Low Temperature Atmospheric Pressure Plasmas to Cancerous Cell Treatment and Tooth Bleaching. Jpn J Appl Phys. 2011;50: 08JF01. doi:10.1143/JJAP.50.08JF01

56. Welz C, Emmert S, Canis M, Becker S, Baumeister P, Shimizu T, et al. Cold Atmospheric Plasma: A Promising Complementary Therapy for Squamous Head and Neck Cancer. PloS One. 2015;10: e0141827. doi:10.1371/journal.pone.0141827

Figures legends

Fig. 1: Geographical repartition and type of the included studies

(A) Cumulative histogram of the evolution over years of the number of articles and reviews. (B) Proportion of articles and reviews by year. (C) Geographical repartition of the included studies. Each authors' nationality was recorded; consequently, a study may be related to several countries. Only original articles and reviews were included (N=172).

Fig. 2: Evolution of the number of studies dealing with DBD or plasma jet over time

Only non-reviews articles were included (N=152), a study could be considered in multiple categories.

Fig. 3: Yearly repartition of the articles according to the type of carrier gas

Only non-reviews articles were included (N=152), a study could be considered in multiple categories.

Fig. 4: Yearly repartition of the articles according to the methodology (*in-vitro*, *in-vivo* or clinical trials data)

Only non-reviews articles were included (N=152), a study could be considered in multiple categories.

Fig. 5: Cumulative evolution of the number of articles according to the method of treatment employed over time

Only non-reviews articles were included (N=152), a study could be considered in multiple categories.

Fig. 6: Cumulative histogram of the evolution over year of the number of articles according to the type of cancer studied

(A) Human cancers. (B) Murine cancers. Only non-reviews articles were included (N=152), a study could be considered in multiple categories.

S1 Figure: Flow diagram

Figure 1

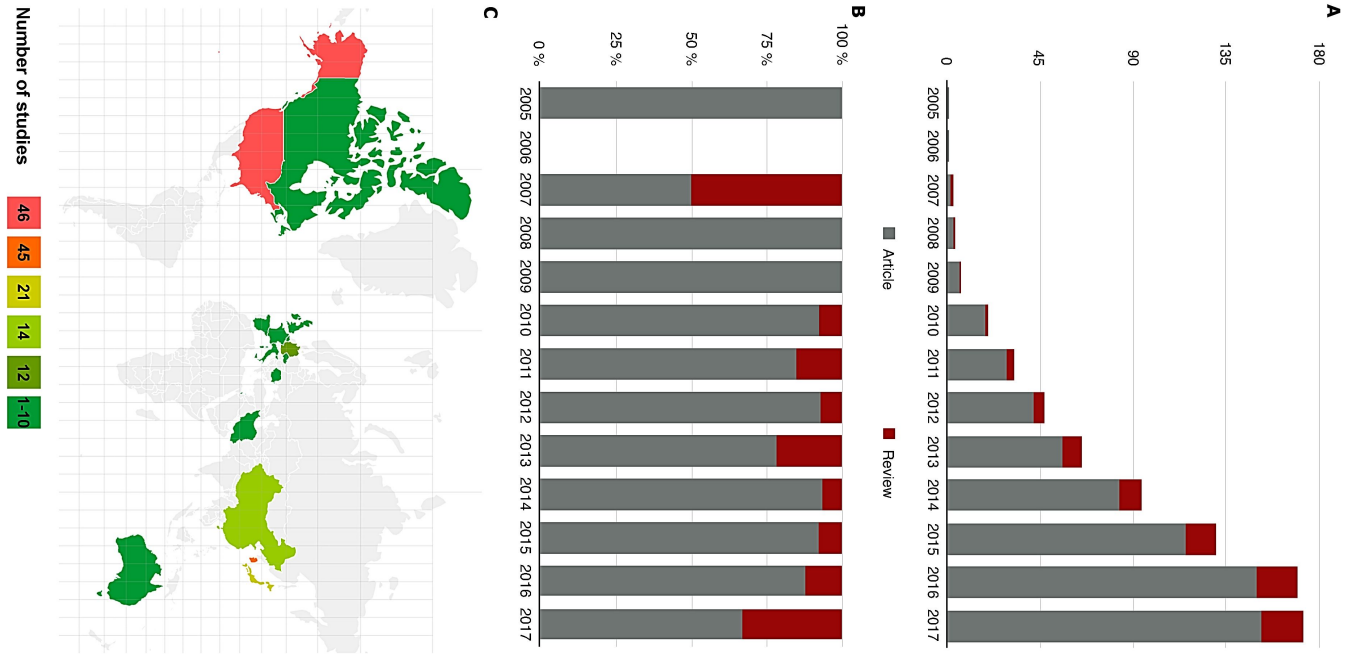


Figure 2

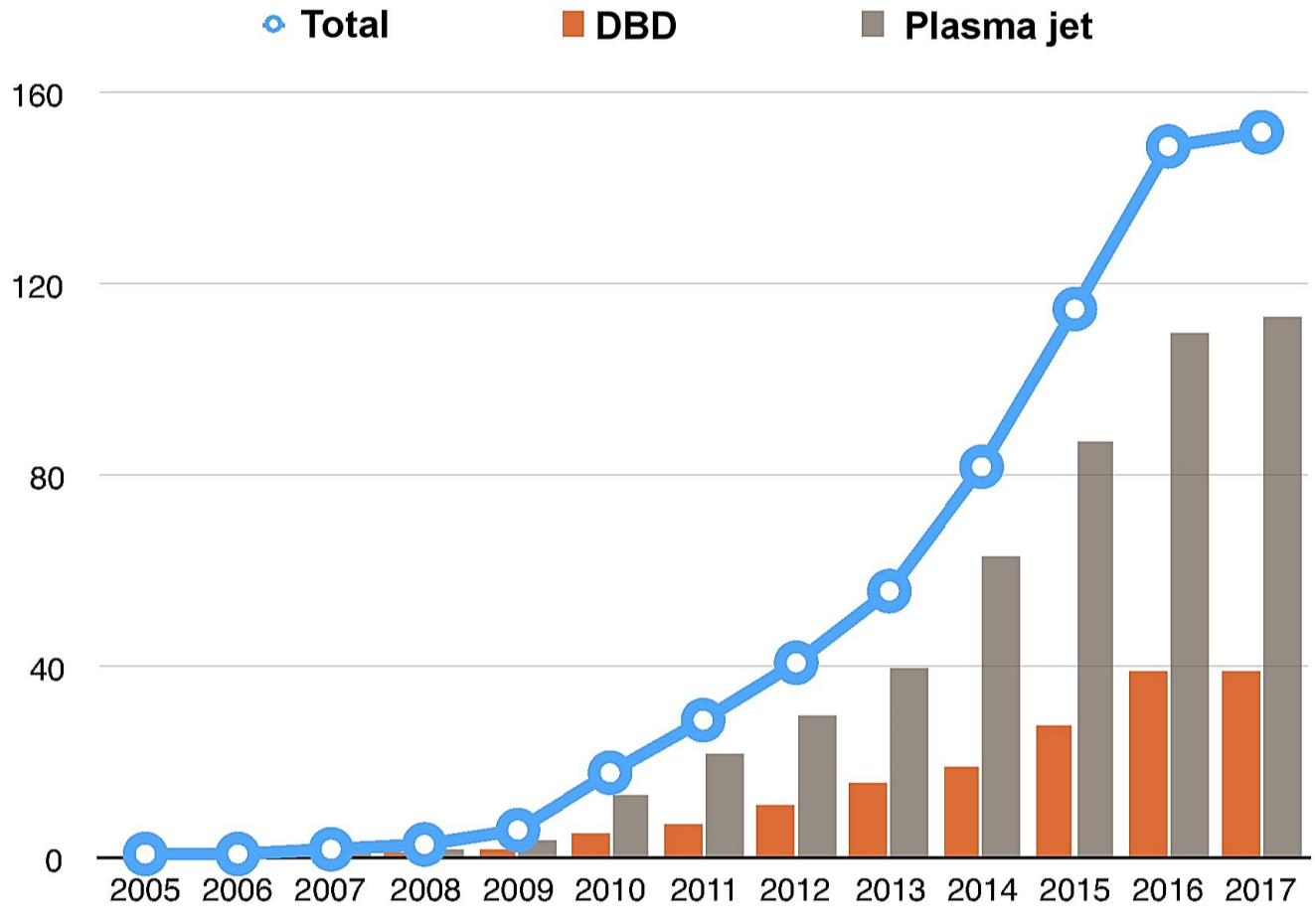


Figure 3

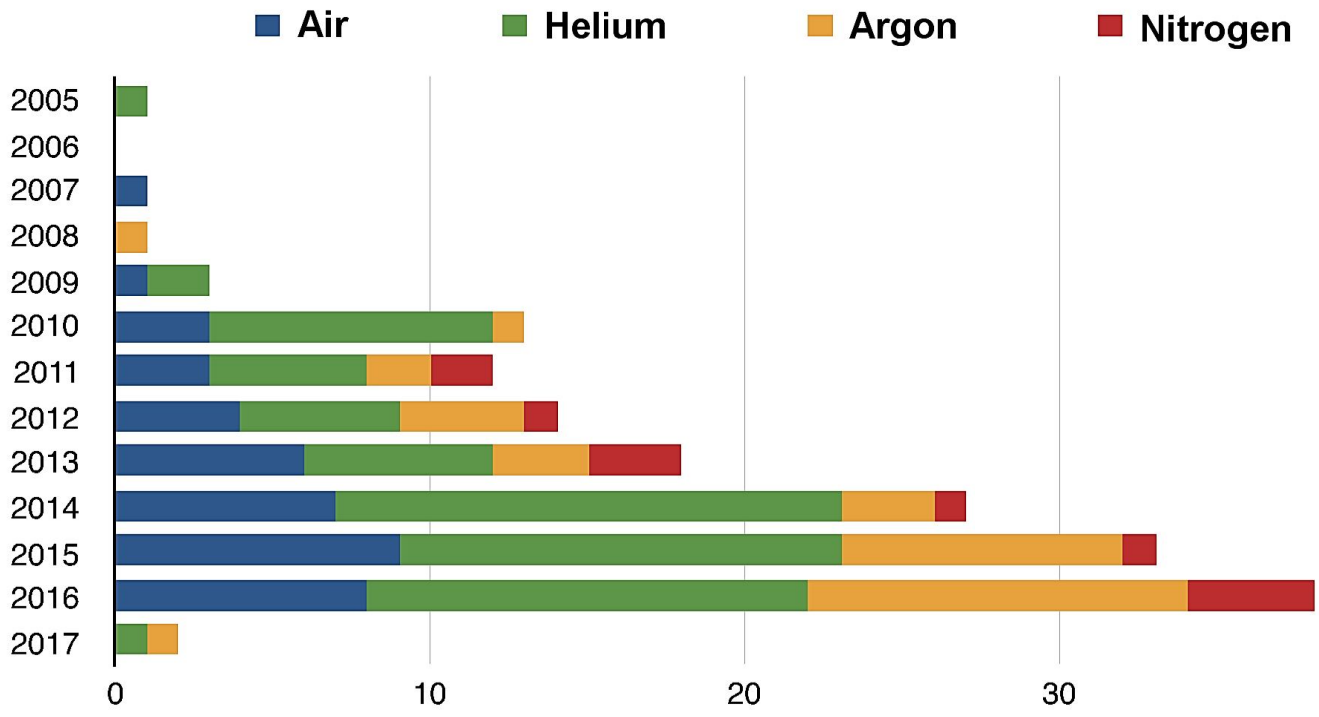


Figure 4

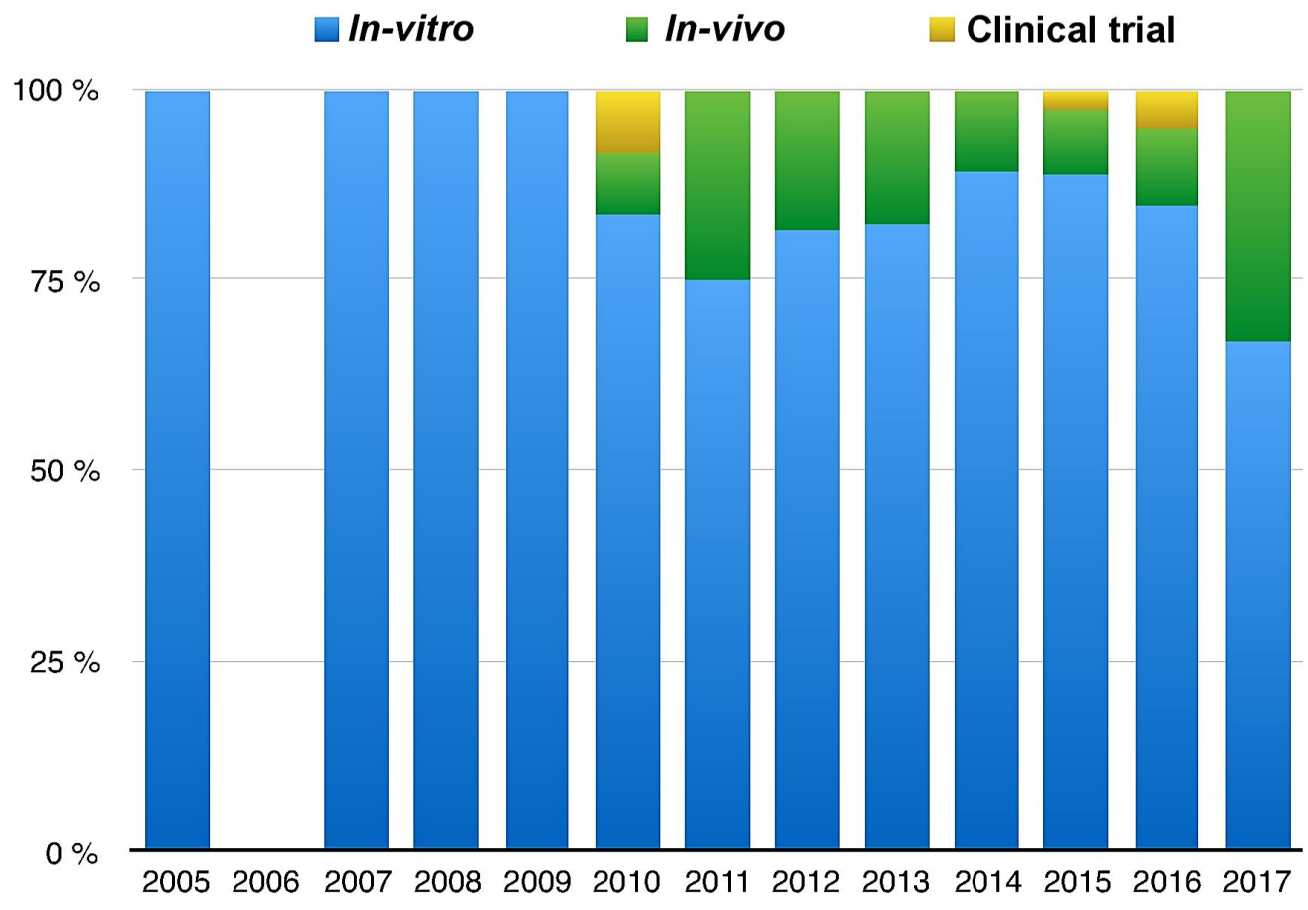


Figure 5

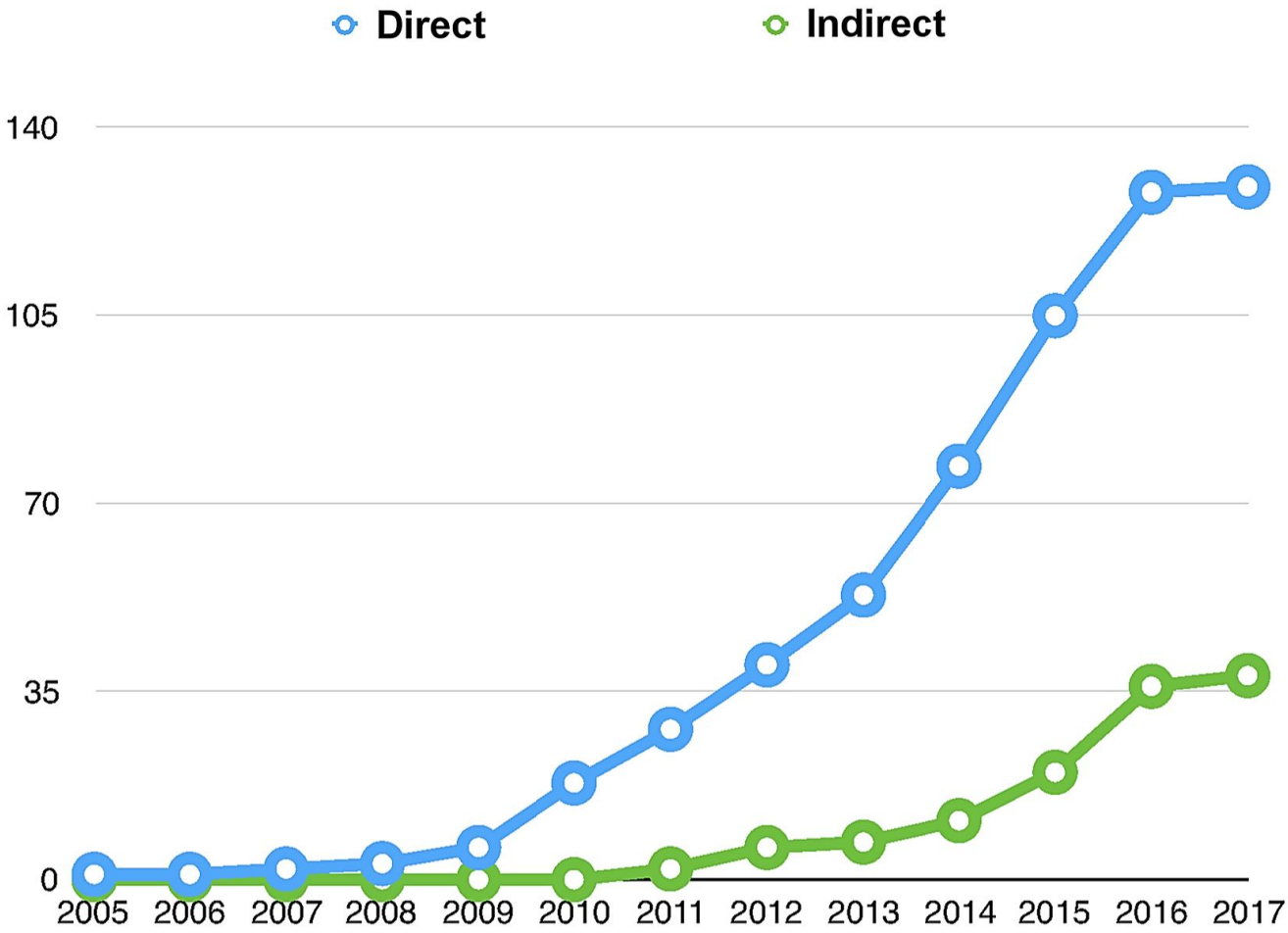
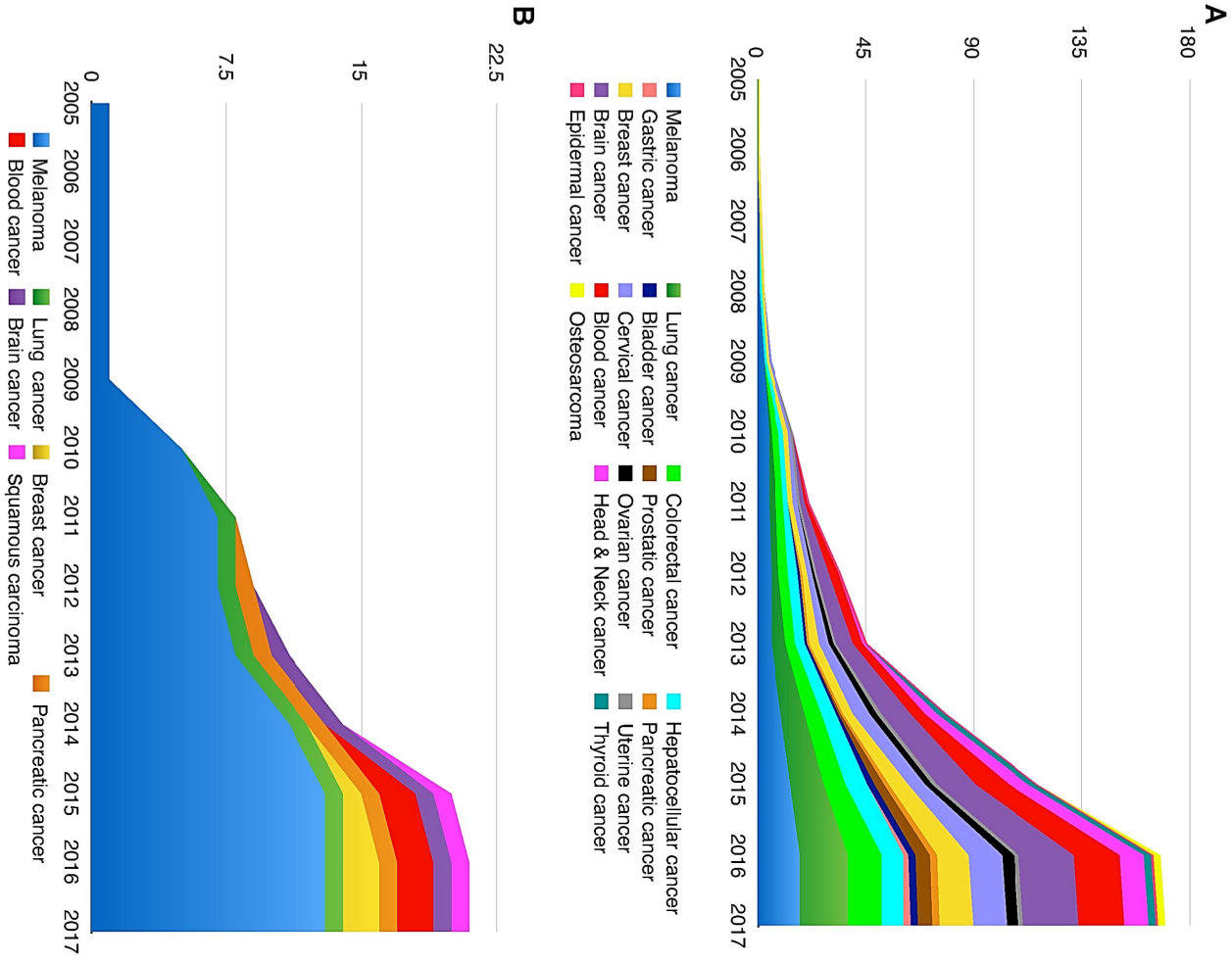
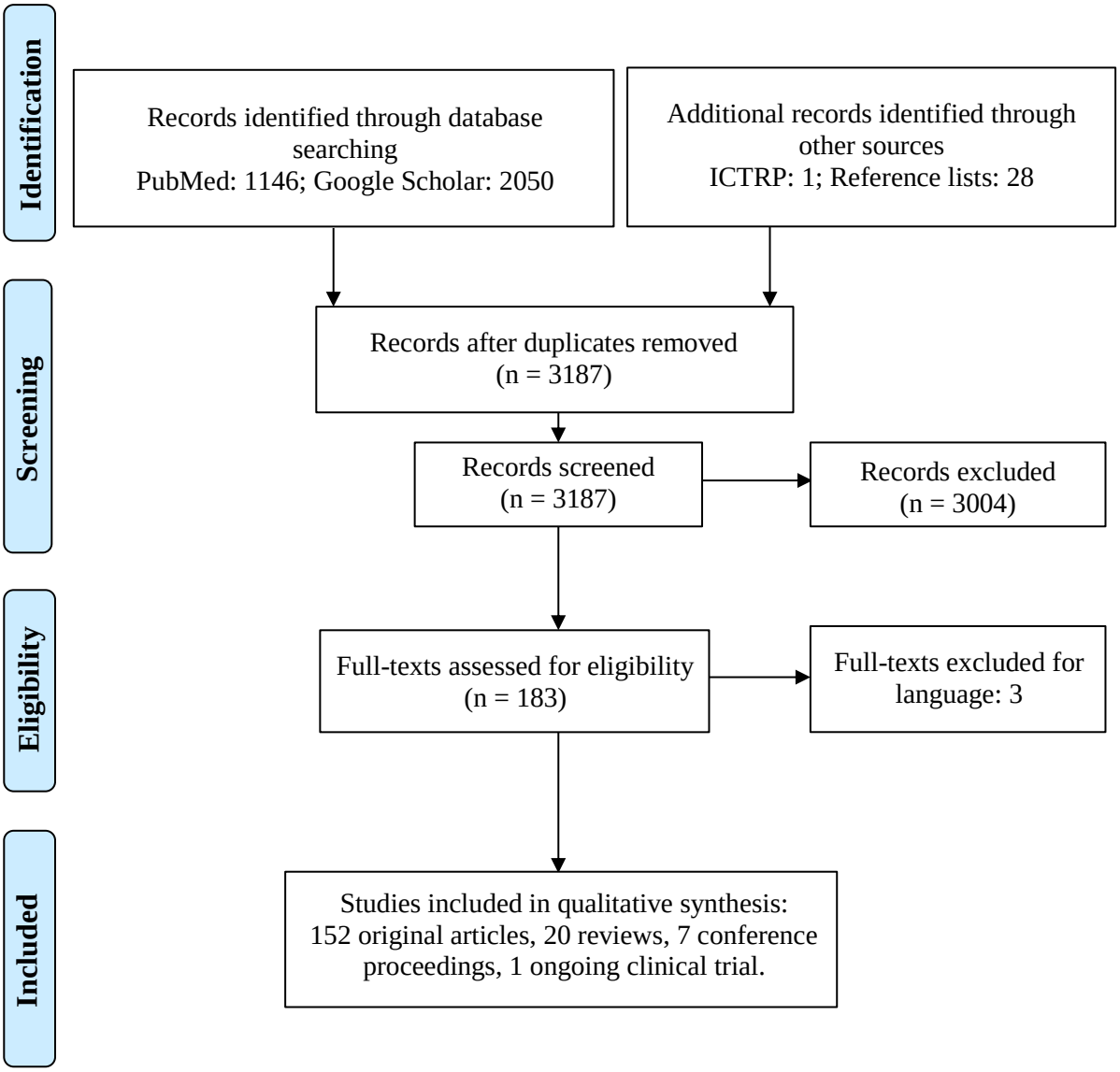


Figure 6



S1 Figure: Flow Diagram



S1 Table. Search strategy

Database	Search Strategy
Pubmed	(“plasma discharge” OR “plasma DBD” OR “non equilibrium plasma” OR “non-equilibrium plasma” OR “plasma jet” OR “cold plasma” OR “gaseous plasma” OR “atmospheric plasma” OR “non atmospheric plasma” OR “non-atmospheric plasma” OR “streamers plasma” OR “non thermal plasma” OR “non-thermal plasma” OR “Plasma Gases”[mh:exp]) AND (cell OR cellular OR tissue OR tissular OR tumor OR tumoral OR dermatology OR cancer OR oncolog*)
Google Scholar	(“cold plasma” OR “atmospheric plasma” OR “plasma jet”) AND (tumor OR cancer OR cell) - bacterial - viral
ICTRP	“cold atmospheric plasma” OR “cold plasma” OR “non thermal plasma” OR “non-thermal plasma” OR “atmospheric plasma”

S2 Table. Characteristics of included studies

Auteur	Year of publication	Country	Type of plasma	Gas	Target cell, tumor	Direct or indirect treatment	Methodology
Adachi *et al* [1]	2015	Japan	Plasma Jet	Argon	Human lung carcinoma cells (A549), Human liver hepatocellular carcinoma cells (HepG2) and Human breast cancer cells (MCF-7)	Indirect	*In-vitro*
Adachi *et al* [2]	2016	Japan	Plasma Jet	Argon	Human lung carcinoma cells (A549), Human aortic smooth muscle cells (SMCs) and Human skin keratinocytes (HaCaT)	Indirect	*In-vitro*
Ahn *et al* [3]	2014	South Korea	Plasma Jet	Air	Human cervical cancer cells (HeLa), Human lung cancer cells (A549) and normal lung cells (MRC5)	Direct	*In-vitro*
Ahn *et al* [4]	2011	South Korea	Plasma Jet	Air, Nitrogen	Human cervical cancer cells (HeLa).	Direct	*In-vitro*
Akhlaghi *et al* [5]	2015	Iran	Plasma Jet	Helium	Murine breast cancer cells (4T1)	Direct	*In-vitro*
Anderson *et al* [6]	2013	USA					Conference proceeding
Arndt *et al* [7]	2013	Germany	Surface micro DBD	Air	Human melanoma cells (Mel Ju and HTZ19)	Direct	*In-vitro*
Avellan *et al* [8]	2016	USA					Conference proceeding
Babington *et al* [9]	2015	USA					Review
Barekzi *et al* [10]	2012	USA	Plasma Jet	Helium	Human T cell line isolated from a patient suffering of acute lymphoblastic leukemia	Direct	*In-vitro*
Barekzi *et al* [11]	2013	USA					Review
Boehm *et al* [12]	2016	Ireland, Australia	DBD	Air	Human cervical cancer cells (HeLa) and Chinese hamster cells (CHO-K1)	Direct, Indirect	*In-vitro*
Brullé *et al* [13]	2012	France	DBD	Helium	Human pancreatic carcinoma cells (MIA PACA2)., Female nude mice implanted with pancreatic orthotopic xenograft tumors.	Direct	*In-vitro*, *In-vivo*
Calugaru *et al* [14]	2005	Romania	Plasma Jet	Helium	Human breast cancer (BrSk) and murine melanoma cells (B16)	Direct	*In-vitro*
Chang *et al* [15]	2014	South Korea, USA	Plasma Jet	Helium + Oxygen	Human squamous carcinoma cell lines originating from oral cavity cancer (MSK QLL1, SCC1483, SCC15, and SCC25)	Direct	*In-vitro*
Chang *et al* [16]	2014	South Korea, USA	Plasma Jet	Helium + Oxygen	Human thyroid papillary carcinoma cell lines (BHP10-3 and TPC1)	Direct	*In-vitro*
Chang *et al* [17]	2015	South Korea, USA	Plasma Jet	Helium + Oxygen	Human oral Squamous Cancer cells culture (MSKQLL1, SCCQLL1, HN6, SCC25, SCC15, Cal27, and SCC1483)	Direct	*In-vitro*

Chen *et al* [18]	2016	USA	Plasma Jet	Argon + Deionized water	Human gastric cancer cell line, (NCI-N87)	Direct	*In-vitro*
Chen *et al* [19]	2016	USA	Plasma Jet	Helium + Deionized water	Human breast cancer cell line, (MDA-MB-231) and gastric cancer cell line, (NCI-N87)	Indirect	*In-vitro*
Cheng *et al* [20]	2014	USA	Plasma Jet	Helium	Human glioblastoma cancer cell line (U87)	Direct	*In-vitro*
Cheng *et al* [21]	2014	USA	Plasma Jet	Helium + Oxygen	Human glioblastoma cancer cells culture (U87) and astrocytes (E6, E7)	Direct	*In-vitro*
Cheng *et al* [22]	2017	USA	Plasma Jet	Helium	Human breast cancer cells (MDA-MB-231)	Direct, Indirect	*In-vitro*
Chernets *et al* [23]	2015	USA	DBD	Air	Murine subdermal melanoma model (B16)	Direct	*In-vivo*
Choi *et al* [24]	2015	South Korea	DBD	Air	Human melanoma (G361) and keratinocyte (HaCaT) cell lines.	Direct	*In-vitro*
Choi *et al* [25]	2016	South Korea	Plasma Jet	Helium + Oxygen	Wild-type mouse embryonic fibroblasts (WT-MEF), CRY1 and CRY2 double knockout mouse embryonic fibroblasts (CRYDKO MEF), Human lung carcinoma (A549) and melanoma (SK-MEL2) cells	Direct	*In-vitro*
Conway *et al* [26]	2016	Ireland, Australia	DBD	Air	Human Glioma cells culture (U373MG) and cervical carcinoma cells (HeLa)	Direct	*In-vitro*
Daeschlein *et al* [27]	2013	Germany	Plasma Jet or DBD	Argon	Female mice injected with melanoma cells (B16-F10)	Direct	*In-vivo*
Fridman *et al* [28]	2007	USA	Floating electrode DBD	Air	Human melanoma cells (A2058)	Direct	*In-vitro*
Gay-Mimbrera *et al* [29]	2016	Spain	-	-	-	-	Review
Georgescu *et al* [30]	2010	Romania	Plasma Jet	Helium + Oxygen	Murine melanoma cells (B16), Human colon cancer cells (COLO320)	Direct	*In-vitro*
Gherardi *et al* [31]	2015	Italy	DBD	Air	Murine Lymphoma cells (L5178Y TK)	Direct, Indirect	*In-vitro*
Gibson *et al* [32]	2014	United Kingdom	Plasma Jet	Helium + Oxygen	Human prostate cancer cells (PC-3)	Direct	*In-vitro*
Girard *et al* [33]	2016	France	Plasma Jet	Helium	Human normal skin fibroblast, immortalized human lung fibroblast (SV-40 transformed), Human colon cancer cells (HTC116), Human melanoma cells (Lu1205)	Direct	*In-vitro*
Guerrero-Preston *et al* [34]	2014	USA	Plasma Jet	Helium	Human head and neck carcinoma cells (JHU-022, JHU-028, JHU-029, SCC25)	Direct	*In-vitro*
Gümbel *et al* [35]	2016	Germany	Plasma Jet	Argon	Human osteosarcoma cells (U2-OS, MNNG, HOS)	Direct	*In-vitro*

Han *et al* [36]	2013	USA	Plasma Jet	Nitrogen	Human oral carcinoma cells (SCC-25)	Direct	*In-vitro*
Hara *et al* [37]	2015	Japan	Plasma Jet	Argon	Human neuroblastoma cells (SH-SY5Y)	Indirect	*In-vitro*
Hattori *et al* [38]	2015	Japan	Plasma Jet	Argon	Human pancreatic cancer cells (PANC-1, Capan-2, BxPC-3, MIA Paca-2)., mouse xenograft model	Indirect	*In-vitro, In-vivo*
Hirst *et al* [39]	2016	United Kingdom	-	-	-	-	Review
Hoentsch *et al* [40]	2012	Germany	Plasma Jet	Argon	Immortalized epithelial cells (mHepR1)	Direct, Indirect	*In-vitro*
Hoffman *et al* [41]	2010	Germany	Plasma Jet	Helium	Diaphragm and pericardium of stage III patient in combination with chemotherapy	Direct	Clinical trial
Hoffman *et al* [42]	2013	Germany	-	-	-		Review
Hou *et al* [43]	2015	China	DBD	Helium	Human lung cancer cells (A549)	Direct	*In-vitro*
Huang *et al* [44]	2011	China, Australia	Plasma Jet	Helium	Human lung cancer cells (A549)	Direct	*In-vitro*
Irani *et al* [45]	2015	Iran	Plasma Jet	Helium	Human colorectal cancer cells (HTC116)	Direct	*In-vitro*
Iseki *et al* [46]	2012	Japan	Plasma Jet	Argon	Human ovarian cancer cells (SKOV3, HRA)	Direct	*In-vitro*
Ishaq *et al* [47]	2015	Australia	Plasma Jet	Helium	Human melanoma cells (Mel007)	Direct	*In-vitro*
Ishaq *et al* [48]	2015	Australia	Plasma Jet	Helium	Human melanoma cells (Mel007)	Direct	*In-vitro*
Isahq *et al* [49]	2014	Australia	Plasma Jet	Helium	Human melanoma cells (Mel007, Mel-RM, Mel-JD)	Direct, Indirect	*In-vitro*
Ishaq *et al* [50]	2015	Australia	Plasma Jet	Helium	Human colon cancer cells (HT29, HCT116)	Direct, Indirect	*In-vitro*
Ishaq *et al* [51]	2014	Australia	-	-	-	-	*Review*
Jalili *et al* [52]	2016	Iran	Plasma Jet	Helium + Oxygen	Human breast cancer cells (MCF-7)	Direct	*In-vitro*
Jawaid *et al* [53]	2016	Japan	Plasma Jet	Helium	Human melanocytic lymphoma (U937), cervical cancer (HeLa), colon cancer (HCT116), acute lymphoblastic cells (MOLT4, JurKat-T)	Direct	*In-vitro*
Joh *et al* [54]	2013	South Korea	Plasma Jet	Argon or Helium or Nitrogen	Human lung cancer cells (A549), bladder cancer cells (EJ)	Direct	*In-vitro*
Joh *et al* [55]	2014	South Korea	Plasma Jet	Helium + oxygen (mix or separate)	Human lung cancer (A549)	Direct	*In-vitro*
Judée *et al* [56]	2016	France	Plasma Jet	Helium	Colorectal multicellular tumor spheroids (HCT116)	Indirect	*In-vitro*

Kalghatgi *et al* [57]	2009	USA	-	-	-	-	Conference proceeding
Kalghatgi *et al* [58]	2011	USA	DBD	Air	Mammalian breast epithelial cells (MCF10A)	Direct, Indirect	*In-vitro*
Kalghatgi *et al* [59]	2012	USA	DBD	Air	Mammalian breast epithelial cells (MCF10A)	Direct, Indirect	*In-vitro*
Kang *et al* [60]	2014	USA, South Korea	Plasma Jet	Helium + Oxygen	Human head and neck carcinoma (FaDu, SNU1041, SNU899, HN9), mice with subcutaneous tumor xenograft	Direct	*In-vitro*, *In-vivo*
Kaushik *et al* [61]	2012	South Korea	DBD	Air	Human brain cancer cells (T98G)	Direct	*In-vitro*
Kaushik *et al* [62]	2013	South Korea	DBD	AIR	Human brain cancer cells (T98G)	Direct	*In-vitro*
Kaushik *et al* [63]	2014	South Korea	DBD	Air	Human brain cancer cells (T98G), Thyroid carcinoma cells (SNU80), Oral carcinoma cells (KB)	Direct	*In-vitro*
Kaushik *et al* [64]	2014	South Korea	DBD	Air	Human monocytic lymphoma cells (U937G)	Direct	*In-vitro*
Kaushik *et al* [65]	2013	South Korea	Plasma Jet	Air	Human brain cancer cells (T98G)	Direct	*In-vitro*
Kaushik *et al* [66]	2015	South Korea	Plasma Jet	Air	Human blood cancer cells (THP-1, U937G), Murine leukemia cells (RAW 264.7)	Direct	*In-vitro*
Kaushik *et al* [67]	2015	South Korea	Plasma Jet	Air	Human brain cancer cells (T98G), Lung cancer cells (A549)	Direct	*In-vitro*
Kaushik *et al* [68]	2016	South Korea	Surface micro DBD	Air	Human brain cancer cells (T98G) and lung cancer cells (A540), Nude mice glioma xenograft tumor.	Direct, Indirect	*In-vitro*, *In-vivo*
Kaushik *et al* [69]	2016	South Korea	Surface micro DBD	Air	Human brain cancer cells (T98G) and lung cancer cells (A540), Nude mice glioma xenograft tumor.	Direct, Indirect	*In-vitro*, *In-vivo*
Keidar *et al* [70]	2011	USA	Plasma Jet	Helium	Human lung cancer cells (SW900), Murine melanoma cells (B16-F10), human primary bone marrow macrophage., Nude mice with subcutaneous B16 tumor	Direct	*In-vitro*, *In-vivo*
Keidar *et al* [71]	2013	USA	-	-	-	-	Review
Kim et al [72]	2009	South Korea	-	-	-	-	Conference proceeding
Kim et al [73]	2009	South Korea	DBD	Air	Human melanoma cells (G361)	Direct	*In-vitro*
Kim et al [74]	2010	South Korea	DBD	Air	Murine melanoma cells (B16F10)	Direct	*In-vitro*
Kim et al [75]	2011	USA	Plasma Jet	Helium	Murine lung cancer cells (TC-1)	Direct	*In-vitro*
Kim et al [76]	2010	USA	Plasma Jet	Helium	Murine melanoma cells (B16F10)	Direct	*In-vitro*
Kim et al [77]	2011	South Korea	Plasma Jet	nitrogen	Human embryonic kidney cells (293T)	Direct	*In-vitro*

Kim et al [78]	2014	South Korea	Plasma Jet	Air	Human cervical cancer (HeLa)	Direct	*In-vitro*
Kim et al [79]	2010	South Korea	Plasma Jet	Argon +- oxygen or, Helium +- Oxygen	Human breast cancer cells (MCF-7)	Direct	*In-vitro*
Kim et al [80]	2010	USA	Plasma Jet	Helium	Murine melanoma cells (B16F10)	Direct	*In-vitro*
Kim et al [81]	2010	USA, South Korea	Plasma Jet	Helium + oxygen	Human colorectal cancer cells (SW480)	Direct	*In-vitro*
Kim et al [82]	2010	South Korea, USA	Plasma Jet	Helium + Oxygen	Human colorectal cancer cells (HCT116, SW480, LoVo)	Direct	*In-vitro*
Kim et al [83]	2013	South Korea	Plasma Jet	Helium	Human lung cancer cells (A549)	Direct	*In-vitro*
Kim et al [84]	2011	USA	Plasma Jet	Helium	Murine melanoma cells (B16F10), Mice with subcutaneous tumor graft	Direct	*In-vitro, In-vivo*
Kim et al [85]	2015	South Korea, USA	Plasma Jet	Helium + Oxygen	Human head and neck cancer cells (SCC15, SCC-QLL1, SCC1483), murine squamous carcinoma cells (SCC7)	Direct, Indirect	*In-vitro, In-vivo*
Kim *et al* [86]	2011	South Korea	-	-	-	-	Review
Kim *et al* [87]	2016	South Korea	Plasma Jet	Helium	Human prostate cancer cells (PC-3), lung cancer cells (A549), melanoma cells (SK-MEL2)	Direct	*In-vitro*
Knecht *et al* [88]	2015	USA	-	-	-	-	conference proceeding
Kong et al .[89]	2011	USA, United Kingdom, Australia	-	-	-	-	Review
Köritzer *et al* [90]	2013	Germany	Surface micro DBD	Air	Human brain cancer cells (LN18, LN229, U87MG)	Direct	*In-vitro*
Kumar *et al* [91]	2016	South Korea, Japan	Plasma Jet	-	Human lung cancer cells (H460)	Indirect	*In-vitro*
Kumar *et al* [92]	2014	South Korea	Plasma Jet	Nitrogen + Deuterium oxide	Human melanoma cells (G361)	Direct	*In-vitro*
Kumar *et al* [93]	2015	South Korea	Plasma Jet	Nitrogen + Deuterium oxide	Human breast cancer cells (SK-BR3)	Direct	*In-vitro*
Kurake *et al* [94]	2016	Japan	Plasma Jet	Argon	Human brain cancer cells (U251SP)	Indirect	*In-vitro*
Kwon *et al* [95]	2016	South Korea	DBD	Nitrogen	Human cervical cancer cells (HeLa)	Direct	*In-vitro*
Laroussi *et al* [96]	2015	USA	Plasma Jet	Helium + Oxygen	Human acute leukemia T cells (CCL-119), bladder cancer cell line (SCaBER) and prostate cancer cells (DU 145)	Direct	*In-vitro*

Leduc et al [97]	2009	Canada	Plasma Jet	Helium	Human cervical cancer cells (HeLa)	Direct	*In-vitro*
Lee *et al* [98]	2016	South Korea	Plasma Jet	Argon	Human breast cancer cells (MCF-7)	Direct	*In-vitro*
Lee *et al* [99]	2011	South Korea	Plasma Jet	Helium	Human head and neck cancer cells (SCC25)	Direct	*In-vitro*
Lee *et al* [100]	2016	South Korea	Plasma Jet	Nitrogen	Human head and neck cancer cells (SCC25, HSC-2)	Direct	*In-vitro*
Lee *et al* [101]	2009	South Korea, USA	Plasma Jet	Helium	Human melanoma cells (G361)	Direct	*In-vitro*
Li *et al* [102]	2016	China	DBD	Helium	Human cervical cancer cells (HeLa)	Direct	*In-vitro*
Lin *et al* [103]	2015	USA, China	DBD	Air	Radioresistant nasopharyngeal carcinoma (CNE-1) and Human acute monocytic leukemia cell line (THP-1).	Direct	*In-vitro*
Lunov *et al* [104]	2014	Czech Republic	Plasma Jet	Air or Helium	Murine brain cancer cells (C6)	Direct	*In-vitro*
Ma *et al* [105]	2014	South Korea	Plasma Jet	Helium	Huma, cervical cancer (HeLa), oral squamous carcinoma (YD-9), malignant melanoma, (G-361), colorectal carcinoma (p53+, +) (HCT 116), colorectal carcinoma (p53 -, -) (HCT 116-E6), non-small cell lung cancer (H1299), colorectal carcinoma (RKO), uterine sarcoma (MES-SA, MES-SA, Dx5), hepatocellular carcinoma (HepG2), colorectal adenocarcinoma (HT29, LoVo, DLD-1, HCT1, HCT15, CL02)	Direct	*In-vitro*
Mashayekh *et al* [106]	2015	Iran	Plasma Jet	Helium + oxygen	Murine melanoma cells (B16F10), mice with subcutaneous tumor graft (C57)	Direct	*In-vitro, In-vivo*
Metelman *et al*[107]	2015	Germany, USA	Plasma Jet	Argon	Patients presenting oral squamous carcinoma	Direct	Clinical follow up
Miller *et al* [108]	2016	USA	-	-	-	-	Review
Min Joh *et al* [109]	2012	South Korea	Plasma Jet	Helium or Argon or Nitrogen + oxygen	Human bladder cancer cells	Direct	*In-vitro*
Mirpour *et al* [110]	2012	Iran	-	-	-	-	Conference proceeding
Mirpour *et al* [111]	2016	Iran, USA	Plasma Jet	Helium	Murine breast cancer cells (4T1), Mice with subcutaneous tumor graft (4T1)	Direct	*In-vivo, In-vitro*
Mohades *et al* [112]	2015	USA	Plasma Jet	Helium	Human bladder cancer cells (SCaBER)	Indirect	*In-vitro*
Naciri *et al* [113]	2014	Ireland	Plasma Jet	Helium	Human colon cancer cells (SW480)	Direct	*In-vitro*
Nguyen *et al* [114]	2016	South Korea	Plasma Jet	Air	Human cervical cancer (HeLa), sarcoma (U2OS, SaOS2), breast cancer (MDA-MB-231, MDA-MB-453, MDA-MB-468), colon cancer (HTC116) cells.	Indirect	*In-vitro*
Ninomiya *et al* [115]	2013	Japan	Plasma Jet	Helium	Human breast cancer cells (MCF-7, MDA-MB-231)	Direct	*In-vitro*

O'connell *et al* [116]	2011	United Kingdom	Plasma Jet	Helium	Plasmid DNA in solution (pCDNA 3,1)	Direct	*In-vitro*
Omata *et al* [117]	2014	Japan	-	-	Hairless model mice (HEL-RET) with melanoma	Direct	*In-vitro*
Ono *et al* [118]	2016	Japan	DBD	Air	Human oral cancer cells (HSC2)	Direct	*In-vitro*
Panngom *et al* [119]	2013	South Korea	DBD	Air	Human lung cancer cells (H460, HCC1588),	Direct	*In-vitro*
Park *et al* [120]	2015	South Korea	DBD	Argon	Human breast cancer (MCF-7, MDA-MB-231), colon cancer (HCT-15) and lung cancer (NCI-H1299) cells	Direct	*In-vitro*
Park *et al* [121]	2016	South Korea	DBD	Helium	Human cervical cancer cells (HeLa)	Direct	*In-vitro*
Partecke *et al* [122]	2012	Germany	Plasma Jet	Argon	Human pancreatic cancer (Colo-357, PaTu8988T) cells. Murine pancreatic cancer cells (6606PDA), Tumor chorio allantoic membrane model.	Direct	*In-vitro, In-vivo*
Plewa *et al* [123]	2014	France	Plasma Jet	Helium	Human colorectal cancer cells (HCT116) forming multicellular tumor spheroids	Direct	*In-vitro*
Ratovitski *et al* [124]	2014	USA, Israel	-	-	-	-	Review
Recek *et al* [125]	2011	Slovenia, USA	Plasma Jet	Helium	Human brain cancer cells (U87)	Direct	*In-vitro*
Ruwan Kumara *et al* [126]	2016	South Korea	DBD	Oxygen + Argon	Human colon cancer cells (SNUC5)	Direct	*In-vitro*
Saito et al. [127]	2016	Japan	Plasma Jet	Helium	Human melanoma (A375, A2058), lung cancer (A549) and osteosarcoma (MG63, SAOS-2, HOS) cells	Indirect	*In-vitro*
Schlegle *et al* [128]	2013	Germany	-	-	-	-	Review
Schmidt *et al* [129]	2015	Germany	Plasma Jet	Argon	Human melanoma cells (SK-Mel-147)	Direct	*In-vitro*
Schuster *et al* [130]	2016	Germany	Plasma Jet	Argon	Patients suffering of squamous cell carcinoma.	Direct	Clinical trial
Sensenig *et al* [131]	2010	USA	DBD	Air	Human melanoma cells (A2058)	Direct	*In-vitro*
Shi *et al* [132]	2014	China	Plasma Jet	Argon	Murine melanoma cells (B16F10)	Direct	*In-vitro*
Siu *et al* [133]	2015	USA	Plasma Jet	Helium	Human brain cancer cells (U87, U373, A172)	Direct	*In-vitro*
Stoffels et al. [134]	2007	Germany	-	-	-	-	Review
Stoffels *et al* [135]	2011	Germany	-	-	-	-	Review
Tabuchi *et al* [136]	2016	Japan	Plasma Jet	Argon +- Nitrogen	Human myelomonocytic lymphoma cells (U937)	Direct	*In-vitro*

Takeda *et al* [137]	2017	Japan	Plasma Jet	Argon	Human gastric cancer cells (SC-2-NU, AGS, fluorescent GCIY)., Mice with intraperitoneal GCIY	Indirect	*In-vitro, In-vivo*
Tan *et al* [138]	2014	China, Australia	Plasma Jet	Helium	Human hepatocellular cancer (HepG2), cervical cancer (HeLa) cells.	Direct	*In-vitro*
Tanaka *et al* [139]	2011	Japan	Plasma Jet	Argon	Human brain cancer cells (U251SP)	Indirect	*In-vitro*
Tanaka *et al* [140]	2016	Japan	DBD	Argon	Human brain cancer (U251SP), cervical cancer (SiHa), ovarian cancer (SK-OV-3), Nude mice with subcutaneous tumor (SiHa)	Indirect	*In-vitro, In-vivo*
Tanaka *et al* [141]	2015	Japan	-	-	-	-	Review
Taylor *et al* [142]	2014	USA, South Korea	-	-	-	-	Conference proceeding
Tazdia *et al* [143]	2016	USA	Plasma Jet	Helium	Lymphoceles following Pelvic Lymph Node Dissection	-	Clinical trial (ongoing)
Thiyagarajan *et al* [144]	2012	USA	Plasma Jet	Air	Human monocytic leukemia cancer cells (THP-1)	Indirect	*In-vitro*
Thiyagarajan *et al* [145]	2014	USA	Plasma Jet	Air	Human monocytic leukemia cancer cells (THP-1)	Direct	*In-vitro*
Thiyagarajan *et al* [146]	2012	USA	-	-	Human monocytic leukemia cancer cells (THP-1)	Direct	*In-vitro*
Toyokuni *et al* [147]	2016	Japan	-	-	-	-	*Review*
Utsumi *et al* [148]	2014	Japan	Plasma Jet	Argon	Human ovarian cancer cells (TOV21G, ES2, SKOV3)	Indirect	*In-vitro*
Utsumi *et al* [149]	2016	Japan	Plasma Jet	Argon	Human ovarian cancer cells (OVCAR-3, TOV21G, ES2, SKOV3)	Indirect	*In-vitro*
Utsumi *et al* [150]	2013	Japan	Plasma Jet	Argon	Human resistant ovarian cancer cells (NOS2CR, NOS2TR, NOS3CR, NOS3TR), Mice with subcutaneous tumor xenograft	Indirect	*In-vitro, In-vivo*
Van der Paal *et al* [151]	2017	Belgium	-	-	-	-	Review
Vandamme *et al* [152]	2012	France	Floating Eelectrode DBD	Air	Human brain cancer (U87MG-Luc2), colorectal cancer (HTC116-Luc2) cells, Mice with subcutaneous tumor xenograft	Direct, Indirect	*In-vitro, In-vivo*
Vandamme *et al* [153]	2010	France	DBD	Air	Mice with subcutaneous tumor xenograft (U87)	Direct	*In-vivo*
Vandamme *et al* [154]	2011	France	DBD	Air	Mice with subcutaneous tumor xenograft (U87)	Direct	*In-vivo*
Vandamme *et al* [155]	2012	France	-	-	-	-	Review
Vermeylen *et al* [156]	2016	Belgium	Plasma Jet	Helium + oxygen or, Helium + oxygen + nitrogen	Human melanoma (Malme-3M, SK-MEL-28), brain cancer (LN229, U87) cells	Direct, Indirect	*In-vitro*
Volotskova *et al* [157]	2012	USA	Plasma Jet	Helium	Human papilloma (308), epidermal carcinoma (PAM2012) cells.	Direct	*In-vitro*
Walk *et al* [158]	2013	USA	Plasma Jet	Helium	Murine brain cancer cells (Neuro2a)., Mice with subcutaneous tumor	Direct	*In-vitro, In-vivo*

					xenograft		
Wang *et al* [159]	2015	China	DBD	Air	Human leukemia cells (LT-12)	Direct	*In-vivo*
Wang *et al* [160]	2013	USA	Plasma Jet	Helium	Human metastatic cells (MDA-MB-231 BrCa)	Direct	*In-vitro*
Weiss *et al* [161]	2015	Germany	Plasma Jet	Argon	Human prostate cancer cells (LNCaP, PC-3)	Direct	*In-vitro*
Weiss *et al* [162]	2015	Germany	Plasma Jet	Argon	Human prostate cancer cells (LNCaP)	Direct	*In-vitro*
Welz *et al* [163]	2015	Germany	DBD	Air	Human head and neck cancer cells (FaDu, OSC-19)	Direct	*In-vitro*
Xu *et al* [164]	2016	China, USA	Plasma Jet	Helium	Human myeloma cells (LP-1)	Direct	*In-vitro*
Xu *et al* [165]	2015	China, USA	Plasma Jet	Helium + oxygen + argon	Human myeloma cells (LP-1)	Direct	*In-vitro*
Yajima et al [166].	2014	Japan	Plasma Jet	Argon	Hairless mice with melanocytic tumor	Direct	*In-vivo*
Yan *et al* [167]	2010	China	Plasma Jet	Helium	Human hepatocellular cancer cells (HepG2)	Direct	*In-vitro*
Yan *et al* [168]	2014	USA	Plasma Jet	Helium	Human brain cancer cells (U87)	Indirect	*In-vitro*
Yan *et al* [169]	2015	USA	Plasma Jet	Helium	Human brain cancer (U87), breast cancer (MDA-MB-231, MCF-7) cells	Indirect	*In-vitro*
Yan *et al* [170]	2016	USA	Plasma Jet	Helium	Human brain cancer cells (U87MG)	Indirect	*In-vitro*
Yan *et al* [171]	2012	China, Australia	Plasma Jet	Helium + oxygen	Human hepatocellular cancer cells (HepG2)	Direct	*In-vitro*
Yan *et al* [172]	2016	USA	-	-	-	-	Review
Yan *et al* [173]	2015	USA	-	-	-	-	Review
Yang *et al* [174]	2015	China	DBD	Air	Human hepatocellular cancer cells (Bel7402) and Human hepatocellular cancer cells 5-FU resistant (Bel7402, 5FU)	Direct, Indirect	*In-vitro*
Yokoyama *et al* [175]	2014	Japan	DBD	Air	Human cervical cancer cells (HeLa)	Indirect	*In-vitro*
Zhao *et al* [176]	2013	China	Plasma Jet	Helium + oxygen	Human hepatocellular cancer cells (HepG2)	Direct	*In-vitro*
Zhang *et al* [177]	2008	China	Plasma Jet	Argon + oxygen	Human hepatocellular cancer cells (Bel7402)	Direct	*In-vitro*
Zhu *et al* [178]	2016	USA	Plasma Jet	-	Human breast cancer (MDA-MB-231, MCF-7), pancreatic cancer (PaTu 8988) cells	Direct	*In-vitro*
Zhunussova *et al* [179]	2016	USA	DBD	Air	Human prostate metastatic cells (DU145)	Indirect	*In-vitro*
Zirnheld *et al* [180]	2010	USA	Plasma Jet	helium	Human metastatic melanoma cells (1205Lu)	Direct	*In-vitro*

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. Quote: “Use of cold atmospheric plasma in oncology: a concise systematic review”	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. Reported	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Reported	P4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). Quote: “We are keen to provide an overview of this constantly evolving and promising field of the use of plasma in oncology. The aim of this systematic review is to map the use of plasma in oncology and the different methodologies implemented so far (cell targets, physical parameters, direct or indirect therapies).”	P5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. Not applicable	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. See “Inclusion criteria”, “Outcomes”	P6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. See “Sources of data and search strategy”	P6

PRISMA 2009 Checklist

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. See “Sources of data and search strategy”	P6, S1 Table
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). See “Study Selection and data extraction”	P7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. Quote: “A standardized extraction form was created to collect data according to outcomes detailed above (S2 Table). Data extraction was performed twice by one author (AD) at one-month interval”	P7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. Quote: “The following outcomes were considered: the countries of author’s affiliations […], the type of methodology […], the type of plasma used […], the gas used to produce the plasma […], the application protocol […], and when applicable, type of tumor cells […].”	P6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. Not applicable	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Not applicable	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. Not applicable	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). Not applicable	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. Not applicable	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. Quote: "We identified 3324 results, corresponding to 3187 unique citations. Final, 180 results were included: 152 original articles (84.4%), 20 reviews (11.1%), 7 conference proceedings and one ongoing clinical trial. Three studies, 1 in Chinese, 1 in Korean and 1 in German were excluded [16–18]. Flow diagram was available (S1 Figure). Details for each study are presented in S2 Table."	P8, S1 Figure
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. Reported	P8-P10, S2 Table
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). Not applicable	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N.A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. Not applicable	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15). Not applicable	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). Not applicable	NA

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DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). See “Discussion”	P11-P15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). Not applicable	NA
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. See “Conclusion”	P15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. Quote: “This study was supported by funding from the Midi-Pyrenees region, Paul Sabatier University and the research platform from Toulouse Dental Faculty. We declare no conflicts of interest.”	P16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

References

1. Adachi T, Tanaka H, Nonomura S, Hara H, Kondo S, Hori M. Plasma-activated medium induces A549 cell injury via a spiral apoptotic cascade involving the mitochondrial-nuclear network. Free Radic Biol Med. 2015;79: 28–44. doi:10.1016/j.freeradbiomed.2014.11.014
2. Adachi T, Nonomura S, Horiba M, Hirayama T, Kamiya T, Nagasawa H, et al. Iron stimulates plasma-activated medium-induced A549 cell injury. Sci Rep. 2016;6. doi:10.1038/srep20928
3. Ahn HJ, Kim KI, Hoan NN, Kim CH, Moon E, Choi KS, et al. Targeting Cancer Cells with Reactive Oxygen and Nitrogen Species Generated by Atmospheric-Pressure Air Plasma. PLOS ONE. 2014;9: e86173. doi:10.1371/journal.pone.0086173
4. Ahn HJ, Kim KI, Kim G, Moon E, Yang SS, Lee J-S. Atmospheric-pressure plasma jet induces apoptosis involving mitochondria via generation of free radicals. PloS One. 2011;6: e28154. doi:10.1371/journal.pone.0028154
5. Akhlaghi M, Rajayi H, Mashayekh AS, Khani M, Hassan ZM, Shokri B. On the design and characterization of a new cold atmospheric pressure plasma jet and its applications on cancer cells treatment. Biointerphases. 2015;10: 29510. doi:10.1116/1.4918806
6. Anderson H, Gonzales X, Valdez S, Thiyagarajan M. Activation of apoptotic cell death in human myeloid leukemia cells by RNS: A novel antitumor approach using resistive barrier plasma. 2013 Abstracts IEEE International Conference on Plasma Science (ICOPS). 2013. pp. 1–1. doi:10.1109/PLASMA.2013.6634817
7. Arndt S, Wacker E, Li Y-F, Shimizu T, Thomas HM, Morfill GE, et al. Cold atmospheric plasma, a new strategy to induce senescence in melanoma cells. Exp Dermatol. 2013;22: 284–289. doi:10.1111/exd.12127
8. Avellan A, Jain R, Diwakar P, Savran C, Hassanein A. Synergy of Cold Atmospheric Plasma and Electroporation for Treatment of Cancer Cells. Summer Undergrad Res Fellowsh SURF Symp. 2016; Available: http://docs.lib.purdue.edu/surf/2016/presentations/8
9. Babington P, Rajjoub K, Canady J, Siu A, Keidar M, Sherman JH. Use of cold atmospheric plasma in the treatment of cancer. Biointerphases. 2015;10: 29403. doi:10.1116/1.4915264
10. Barekzi N, Laroussi M. Dose-dependent killing of leukemia cells by low-temperature plasma. J Phys Appl Phys. 2012;45: 422002. doi:10.1088/0022-3727/45/42/422002
11. Barekzi N, Laroussi M. Effects of Low Temperature Plasmas on Cancer Cells. Plasma Process Polym. 2013;10: 1039–1050. doi:10.1002/ppap.201300083
12. Boehm D, Heslin C, Cullen PJ, Bourke P. Cytotoxic and mutagenic potential of solutions exposed to cold atmospheric plasma. Sci Rep. 2016;6. doi:10.1038/srep21464
13. Brullé L, Vandamme M, Riès D, Martel E, Robert E, Lerondel S, et al. Effects of a non thermal plasma treatment alone or in combination with gemcitabine in a MIA PaCa2-luc orthotopic pancreatic carcinoma model. PloS One. 2012;7: e52653. doi:10.1371/journal.pone.0052653
14. Calugaru A, Cremer L, Herold A, Lupu A, Szegli G, Lungu C, et al. The effect of the plasma needle on tumoral cell lines apoptosis. Roum Arch Microbiol Immunol. 2005;64: 57–64.
15. Chang JW, Kang SU, Shin YS, Kim KI, Seo SJ, Yang SS, et al. Non-thermal atmospheric pressure plasma induces apoptosis in oral cavity squamous cell carcinoma: Involvement of DNA-damage-triggering sub-G(1) arrest via the ATM/p53 pathway. Arch Biochem Biophys. 2014;545: 133–140. doi:10.1016/j.abb.2014.01.022
16. Chang JW, Kang SU, Shin YS, Kim KI, Seo SJ, Yang SS, et al. Non-Thermal Atmospheric Pressure Plasma Inhibits Thyroid Papillary Cancer Cell Invasion via Cytoskeletal Modulation, Altered MMP-2/-9/uPA Activity. PLoS ONE. 2014;9. doi:10.1371/journal.pone.0092198
17. Chang JW, Kang SU, Shin YS, Seo SJ, Kim YS, Yang SS, et al. Combination of NTP with cetuximab inhibited invasion/migration of cetuximab-resistant OSCC cells: Involvement of NF-κB signaling. Sci Rep. 2015;5: 18208. doi:10.1038/srep18208
18. Chen Z, Lin L, Cheng X, Gjika E, Keidar M. Treatment of gastric cancer cells with nonthermal atmospheric plasma generated in water. Biointerphases. 2016;11: 31010. doi:10.1116/1.4962130
19. Chen Z, Lin L, Cheng X, Gjika E, Keidar M. Effects of cold atmospheric plasma generated in deionized water in cell cancer therapy. Plasma Process Polym. 2016; Available: http://adsabs.harvard.edu/abs/2016arXiv160706775C
20. Cheng X, Murphy W, Recek N, Yan D, Cvelbar U, Vesel A, et al. Synergistic effect of gold nanoparticles and cold plasma on glioblastoma cancer therapy. J Phys Appl Phys. 2014;47: 335402. doi:10.1088/0022-3727/47/33/335402
21. Cheng X, Sherman J, Murphy W, Ratovitski E, Canady J, Keidar M. The Effect of Tuning Cold Plasma Composition on Glioblastoma Cell Viability. PLoS ONE. 2014;9. doi:10.1371/journal.pone.0098652
22. Cheng X, Rajjoub K, Shashurin A, Yan D, Sherman JH, Bian K, et al. Enhancing cold atmospheric plasma treatment of cancer cells by static magnetic field. Bioelectromagnetics. 2017;38: 53–62. doi:10.1002/bem.22014
23. Chernets N, Kurpad DS, Alexeev V, Rodrigues DB, Freeman TA. Reaction Chemistry Generated by Nanosecond Pulsed Dielectric Barrier Discharge Treatment is Responsible for the Tumor Eradication in the B16 Melanoma Mouse Model. Plasma Process Polym. 2015;12: 1400–1409. doi:10.1002/ppap.201500140
24. Choi BB, Kim MS, Kim UK, Hong JW, Lee HJ, Kim GC. Targeting NEU Protein in Melanoma Cells with Non-Thermal Atmospheric Pressure Plasma and Gold Nanoparticles. J Biomed Nanotechnol. 2015;11: 900–905.
25. Choi JY, Joh HM, Park J-M, Kim MJ, Chung TH, Kang T-H. Non-thermal plasma-induced apoptosis is

modulated by ATR- and PARP1-mediated DNA damage responses and circadian clock. Oncotarget. 2016;7: 32980–32989. doi:10.18632/oncotarget.9087
26. Conway GE, Casey A, Milosavljevic V, Liu Y, Howe O, Cullen PJ, et al. Non-thermal atmospheric plasma induces ROS-independent cell death in U373MG glioma cells and augments the cytotoxicity of temozolomide. Br J Cancer. 2016;114: 435–443. doi:10.1038/bjc.2016.12
27. Daeschlein G, Scholz S, Lutze S, Arnold A, von Podewils S, Kiefer T, et al. Comparison between cold plasma, electrochemotherapy and combined therapy in a melanoma mouse model. Exp Dermatol. 2013;22: 582–586. doi:10.1111/exd.12201
28. Fridman G, Shereshevsky A, Jost MM, Brooks AD, Fridman A, Gutsol A, et al. Floating Electrode Dielectric Barrier Discharge Plasma in Air Promoting Apoptotic Behavior in Melanoma Skin Cancer Cell Lines. Plasma Chem Plasma Process. 2007;27: 163–176. doi:10.1007/s11090-007-9048-4
29. Gay-Mimbrera J, García MC, Isla-Tejera B, Rodero-Serrano A, García-Nieto AV, Ruano J. Clinical and Biological Principles of Cold Atmospheric Plasma Application in Skin Cancer. Adv Ther. 2016;33: 894–909. doi:10.1007/s12325-016-0338-1
30. Georgescu N, Lupu AR. Tumoral and Normal Cells Treatment With High-Voltage Pulsed Cold Atmospheric Plasma Jets. IEEE Trans Plasma Sci. 2010;38: 1949–1955. doi:10.1109/TPS.2010.2041075
31. Gherardi M, Turrini E, Laurita R, De Gianni E, Ferruzzi L, Liguori A, et al. Atmospheric Non-Equilibrium Plasma Promotes Cell Death and Cell-Cycle Arrest in a Lymphoma Cell Line. Plasma Process Polym. 2015;12: 1354–1363. doi:10.1002/ppap.201500033
32. Gibson AR, McCarthy HO, Ali AA, O'Connell D, Graham WG. Interactions of a Non-Thermal Atmospheric Pressure Plasma Effluent with PC-3 Prostate Cancer Cells. Plasma Process Polym. 2014;11: 1142–1149. doi:10.1002/ppap.201400111
33. Girard P-M, Arbabian A, Fleury M, Bauville G, Puech V, Dutreix M, et al. Synergistic Effect of H2O2 and NO2 in Cell Death Induced by Cold Atmospheric He Plasma. Sci Rep. 2016;6. doi:10.1038/srep29098
34. Guerrero-Preston R, Ogawa T, UEMURA M, Shumulinsky G, Valle BL, Pirini F, et al. Cold atmospheric plasma treatment selectively targets head and neck squamous cell carcinoma cells. Int J Mol Med. 2014;34: 941–946. doi:10.3892/ijmm.2014.1849
35. Gümbel D, Gelbrich N, Weiss M, Napp M, Daeschlein G, Sckell A, et al. New Treatment Options for Osteosarcoma - Inactivation of Osteosarcoma Cells by Cold Atmospheric Plasma. Anticancer Res. 2016;36: 5915–5922.
36. Han X, Klas M, Liu Y, Sharon Stack M, Ptasinska S. DNA damage in oral cancer cells induced by nitrogen atmospheric pressure plasma jets. Appl Phys Lett. 2013;102: 233703. doi:10.1063/1.4809830
37. Hara H, Taniguchi M, Kobayashi M, Kamiya T, Adachi T. Plasma-activated medium-induced intracellular zinc liberation causes death of SH-SY5Y cells. Arch Biochem Biophys. 2015;584: 51–60. doi:10.1016/j.abb.2015.08.014
38. Hattori N, Yamada S, Torii K, Takeda S, Nakamura K, Tanaka H, et al. Effectiveness of plasma treatment on pancreatic cancer cells. Int J Oncol. 2015;47: 1655–1662. doi:10.3892/ijo.2015.3149
39. Hirst AM, Frame FM, Arya M, Maitland NJ, O'Connell D. Low temperature plasmas as emerging cancer therapeutics: the state of play and thoughts for the future. Tumour Biol J Int Soc Oncodevelopmental Biol Med. 2016;37: 7021–7031. doi:10.1007/s13277-016-4911-7
40. Hoentsch M, Woedtke T von, Weltmann K-D, Nebe JB. Time-dependent effects of low-temperature atmospheric-pressure argon plasma on epithelial cell attachment, viability and tight junction formation *In-vitro*. J Phys Appl Phys. 2012;45: 25206. doi:10.1088/0022-3727/45/2/025206
41. Hoffmann M, Bruch H-P, Kujath P, Limmer S. Cold-plasma coagulation in the treatment of malignant pleural mesothelioma: results of a combined approach. Interact Cardiovasc Thorac Surg. 2010;10: 502–505. doi:10.1510/icvts.2009.223768
42. Hoffmann C, Berganza C, Zhang J. Cold Atmospheric Plasma: methods of production and application in dentistry and oncology. Med Gas Res. 2013;3: 21. doi:10.1186/2045-9912-3-21
43. Hou J, Ma J, Yu KN, Li W, Cheng C, Bao L, et al. Non-thermal plasma treatment altered gene expression profiling in non-small-cell lung cancer A549 cells. BMC Genomics. 2015;16: 435. doi:10.1186/s12864-015-1644-8
44. Huang J, Li H, Chen W, Lv G-H, Wang X-Q, Zhang G-P, et al. Dielectric barrier discharge plasma in Ar/O2 promoting apoptosis behavior in A549 cancer cells. Appl Phys Lett. 2011;99: 253701. doi:10.1063/1.3666819
45. Irani S, Shahmirani Z, Atyabi SM, Mirpoor S. Induction of growth arrest in colorectal cancer cells by cold plasma and gold nanoparticles. Arch Med Sci AMS. 2015;11: 1286–1295. doi:10.5114/aoms.2015.48221
46. Iseki S, Nakamura K, Hayashi M, Tanaka H, Kondo H, Kajiyama H, et al. Selective killing of ovarian cancer cells through induction of apoptosis by nonequilibrium atmospheric pressure plasma. Appl Phys Lett. 2012;100: 113702. doi:10.1063/1.3694928
47. Ishaq M, Bazaka K, Ostrikov K. Intracellular effects of atmospheric-pressure plasmas on melanoma cancer cells. Phys Plasmas. 2015;22: 122003–(1.
48. Ishaq M, Bazaka K, Ostrikov K. Pro-apoptotic NOXA is implicated in atmospheric-pressure plasma-induced melanoma cell death. J Phys Appl Phys. 2015;48: 464002. doi:10.1088/0022-3727/48/46/464002
49. Ishaq M, Kumar S, Varinli H, Han ZJ, Rider AE, Evans MDM, et al. Atmospheric gas plasma–induced ROS production activates TNF-ASK1 pathway for the induction of melanoma cancer cell apoptosis. Mol Biol Cell. 2014;25: 1523–1531. doi:10.1091/mbc.E13-10-0590
50. Ishaq M, Han ZJ, Kumar S, Evans MDM, Ostrikov K (Ken). Atmospheric-Pressure Plasma- and TRAIL-Induced

Apoptosis in TRAIL-Resistant Colorectal Cancer Cells. Plasma Process Polym. 2015;12: 574–582. doi:10.1002/ppap.201400207
51. Ishaq M, Evans MM, Ostrikov KK. Effect of atmospheric gas plasmas on cancer cell signaling. Int J Cancer. 2014;134: 1517–1528. doi:10.1002/ijc.28323
52. Jalili A, Irani S, Mirfakhraie R. Combination of cold atmospheric plasma and iron nanoparticles in breast cancer: gene expression and apoptosis study. OncoTargets Ther. 2016;9: 5911–5917. doi:10.2147/OTT.S95644
53. Jawaid P, Rehman MU, Zhao QL, Takeda K, Ishikawa K, Hori M, et al. Helium-based cold atmospheric plasma-induced reactive oxygen species-mediated apoptotic pathway attenuated by platinum nanoparticles. J Cell Mol Med. 2016;20: 1737–1748. doi:10.1111/jcmm.12880
54. Joh HM, Kim SJ, Chung TH, Leem SH. Comparison of the characteristics of atmospheric pressure plasma jets using different working gases and applications to plasma-cancer cell interactions. AIP Adv. 2013;3: 92128. doi:10.1063/1.4823484
55. Joh HM, Choi JY, Kim SJ, Chung TH, Kang T-H. Effect of additive oxygen gas on cellular response of lung cancer cells induced by atmospheric pressure helium plasma jet. Sci Rep. 2014;4. doi:10.1038/srep06638
56. Judée F, Fongia C, Ducommun B, Yousfi M, Lobjois V, Merbahi N. Short and long time effects of low temperature Plasma Activated Media on 3D multicellular tumor spheroids. Sci Rep. 2016;6: 21421. doi:10.1038/srep21421
57. Kalghatgi S, Cerchar E, Podolsky E, Arjunan K, Sensenig R, Shereshevsky A, et al. Mechanism of induction of apoptosis in melanoma cancer cells by non-thermal plasma. IEEE International Conference on Plasma Science - Abstracts, 2009 ICOPS 2009. 2009. pp. 1–1. doi:10.1109/PLASMA.2009.5227452
58. Kalghatgi S, Kelly CM, Cerchar E, Torabi B, Alekseev O, Fridman A, et al. Effects of Non-Thermal Plasma on Mammalian Cells. PLOS ONE. 2011;6: e16270. doi:10.1371/journal.pone.0016270
59. Kalghatgi S, Fridman A, Azizkhan-Clifford J, Friedman G. DNA Damage in Mammalian Cells by Non-thermal Atmospheric Pressure Microsecond Pulsed Dielectric Barrier Discharge Plasma is not Mediated by Ozone. Plasma Process Polym. 2012;9: 726–732. doi:10.1002/ppap.201100156
60. Kang SU, Cho J-H, Chang JW, Shin YS, Kim KI, Park JK, et al. Nonthermal plasma induces head and neck cancer cell death: the potential involvement of mitogen-activated protein kinase-dependent mitochondrial reactive oxygen species. Cell Death Dis. 2014;5: e1056. doi:10.1038/cddis.2014.33
61. Kaushik NK, Uhm H, Ha Choi E. Micronucleus formation induced by dielectric barrier discharge plasma exposure in brain cancer cells. Appl Phys Lett. 2012;100: 84102. doi:10.1063/1.3687172
62. Kaushik NK, Attri P, Kaushik N, Choi EH. A preliminary study of the effect of DBD plasma and osmolytes on T98G brain cancer and HEK non-malignant cells. Mol Basel Switz. 2013;18: 4917–4928. doi:10.3390/molecules18054917
63. Kaushik NK, Kaushik N, Park D, Choi EH. Altered Antioxidant System Stimulates Dielectric Barrier Discharge Plasma-Induced Cell Death for Solid Tumor Cell Treatment. PLoS ONE. 2014;9. doi:10.1371/journal.pone.0103349
64. Kaushik N, Kumar N, Kim CH, Kaushik NK, Choi EH. Dielectric Barrier Discharge Plasma Efficiently Delivers an Apoptotic Response in Human Monocytic Lymphoma. Plasma Process Polym. 2014;11: 1175–1187. doi:10.1002/ppap.201400102
65. Kaushik NK, Kim YH, Han YG, Choi EH. Corrigendum to “Effect of jet plasma on T98G human brain cancer cells”[Curr. Appl. Phys. 13 (2012) 176–180]. Curr Appl Phys. 2013;13: 4e618.
66. Kaushik N, Lee SJ, Choi TG, Baik KY, Uhm HS, Kim CH, et al. Non-thermal plasma with 2-deoxy-D-glucose synergistically induces cell death by targeting glycolysis in blood cancer cells. Sci Rep. 2015;5: 8726. doi:10.1038/srep08726
67. Kaushik N, Uddin N, Sim GB, Hong YJ, Baik KY, Kim CH, et al. Responses of Solid Tumor Cells in DMEM to Reactive Oxygen Species Generated by Non-Thermal Plasma and Chemically Induced ROS Systems. Sci Rep. 2015;5. doi:10.1038/srep08587
68. Kaushik NK, Kaushik N, Yoo KC, Uddin N, Kim JS, Lee SJ, et al. Low doses of PEG-coated gold nanoparticles sensitize solid tumors to cold plasma by blocking the PI3K/AKT-driven signaling axis to suppress cellular transformation by inhibiting growth and EMT. Biomaterials. 2016;87: 118–130. doi:10.1016/j.biomaterials.2016.02.014
69. Kaushik NK, Kaushik N, Yoo KC, Uddin N, Kim JS, Lee SJ, et al. Data on combination effect of PEG-coated gold nanoparticles and non-thermal plasma inhibit growth of solid tumors. Data Brief. 2016;9: 318–323. doi:10.1016/j.dib.2016.08.059
70. Keidar M, Walk R, Shashurin A, Srinivasan P, Sandler A, Dasgupta S, et al. Cold plasma selectivity and the possibility of a paradigm shift in cancer therapy. Br J Cancer. 2011;105: 1295–1301. doi:10.1038/bjc.2011.386
71. Keidar M, Shashurin A, Volotskova O, Stepp MA, Srinivasan P, Sandler A, et al. Cold atmospheric plasma in cancer therapy. Phys Plasmas 1994-Present. 2013;20: 57101. doi:10.1063/1.4801516
72. Kim D, Gweon B, Kim DB, Choe W, Shin JH. A Feasibility Study for the Cancer Therapy Using Cold Plasma. In: Lim CT, Goh JCH, editors. 13th International Conference on Biomedical Engineering. Springer Berlin Heidelberg; 2009. pp. 355–357. doi:10.1007/978-3-540-92841-6_87
73. Kim GC, Kim GJ, Park SR, Jeon SM, Seo HJ, Iza F, et al. Air plasma coupled with antibody-conjugated nanoparticles: a new weapon against cancer. J Phys Appl Phys. 2009;42: 32005. doi:10.1088/0022-3727/42/3/032005
74. Kim GJ, Kim W, Kim KT, Lee JK. DNA damage and mitochondria dysfunction in cell apoptosis induced by nonthermal air plasma. Appl Phys Lett. 2010;96: 21502. doi:10.1063/1.3292206

75. Kim JY, Ballato J, Foy P, Hawkins T, Wei Y, Li J, et al. Apoptosis of lung carcinoma cells induced by a flexible optical fiber-based cold microplasma. Biosens Bioelectron. 2011;28: 333–338. doi:10.1016/j.bios.2011.07.039
76. Kim JY, Kim S-O, Wei Y, Li J. A flexible cold microplasma jet using biocompatible dielectric tubes for cancer therapy. Appl Phys Lett. 2010;96: 203701. doi:10.1063/1.3431392
77. Kim K, Choi JD, Hong YC, Kim G, Noh EJ, Lee J-S, et al. Atmospheric-pressure plasma-jet from micronozzle array and its biological effects on living cells for cancer therapy. Appl Phys Lett. 2011;98: 73701. doi:10.1063/1.3555434
78. Kim K, Jun Ahn H, Lee J-H, Kim J-H, Sik Yang S, Lee J-S. Cellular membrane collapse by atmospheric-pressure plasma jet. Appl Phys Lett. 2014;104: 13701. doi:10.1063/1.4861373
79. Kim SJ, Chung TH, Bae SH, Leem SH. Induction of apoptosis in human breast cancer cells by a pulsed atmospheric pressure plasma jet. Appl Phys Lett. 2010;97: 23702. doi:10.1063/1.3462293
80. Kim J, WEI Y, Li J, Kim S. 15-μm-sized single-cellular-level and cell-manipulatable microplasma jet in cancer therapies. Biosens Bioelectron. 2010;26: 555–559. doi:10.1016/j.bios.2010.07.043
81. Kim C-H, Kwon S, Bahn JH, Lee K, Jun SI, Rack PD, et al. Effects of atmospheric nonthermal plasma on invasion of colorectal cancer cells. Appl Phys Lett. 2010;96: 243701. doi:10.1063/1.3449575
82. Kim C-H, Bahn JH, Lee S-H, Kim G-Y, Jun S-I, Lee K, et al. Induction of cell growth arrest by atmospheric non-thermal plasma in colorectal cancer cells. J Biotechnol. 2010;150: 530–538. doi:10.1016/j.jbiotec.2010.10.003
83. Kim SJ, Min Joh H, Chung TH. Production of intracellular reactive oxygen species and change of cell viability induced by atmospheric pressure plasma in normal and cancer cells. Appl Phys Lett. 2013;103: 153705. doi:10.1063/1.4824986
84. Kim JY, Wei Y, Li J, Foy P, Hawkins T, Ballato J, et al. Single-Cell-Level Microplasma Cancer Therapy. Small. 2011;7: 2291–2295. doi:10.1002/smll.201100456
85. Kim S-Y, Kim H-J, Kang SU, Kim YE, Park JK, Shin YS, et al. Non-thermal plasma induces AKT degradation through turn-on the MUL1 E3 ligase in head and neck cancer. Oncotarget. 2015;6: 33382–33396. doi:10.18632/oncotarget.5407
86. Kim W, Woo K-C, Kim G-C, Kim K-T. Nonthermal-plasma-mediated animal cell death. J Phys Appl Phys. 2011;44: 13001. doi:10.1088/0022-3727/44/1/013001
87. Kim SJ, Chung TH. Cold atmospheric plasma jet-generated RONS and their selective effects on normal and carcinoma cells. Sci Rep. 2016;6. doi:10.1038/srep20332
88. Knecht S, Bilen S, Micci M, Brubaker T, Wilson M, Cook I, et al. Low-temperature plasma needle effects on cultured metastatic breast cancer cells. APS Meeting Abstracts. 2015. Available: http://adsabs.harvard.edu/abs/2015APS..DPPJP2156K
89. Kong MG, Keidar M, Ostrikov K. Plasmas meet nanoparticles—where synergies can advance the frontier of medicine. J Phys Appl Phys. 2011;44: 174018. doi:10.1088/0022-3727/44/17/174018
90. Köritzer J, Boxhammer V, Schäfer A, Shimizu T, Klämpfl TG, Li Y-F, et al. Restoration of Sensitivity in Chemo — Resistant Glioma Cells by Cold Atmospheric Plasma. PLoS ONE. 2013;8. doi:10.1371/journal.pone.0064498
91. Kumar N, Park JH, Jeon SN, Park BS, Choi EH, Attri P. The action of microsecond-pulsed plasma-activated media on the inactivation of human lung cancer cells. J Phys Appl Phys. 2016;49: 115401. doi:10.1088/0022-3727/49/11/115401
92. Kumar N, Attri P, Yadav DK, Choi J, Choi EH, Uhm HS. Induced apoptosis in melanocytes cancer cell and oxidation in biomolecules through deuterium oxide generated from atmospheric pressure non-thermal plasma jet. Sci Rep. 2014;4. doi:10.1038/srep07589
93. Kumar N, Attri P, Choi EH, Uhm HS. Influence of water vapour with non-thermal plasma jet on the apoptosis of SK-BR-3 breast cancer cells. R Soc Chem. 2015;5: 14670–14677. doi:10.1039/C4RA15879B
94. Kurake N, Tanaka H, Ishikawa K, Kondo T, Sekine M, Nakamura K, et al. Cell survival of glioblastoma grown in medium containing hydrogen peroxide and/or nitrite, or in plasma-activated medium. Arch Biochem Biophys. 2016;605: 102–108. doi:10.1016/j.abb.2016.01.011
95. Kwon B-S, Choi EH, Chang B, Choi J-H, Kim KS, Park H-K. Selective cytotoxic effect of non-thermal micro-DBD plasma. Phys Biol. 2016;13: 56001. doi:10.1088/1478-3975/13/5/056001
96. Laroussi M, Mohades S, Barekzi N. Killing adherent and nonadherent cancer cells with the plasma pencil. Biointerphases. 2015;10: 29401. doi:10.1116/1.4905666
97. Leduc M, Guay D, Leask RL, Coulombe S. Cell permeabilization using a non-thermal plasma. New J Phys. 2009;11: 115021. doi:10.1088/1367-2630/11/11/115021
98. Lee S, Lee H, Bae H, Choi EH, Kim SJ. Epigenetic silencing of miR-19a-3p by cold atmospheric plasma contributes to proliferation inhibition of the MCF-7 breast cancer cell. Sci Rep. 2016;6. doi:10.1038/srep30005
99. Lee JK, Kim MS, Byun JH, Kim KT, Kim GC, Park GY. Biomedical Applications of Low Temperature Atmospheric Pressure Plasmas to Cancerous Cell Treatment and Tooth Bleaching. Jpn J Appl Phys. 2011;50: 08JF01. doi:10.1143/JJAP.50.08JF01
100. Lee J-H, Om J-Y, Kim Y-H, Kim K-M, Choi E-H, Kim K-N. Selective Killing Effects of Cold Atmospheric Pressure Plasma with NO Induced Dysfunction of Epidermal Growth Factor Receptor in Oral Squamous Cell Carcinoma. PloS One. 2016;11: e0150279. doi:10.1371/journal.pone.0150279
101. Lee HJ, Shon CH, Kim YS, Kim S, Kim GC, Kong MG. Degradation of adhesion molecules of G361 melanoma cells by a non-thermal atmospheric pressure microplasma. New J Phys. 2009;11: 115026. doi:10.1088/1367-2630/11/11/115026

102. Li W, Yu KN, Bao L, Shen J, Cheng C, Han W. Non-thermal plasma inhibits human cervical cancer HeLa cells invasiveness by suppressing the MAPK pathway and decreasing matrix metalloproteinase-9 expression. Sci Rep. 2016;6. doi:10.1038/srep19720
103. Lin A, Truong B, Pappas A, Kirifides L, Oubarri A, Chen S, et al. Uniform Nanosecond Pulsed Dielectric Barrier Discharge Plasma Enhances Anti-Tumor Effects by Induction of Immunogenic Cell Death in Tumors and Stimulation of Macrophages. Plasma Process Polym. 2015;12: 1392–1399. doi:10.1002/ppap.201500139
104. Lunov O, Zablotskii V, Churpita O, Chánová E, Syková E, Dejneka A, et al. Cell death induced by ozone and various non-thermal plasmas: therapeutic perspectives and limitations. Sci Rep. 2014;4. doi:10.1038/srep07129
105. Ma Y, Ha CS, Hwang SW, Lee HJ, Kim GC, Lee K-W, et al. Non-Thermal Atmospheric Pressure Plasma Preferentially Induces Apoptosis in p53-Mutated Cancer Cells by Activating ROS Stress-Response Pathways. PLoS ONE. 2014;9. doi:10.1371/journal.pone.0091947
106. Mashayekh S, Rajaee H, Akhlaghi M, Shokri B, Hassan ZM. Atmospheric-pressure plasma jet characterization and applications on melanoma cancer treatment (B/16-F10). Phys Plasmas. 2015;22: 93508. doi:10.1063/1.4930536
107. Metelmann H-R, Nedrelow DS, Seebauer C, Schuster M, von Woedtke T, Weltmann K-D, et al. Head and neck cancer treatment and physical plasma. Clin Plasma Med. 2015;3: 17–23. doi:10.1016/j.cpme.2015.02.001
108. Miller V, Lin A, Fridman A. Why Target Immune Cells for Plasma Treatment of Cancer. Plasma Chem Plasma Process. 2016;36: 259–268. doi:10.1007/s11090-015-9676-z
109. Min Joh H, Ja Kim S, Chung TH, Leem SH. Reactive oxygen species-related plasma effects on the apoptosis of human bladder cancer cells in atmospheric pressure pulsed plasma jets. Appl Phys Lett. 2012;101: 53703. doi:10.1063/1.4742742
110. Mirpour S, Nikkhah M, Pirouzmand S, Ghomi HR. Effect of non-thermal atmospheric pressure plasma jet on human breast cancer cells. APS Meeting Abstracts. 2012. Available: http://adsabs.harvard.edu/abs/2012APS..GECUF1008M
111. Mirpour S, Piroozmand S, Soleimani N, Jalali Faharani N, Ghomi H, Fotovat Eskandari H, et al. Utilizing the micron sized non-thermal atmospheric pressure plasma inside the animal body for the tumor treatment application. Sci Rep. 2016;6: 29048. doi:10.1038/srep29048
112. Mohades S, Laroussi M, Sears J, Barekzi N, Razavi H. Evaluation of the effects of a plasma activated medium on cancer cells. Phys Plasmas. 2015;22: 122001. doi:10.1063/1.4933367
113. Naciri M, Dowling D, Al-Rubeai M. Differential Sensitivity of Mammalian Cell Lines to Non-Thermal Atmospheric Plasma. Plasma Process Polym. 2014;11: 391–400. doi:10.1002/ppap.201300118
114. Nguyen NH, Park HJ, Yang SS, Choi KS, Lee J-S. Anti-cancer efficacy of nonthermal plasma dissolved in a liquid, liquid plasma in heterogeneous cancer cells. Sci Rep. 2016;6. doi:10.1038/srep29020
115. Ninomiya K, Ishijima T, Imamura M, Yamahara T, Enomoto H, Kenji Takahashi, et al. Evaluation of extra- and intracellular OH radical generation, cancer cell injury, and apoptosis induced by a non-thermal atmospheric-pressure plasma jet. J Phys Appl Phys. 2013;46: 425401. doi:10.1088/0022-3727/46/42/425401
116. O'Connell D, Cox LJ, Hyland WB, McMahon SJ, Reuter S, Graham WG, et al. Cold atmospheric pressure plasma jet interactions with plasmid DNA. Appl Phys Lett. 2011;98: 43701. doi:10.1063/1.3521502
117. Omata Y, Iida M, Yajima I, Takeda K, Ohgami N, Hori M, et al. Non-thermal atmospheric pressure plasmas as a novel candidate for preventive therapy of melanoma. Environ Health Prev Med. 2014;19: 367–369. doi:10.1007/s12199-014-0399-1
118. Ono R, Ohtsubo T, Hayashi N, Aijima R, Yamashita Y, Goto M. Inactivation of Oral Cancer Cell Using Active Species Generated by Atmospheric Plasma. J Photopolym Sci Technol. 2016;29: 443–445. doi:10.2494/photopolymer.29.443
119. Panngom K, Baik KY, Nam MK, Han JH, Rhim H, Choi EH. Preferential killing of human lung cancer cell lines with mitochondrial dysfunction by nonthermal dielectric barrier discharge plasma. Cell Death Dis. 2013;4: e642. doi:10.1038/cddis.2013.168
120. Park S-B, Kim B, Bae H, Lee H, Lee S, Choi EH, et al. Differential Epigenetic Effects of Atmospheric Cold Plasma on MCF-7 and MDA-MB-231 Breast Cancer Cells. PLOS ONE. 2015;10: e0129931. doi:10.1371/journal.pone.0129931
121. Park J, Lee H, Lee HJ, Kim GC, Kim DY, Han S, et al. Non-Thermal Atmospheric Pressure Plasma Efficiently Promotes the Proliferation of Adipose Tissue-Derived Stem Cells by Activating NO-Response Pathways. Sci Rep. 2016;6. doi:10.1038/srep39298
122. Partecke LI, Evert K, Haugk J, Doering F, Normann L, Diedrich S, et al. Tissue Tolerable Plasma (TTP) induces apoptosis in pancreatic cancer cells *In-vitro* and *In-vivo*. BMC Cancer. 2012;12: 473. doi:10.1186/1471-2407-12-473
123. Plewa J-M, Yousfi M, Frongia C, Eichwald O, Ducommun B, Merbahi N, et al. Low-temperature plasma-induced antiproliferative effects on multi-cellular tumor spheroids. New J Phys. 2014;16: 43027.
124. Ratovitski EA, Cheng X, Yan D, Sherman JH, Canady J, Trink B, et al. Anti-Cancer Therapies of 21st Century: Novel Approach to Treat Human Cancers Using Cold Atmospheric Plasma. Plasma Process Polym. 2014;11: 1128–1137. doi:10.1002/ppap.201400071
125. Recek N, Cheng X, Keidar M, Cvelbar U, Vesel A, Mozetic M, et al. Effect of cold plasma on glial cell morphology studied by atomic force microscopy. PloS One. 2015;10: e0119111. doi:10.1371/journal.pone.0119111
126. Ruwan Kumara MHS, Piao MJ, Kang KA, Ryu YS, Park JE, Shilnikova K, et al. Non-thermal gas plasma-induced endoplasmic reticulum stress mediates apoptosis in human colon cancer cells. Oncol Rep. 2016;36: 2268–2274.

doi:10.3892/or.2016.5038
127. Saito K, Asai T, Fujiwara K, Sahara J, Koguchi H, Fukuda N, et al. Tumor-selective mitochondrial network collapse induced by atmospheric gas plasma-activated medium. Oncotarget. 2016;7: 19910–19927. doi:10.18632/oncotarget.7889
128. Schlegel J, Köritzer J, Boxhammer V. Plasma in cancer treatment. Clin Plasma Med. 2013;1: 2–7. doi:10.1016/j.cpme.2013.08.001
129. Schmidt A, Bekeschus S, von Woedtke T, Hasse S. Cell migration and adhesion of a human melanoma cell line is decreased by cold plasma treatment. Clin Plasma Med. 2015;3: 24–31. doi:10.1016/j.cpme.2015.05.003
130. Schuster M, Seebauer C, Rutkowski R, Hauschild A, Podmelle F, Metelmann C, et al. Visible tumor surface response to physical plasma and apoptotic cell kill in head and neck cancer. J Cranio-Maxillo-fac Surg Off Publ Eur Assoc Cranio-Maxillo-fac Surg. 2016;44: 1445–1452. doi:10.1016/j.jcms.2016.07.001
131. Sensenig R, Kalghatgi S, Cerchar E, Fridman G, Shereshevsky A, Torabi B, et al. Non-thermal plasma induces apoptosis in melanoma cells via production of intracellular reactive oxygen species. Ann Biomed Eng. 2011;39: 674–687. doi:10.1007/s10439-010-0197-x
132. Shi XM, Zhang GJ, Chang ZS, Wu XL, Liao WL, Li N. Viability Reduction of Melanoma Cells by Plasma Jet via Inducing G1/S and G2/M Cell Cycle Arrest and Cell Apoptosis. IEEE Trans Plasma Sci. 2014;42: 1640–1647. doi:10.1109/TPS.2014.2320765
133. Siu A, Volotskova O, Cheng X, Khalsa SS, Bian K, Murad F, et al. Differential Effects of Cold Atmospheric Plasma in the Treatment of Malignant Glioma. PloS One. 2015;10: e0126313. doi:10.1371/journal.pone.0126313
134. Stoffels E, Kieft IE, Sladek REJ, Van Zandvoort MAMJ, Slaaf DW. Cold Gas Plasma in Biology and Medicine. In: d'Agostino R, Favia P, Kawai Y, Ikegami H, Sato N, Arefi-Khonsari F, editors. Advanced Plasma Technology. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA; 2007. pp. 301–318. Available: http://doi.wiley.com/10.1002/9783527622184.ch16
135. Stoffels E. BIOMEDICAL APPLICATIONS OF ELECTRIC GAS DISCHARGES. High Temp Mater Process Int Q High-Technol Plasma Process. 2011;15. doi:10.1615/HighTempMatProc.v15.i3.60
136. Tabuchi Y, Uchiyama H, Zhao Q-L, Yunoki T, Andocs G, Nojima N, et al. Effects of nitrogen on the apoptosis of and changes in gene expression in human lymphoma U937 cells exposed to argon-based cold atmospheric pressure plasma. Int J Mol Med. 2016;37: 1706–1714. doi:10.3892/ijmm.2016.2574
137. Takeda S, Yamada S, Hattori N, Nakamura K, Tanaka H, Kajiyama H, et al. Intraperitoneal Administration of Plasma-Activated Medium: Proposal of a Novel Treatment Option for Peritoneal Metastasis From Gastric Cancer. Ann Surg Oncol. 2017; doi:10.1245/s10434-016-5759-1
138. Tan X, Zhao S, Lei Q, Lu X, He G, Ostrikov K. Single-cell-precision microplasma-induced cancer cell apoptosis. PloS One. 2014;9: e101299. doi:10.1371/journal.pone.0101299
139. Tanaka H, Mizuno M, Ishikawa K, Nakamura K, Kajiyama H, Kano H, et al. Plasma-Activated Medium Selectively Kills Glioblastoma Brain Tumor Cells by Down-Regulating a Survival Signaling Molecule, AKT Kinase. Plasma Med. 2011;1. doi:10.1615/PlasmaMed.2012006275
140. Tanaka H, Nakamura K, Mizuno M, Ishikawa K, Takeda K, Kajiyama H, et al. Non-thermal atmospheric pressure plasma activates lactate in Ringer's solution for anti-tumor effects. Sci Rep. 2016;6. doi:10.1038/srep36282
141. Tanaka H, Mizuno M, Toyokuni S, Maruyama S, Kodera Y, Terasaki H, et al. Cancer therapy using non-thermal atmospheric pressure plasma with ultra-high electron density. Phys Plasmas. 2015;22: 122004. doi:10.1063/1.4933402
142. Taylor N, Dobrynin D, Fridman A, Choi EH. Power source effects of soft plasma jet and the differential response of skin cancer and normal cells. APS Meeting Abstracts. 2014. Available: http://adsabs.harvard.edu/abs/2014APS..GECDT3006T
143. ICTRP Search Portal [Internet]. [cited 4 Jul 2017]. Available: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02658851
144. Thiyagarajan M, Sarani A, Gonzalez X. Characterization of Portable Resistive Barrier Plasma Jet and Its Direct and Indirect Treatment for Antibiotic Resistant Bacteria and THP-1 Leukemia Cancer Cells. IEEE Trans Plasma Sci. 2012;40: 3533–3545. doi:10.1109/TPS.2012.2222391
145. Thiyagarajan M, Anderson H, Gonzales XF. Induction of apoptosis in human myeloid leukemia cells by remote exposure of resistive barrier cold plasma. Biotechnol Bioeng. 2014;111: 565–574. doi:10.1002/bit.25114
146. Thiyagarajan M, Waldbeser L, Whitmill A. THP-1 leukemia cancer treatment using a portable plasma device. Stud Health Technol Inform. 2012;173: 515–517.
147. Toyokuni S. The origin and future of oxidative stress pathology: From the recognition of carcinogenesis as an iron addiction with ferroptosis-resistance to non-thermal plasma therapy. Pathol Int. 2016;66: 245–259. doi:10.1111/pin.12396
148. Utsumi F, Kajiyama H, Nakamura K, Tanaka H, Hori M, Kikkawa F. Selective cytotoxicity of indirect nonequilibrium atmospheric pressure plasma against ovarian clear-cell carcinoma. SpringerPlus. 2014;3. doi:10.1186/2193-1801-3-398
149. Utsumi F, Kajiyama H, Nakamura K, Tanaka H, Mizuno M, Toyokuni S, et al. Variable susceptibility of ovarian cancer cells to non-thermal plasma-activated medium. Oncol Rep. 2016;35: 3169–3177. doi:10.3892/or.2016.4726
150. Utsumi F, Kajiyama H, Nakamura K, Tanaka H, Mizuno M, Ishikawa K, et al. Effect of Indirect Nonequilibrium Atmospheric Pressure Plasma on Anti-Proliferative Activity against Chronic Chemo-Resistant Ovarian Cancer Cells *In-vitro* and *In-vivo*. PLoS ONE. 2013;8. doi:10.1371/journal.pone.0081576

151. Van der Paal J, Verheyen C, Neyts EC, Bogaerts A. Hampering Effect of Cholesterol on the Permeation of Reactive Oxygen Species through Phospholipids Bilayer: Possible Explanation for Plasma Cancer Selectivity. Sci Rep. 2017;7. doi:10.1038/srep39526
152. Vandamme M, Robert E, Lerondel S, Sarron V, Ries D, Dozias S, et al. ROS implication in a new antitumor strategy based on non-thermal plasma. Int J Cancer. 2012;130: 2185–2194. doi:10.1002/ijc.26252
153. Vandamme M, Robert E, Pesnel S, Barbosa E, Dozias S, Sobilo J, et al. Antitumor Effect of Plasma Treatment on U87 Glioma Xenografts: Preliminary Results. Plasma Process Polym. 2010;7: 264–273. doi:10.1002/ppap.200900080
154. Vandamme M, Robert E, Dozias S, Sobilo J, Lerondel S, Pape AL, et al. Response of Human Glioma U87 Xenografted on Mice to Non Thermal Plasma Treatment. Plasma Med. 2011;1. doi:10.1615/PlasmaMed.v1.i1.30
155. Vandamme M, Robert E, Lerondel S, Pouvesle J-M, Pape AL. Non thermal plasmas, a new strategy in oncology?. Med Sci MS. 2012;28: 154–6. doi:10.1051/medsci/2012282013
156. Vermeylen S, De Waele J, Vanuytsel S, De Backer J, Van der Paal J, Ramakers M, et al. Cold atmospheric plasma treatment of melanoma and glioblastoma cancer cells. Plasma Process Polym. 2016;13: 1195–1205. doi:10.1002/ppap.201600116
157. Volotskova O, Hawley TS, Stepp MA, Keidar M. Targeting the cancer cell cycle by cold atmospheric plasma. Sci Rep. 2012;2. doi:10.1038/srep00636
158. Walk RM, Snyder JA, Srinivasan P, Kirsch J, Diaz SO, Blanco FC, et al. Cold atmospheric plasma for the ablative treatment of neuroblastoma. J Pediatr Surg. 2013;48: 67–73. doi:10.1016/j.jpedsurg.2012.10.020
159. Wang S, Wang X, Ye Z, Xu C, Zhang M, Ruan B, et al. Curcumin promotes browning of white adipose tissue in a norepinephrine-dependent way. Biochem Biophys Res Commun. 2015;466: 247–253. doi:10.1016/j.bbrc.2015.09.018
160. Wang M, Holmes B, Cheng X, Zhu W, Keidar M, Zhang LG. Cold Atmospheric Plasma for Selectively Ablating Metastatic Breast Cancer Cells. PLoS ONE. 2013;8. doi:10.1371/journal.pone.0073741
161. Weiss M, Gümbel D, Hanschmann E-M, Mandelkow R, Gelbrich N, Zimmermann U, et al. Cold Atmospheric Plasma Treatment Induces Anti-Proliferative Effects in Prostate Cancer Cells by Redox and Apoptotic Signaling Pathways. PLOS ONE. 2015;10: e0130350. doi:10.1371/journal.pone.0130350
162. Weiss M, Gümbel D, Gelbrich N, Brandenburg L-O, Mandelkow R, Zimmermann U, et al. Inhibition of Cell Growth of the Prostate Cancer Cell Model LNCaP by Cold Atmospheric Plasma. Vivo Athens Greece. 2015;29: 611–616.
163. Welz C, Emmert S, Canis M, Becker S, Baumeister P, Shimizu T, et al. Cold Atmospheric Plasma: A Promising Complementary Therapy for Squamous Head and Neck Cancer. PloS One. 2015;10: e0141827. doi:10.1371/journal.pone.0141827
164. Xu D, Luo X, Xu Y, Cui Q, Yang Y, Liu D, et al. The effects of cold atmospheric plasma on cell adhesion, differentiation, migration, apoptosis and drug sensitivity of multiple myeloma. Biochem Biophys Res Commun. 2016;473: 1125–1132. doi:10.1016/j.bbrc.2016.04.027
165. Xu D, Liu D, Wang B, Chen C, Chen Z, Li D, et al. In Situ OH Generation from O2- and H2O2 Plays a Critical Role in Plasma-Induced Cell Death. PloS One. 2015;10: e0128205. doi:10.1371/journal.pone.0128205
166. Yajima I, Iida M, Kumasaka MY, Omata Y, Ohgami N, Chang J, et al. Non-equilibrium atmospheric pressure plasmas modulate cell cycle-related gene expressions in melanocytic tumors of RET-transgenic mice. Exp Dermatol. 2014;23: 424–425. doi:10.1111/exd.12415
167. Yan X, Zou F, Zhao S, Lu X, He G, Xiong Z, et al. On the Mechanism of Plasma Inducing Cell Apoptosis. IEEE Trans Plasma Sci. 2010;38: 2451–2457. doi:10.1109/TPS.2010.2056393
168. Yan D, Sherman JH, Cheng X, Ratovitski E, Canady J, Keidar M. Controlling plasma stimulated media in cancer treatment application. Appl Phys Lett. 2014;105: 224101.
169. Yan D, Talbot A, Nourmohammadi N, Cheng X, Canady J, Sherman J, et al. Principles of using Cold Atmospheric Plasma Stimulated Media for Cancer Treatment. Sci Rep. 2015;5: 18339. doi:10.1038/srep18339
170. Yan D, Nourmohammadi N, Talbot A, Sherman JH, Keidar M. The strong anti-glioblastoma capacity of the plasma-stimulated lysine-rich medium. J Phys Appl Phys. 2016;49: 274001. doi:10.1088/0022-3727/49/27/274001
171. Yan X, Xiong Z, Zou F, Zhao S, Lu X, Yang G, et al. Plasma-Induced Death of HepG2 Cancer Cells: Intracellular Effects of Reactive Species. Plasma Process Polym. 2012;9: 59–66. doi:10.1002/ppap.201100031
172. Yan D, Sherman JH, Keidar M. Cold atmospheric plasma, a novel promising anti-cancer treatment modality. Oncotarget. 2016; doi:10.18632/oncotarget.13304
173. Yan D, Talbot A, Nourmohammadi N, Sherman JH, Cheng X, Keidar M. Toward understanding the selective anticancer capacity of cold atmospheric plasma--a model based on aquaporins (Review). Biointerphases. 2015;10: 40801. doi:10.1116/1.4938020
174. Yang H, Lu R, Xian Y, Gan L, Lu X, Yang X. Effects of atmospheric pressure cold plasma on human hepatocarcinoma cell and its 5-fluorouracil resistant cell line. Phys Plasmas. 2015;22: 122006. doi:10.1063/1.4933405
175. Yokoyama M, Johkura K, Sato T. Gene expression responses of HeLa cells to chemical species generated by an atmospheric plasma flow. Biochem Biophys Res Commun. 2014;450: 1266–1271. doi:10.1016/j.bbrc.2014.06.116
176. Zhao S, Xiong Z, Mao X, Meng D, Lei Q, Li Y, et al. Atmospheric Pressure Room Temperature Plasma Jets Facilitate Oxidative and Nitrative Stress and Lead to Endoplasmic Reticulum Stress Dependent Apoptosis in HepG2 Cells. PLOS ONE. 2013;8: e73665. doi:10.1371/journal.pone.0073665
177. Zhang X, Li M, Zhou R, Feng K, Yang S. Ablation of liver cancer cells *In-vitro* by a plasma needle. Appl Phys

Lett. 2008;93: 21502. doi:10.1063/1.2959735
178. Zhu W, Lee S-J, Castro NJ, Yan D, Keidar M, Zhang LG. Synergistic Effect of Cold Atmospheric Plasma and Drug Loaded Core-shell Nanoparticles on Inhibiting Breast Cancer Cell Growth. Sci Rep. 2016;6. doi:10.1038/srep21974
179. Zhunussova A, Vitol EA, Polyak B, Tuleukhanov S, Brooks AD, Sensenig R, et al. Mitochondria-Mediated Anticancer Effects of Non-Thermal Atmospheric Plasma. PLoS ONE. 2016;11. doi:10.1371/journal.pone.0156818
180. Zirnheld JL, Zucker SN, DiSanto TM, Berezney R, Etemadi K. Nonthermal Plasma Needle: Development and Targeting of Melanoma Cells. IEEE Trans Plasma Sci. 2010;38: 948–952. doi:10.1109/TPS.2010.2041470

Conclusion

Le plasma atmosphérique froid est une modalité de traitement émergente. Le ciblage sélectif est une de ses propriétés prometteuses qui permet une action sur les cellules tumorales tout en préservant les cellules saines[13,15,17,19,20]. Ce pouvoir anti-tumoral n'est pas encore totalement élucidé mais repose sur la production d'espèces réactives de l'oxygène et de l'azote. L'effet, quant à lui, des phénomènes physiques liés au plasma (UV, champs électromagnétiques, chaleur) semble être négligeable [21,22]. L'action du plasma atmosphérique froid sur les cellules cancéreuses pourrait être comparé à celui d'une radiothérapie localisée et sélective.

Les études *in vivo* et *in vitro* réalisées montrent des résultats très prometteurs. Ces résultats positifs semblent être similaires pour de très nombreuses lignées cellulaires cancéreuses et, parfois même, pour des lignées résistantes à des traitements conventionnels par chimiothérapie ou radiothérapie [23–27]. Le mécanisme de mort cellulaire impliqué est l'apoptose [28], voir, la nécrose pour des doses plus élevées [1].

Face à la multitude de facteurs pouvant influencer les traitements par plasma atmosphérique froid et en l'absence de consensus sur la façon de produire ou de mettre en œuvre un traitement par plasma atmosphérique froid, il semble intéressant de mettre en place des mesures standardisées de l'efficacité des différents systèmes. Ceci permettrait de mieux comparer les différentes approches mises au point.
D'autre part, les expérimentations réalisées à ce jour sont artificielles et ne permettent pas d'extrapoler les résultats aux futures expérimentations sur l'homme. La mise au point de nouveaux modèles, plus réalistes, semble à ce stade particulièrement importante.

Le traitement direct ou indirect (via un milieu activé par le plasma) constitue donc un nouvel outil thérapeutique qui pourrait être utilisé en association avec les traitements actuels afin d'obtenir une action synergique et complémentaire sur les tumeurs.

La Présidente

Le 18/07/2017

S. Coustry

Bibliographie

1. Hoffmann C, Berganza C, Zhang J. Cold Atmospheric Plasma: methods of production and application in dentistry and oncology. Med Gas Res. 2013;3: 21. doi:10.1186/2045-9912-3-21

2. Arora V, Nikhil V, Suri N, Arora P. Cold Atmospheric Plasma (CAP) In Dentistry. J Dent. 2014;4. doi:10.4172/2161-1122.1000189

3. Pouvesle J-M, Robert É. Applications thérapeutiques des plasmas froids atmosphériques. Reflets Phys. 2013; 17–22. doi:10.1051/refdp/201333017

4. Weltmann K-D, Woedtke T von. Basic requirements for plasma sources in medicine. Eur Phys J Appl Phys. 2011;55: 13807. doi:10.1051/epjap/2011100452

5. Daeschlein G, Scholz S, Emmert S, von Podewils S, Haase H, von Woedtke T, et al. Plasma Medicine in Dermatology: Basic Antimicrobial Efficacy Testing as Prerequisite to Clinical Plasma Therapy. Plasma Med. 2012;2: 33–69. doi:10.1615/PlasmaMed.2014006217

6. Daeschlein G, Lutze S, Arnold A, von Podewils S, Jünger M. [Importance of modern treatment procedures for infected and colonized wounds in dermatology]. Hautarzt Z Dermatol Venerol Verwandte Geb. 2014;65: 949–959. doi:10.1007/s00105-014-3526-4

7. Daeschlein G, Napp M, Lutze S, Arnold A, von Podewils S, Guembel D, et al. Skin and wound decontamination of multidrug-resistant bacteria by cold atmospheric plasma coagulation. J Dtsch Dermatol Ges J Ger Soc Dermatol JDDG. 2015;13: 143–150. doi:10.1111/ddg.12559

8. Mahasneh A, Darby M, Tolle SL, Hynes W, Laroussi M, Karakas E. Inactivation of Porphyromonas gingivalis by Low-Temperature Atmospheric Pressure Plasma. Plasma Med. 2011;1: 191–204. doi:10.1615/PlasmaMed.2012002854

9. Isbary G, Shimizu T, Li Y-F, Stolz W, Thomas HM, Morfill GE, et al. Cold atmospheric plasma devices for medical issues. Expert Rev Med Devices. 2013;10: 367–377. doi:10.1586/erd.13.4

10. Weltmann K-D, Metelmann H-R, Woedtke T von. Low temperature plasma applications in medicine. Europhys News. 2016;47: 39–42. doi:10.1051/epn/2016507

11. Barekzi N, Laroussi M. Effects of Low Temperature Plasmas on Cancer Cells. Plasma Process Polym. 2013;10: 1039–1050. doi:10.1002/ppap.201300083

12. Hirst AM, Frame FM, Arya M, Maitland NJ, O'Connell D. Low temperature plasmas as emerging cancer therapeutics: the state of play and thoughts for the future. Tumour Biol J Int Soc Oncodevelopmental Biol Med. 2016;37: 7021–7031. doi:10.1007/s13277-016-4911-7

13. Yan D, Sherman JH, Keidar M. Cold atmospheric plasma, a novel promising anti-cancer treatment modality. Oncotarget. 2016; doi:10.18632/oncotarget.13304

14. Chernets N, Kurpad DS, Alexeev V, Rodrigues DB, Freeman TA. Reaction Chemistry Generated by Nanosecond Pulsed Dielectric Barrier Discharge Treatment is Responsible for the Tumor Eradication in the B16 Melanoma Mouse Model. Plasma Process Polym. 2015;12: 1400–1409. doi:10.1002/ppap.201500140

15. Babington P, Rajjoub K, Canady J, Siu A, Keidar M, Sherman JH. Use of cold atmospheric plasma in the treatment of cancer. Biointerphases. 2015;10: 29403. doi:10.1116/1.4915264

16. Schlegel J, Köritzer J, Boxhammer V. Plasma in cancer treatment. Clin Plasma Med. 2013;1: 2–7. doi:10.1016/j.cpme.2013.08.001

17. Ratovitski EA, Cheng X, Yan D, Sherman JH, Canady J, Trink B, et al. Anti-Cancer Therapies of 21st Century: Novel Approach to Treat Human Cancers Using Cold Atmospheric Plasma. Plasma Process Polym. 2014;11: 1128–1137. doi:10.1002/ppap.201400071

18. Van der Paal J, Verheyen C, Neyts EC, Bogaerts A. Hampering Effect of Cholesterol on the Permeation of Reactive Oxygen Species through Phospholipids Bilayer: Possible Explanation for Plasma Cancer Selectivity. Sci Rep. 2017;7. doi:10.1038/srep39526

19. Yan D, Talbot A, Nourmohammadi N, Sherman JH, Cheng X, Keidar M. Toward understanding the selective anticancer capacity of cold atmospheric plasma--a model based on aquaporins (Review). Biointerphases. 2015;10: 40801. doi:10.1116/1.4938020

20. Keidar M, Shashurin A, Volotskova O, Stepp MA, Srinivasan P, Sandler A, et al. Cold atmospheric plasma in cancer therapy. Phys Plasmas 1994-Present. 2013;20: 57101. doi:10.1063/1.4801516

21. Panngom K, Baik KY, Nam MK, Han JH, Rhim H, Choi EH. Preferential killing of human lung cancer cell lines with mitochondrial dysfunction by nonthermal dielectric barrier discharge plasma. Cell Death Dis. 2013;4: e642. doi:10.1038/cddis.2013.168

22. Guerrero-Preston R, Ogawa T, UEMURA M, Shumulinsky G, Valle BL, Pirini F, et al. Cold atmospheric plasma treatment selectively targets head and neck squamous cell carcinoma cells. Int J Mol Med. 2014;34: 941–946. doi:10.3892/ijmm.2014.1849

23. Conway GE, Casey A, Milosavljevic V, Liu Y, Howe O, Cullen PJ, et al. Non-thermal atmospheric plasma induces ROS-independent cell death in U373MG glioma cells and augments the cytotoxicity of temozolomide. Br J Cancer. 2016;114: 435–443. doi:10.1038/bjc.2016.12

24. Chang JW, Kang SU, Shin YS, Seo SJ, Kim YS, Yang SS, et al. Combination of NTP with cetuximab inhibited invasion/migration of cetuximab-resistant OSCC cells: Involvement of NF-κB signaling. Sci Rep. 2015;5: 18208. doi:10.1038/srep18208

25. Köritzer J, Boxhammer V, Schäfer A, Shimizu T, Klämpfl TG, Li Y-F, et al. Restoration of Sensitivity in Chemo — Resistant Glioma Cells by Cold Atmospheric Plasma. PLoS ONE. 2013;8. doi:10.1371/journal.pone.0064498

26. Utsumi F, Kajiyama H, Nakamura K, Tanaka H, Mizuno M, Ishikawa K, et al. Effect of Indirect Nonequilibrium Atmospheric Pressure Plasma on Anti-Proliferative

Activity against Chronic Chemo-Resistant Ovarian Cancer Cells In Vitro and In Vivo. PLoS ONE. 2013;8. doi:10.1371/journal.pone.0081576

27. Lin A, Truong B, Pappas A, Kirifides L, Oubarri A, Chen S, et al. Uniform Nanosecond Pulsed Dielectric Barrier Discharge Plasma Enhances Anti-Tumor Effects by Induction of Immunogenic Cell Death in Tumors and Stimulation of Macrophages. Plasma Process Polym. 2015;12: 1392–1399. doi:10.1002/ppap.201500139

28. Cheng X, Sherman J, Murphy W, Ratovitski E, Canady J, Keidar M. The Effect of Tuning Cold Plasma Composition on Glioblastoma Cell Viability. PLoS ONE. 2014;9. doi:10.1371/journal.pone.0098652

Abréviations

ATM : Ataxia telangectasia mutated

CAP : Cold Atmospheric Plasma

DBD : Dielectric Barrier Discharge

FAK : Focal Adhésion Kinase

FE-DBD : Floating Electrode DBD

RNS : Reactive Nitrogen Species

RONS Reactive Oxygen and Nitrogen Species

ROS Reactive Oxygen Species.

SARM : Staphylocoque doré Multi-Résistant

SMD : Surface Micro Discharge

DUBUC Antoine 2017 TOU3 3056

Utilisation des plasmas gazeux en oncologie : Une revue systématique

RESUME EN FRANÇAIS :

Les applications biomédicales des plasmas gazeux sont très vastes et constituent un champ médical à part entière nommé : Plasma médecine.
De nombreuses études ont mis en évidence la capacité du plasma atmosphérique froid à induire l'apoptose de cellules eucaryotes. Bien que le mécanisme d'action reste partiellement non élucidé, ceci explique le nombre croissant d'articles analysant son utilisation dans le domaine de l'oncologie. L'objectif de cette revue systématique est de faire un état de la littérature concernant l'utilisation du plasma en oncologie et de mettre en évidence les différentes méthodologies mises en œuvre jusqu' à présent (cibles cellulaires, paramètres physiques de production et utilisation directe ou indirect).

TITRE EN ANGLAIS :

Use of cold atmospheric plasma in oncology: a concise systematic review

RESUME EN ANGLAIS :

Biomedical applications of cold atmospheric plasma are various and constitute a medical field called: Plasma medicine.
Numerous studies have demonstrated the ability of cold atmospheric plasma to induce apoptosis of eukaryotic cells. Although the mechanism of action remains partially unclear, it could explain the growing number of articles analyzing its use in oncology. The aim of this systematic review is map the use of plasma in oncology and to highlight the different methodologies implemented so far (targets cells, physical parameters of production and direct or indirect application).

DISCIPLINE ADMINISTRATIVE : Chirurgie dentaire

MOTS-CLES : Plasmas gazeux, Plasma atmosphérique froid, Plasma non-thermique, Oncologie, Review.

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