

## CASE REPORT

# Activity and pharmacology of homemade silver nanoparticles in refractory metastatic head and neck squamous cell cancer

Jasmine Singh MD<sup>1</sup>  | William Moore MD<sup>2,3</sup> | Farjana Fattah PhD<sup>3</sup> | Xingya Jiang BS<sup>4</sup> | Jie Zheng PhD<sup>4</sup> | Pamela Kurian MS<sup>3</sup> | Muhammad S. Beg MD<sup>1,3</sup> | Saad A. Khan MD<sup>1,3</sup> 

<sup>1</sup>Department of Internal Medicine, UT Southwestern Medical Center, Dallas, Texas

<sup>2</sup>Department of Radiology, UT Southwestern Medical Center, Dallas, Texas

<sup>3</sup>UT Southwestern Harold C. Simmons Comprehensive Cancer Center, Department of Pathology, Dallas, Texas

<sup>4</sup>Department of Chemistry and Biochemistry, University of Texas at Dallas, Dallas, Texas

## Correspondence

Saad A. Khan, MD, UT Southwestern Medical Center, Division of Hematology and Oncology, 5323 Harry Hines Blvd, Dallas, TX 75390-8852. Email: saad.khan@utsouthwestern.edu

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## Abstract

**Background:** Silver nanoparticles (AgNP) show efficacy in cancer cell lines. We present the first in-human outcome of AgNP in a cancer patient.

**Methods:** Homemade AgNP solution is manufactured using online instructions by a 78-year old male. He started consuming AgNP while on hospice after he developed nasal cavity squamous cell cancer metastatic to liver and lung.

**Results:** Electron microscopy of AgNP solution revealed bimodal nanoparticle size distribution: 3 and 12 nm. Inductively coupled plasma mass spectrometry showed basal silver ion concentrations of 32 ng/g, rising to 46 ng/g 1 hour after ingesting 60 mL of AgNP solution. Urine showed no AgNP. No toxicities were observed and he had complete radiographic resolution of his cancer. He remains without evidence of cancer 18 months later.

**Conclusions:** AgNP ingestion was associated with sustained radiographic resolution of cancer. Further testing of AgNP should be done to confirm its efficacy in head and neck cancer.

## KEYWORDS

head and neck cancer, nanoparticles, silver, spontaneous regression, supplements

## 1 | INTRODUCTION

Testimonials about the effectiveness of complementary medicine as cancer treatment rarely transform into scientifically provable effective therapies. A large number of oncology patients use complementary medicines in the belief that they will enhance or replace their standard cancer treatment.<sup>1,2</sup> Most studies examining the proven efficacy of these complementary medicines do not identify consistent evidence of tumor response in patients.<sup>3</sup> A notable recent exception is arsenic trioxide, which in the 1990's was transformed from a Chinese folk remedy into an effective treatment for acute promyelocytic leukemia.<sup>4</sup> There remains skepticism about the claims of most other complementary medicine as possible replacements for the effectiveness of traditional, approved anticancer therapy.

Silver nanoparticles (AgNP) are a complementary medicine with activity against cancer cell lines but which have never before been associated with change in the course of a patient's malignancy. In preclinical studies, lab-synthesized AgNP decreased the growth and viability in colon cancer cell lines, resulting in increased apoptosis via increased p53 and decreased Akt and NF- $\kappa$ B.<sup>5</sup> AgNP are also highly cytotoxic to triple-negative breast cancer cell at doses that have little effect on normal breast tissue, while also increasing their sensitivity to radiation.<sup>6</sup> No patients with cancer have been administered AgNP and there are no active or completed trials in patients with cancer.

We examine the components of a homemade AgNP solution and report its pharmacology in a patient. This patient had exhausted all standard surgery, radiation, and chemotherapies and was referred to hospice. He then started

to manufacture and ingest AgNP solution of his own volition believing that it had anticancer properties. We also briefly review the preclinical rationale behind a potential anticancer effect of AgNP, including activity in cell lines. To date, there is no scientific report of the safety and efficacy of AgNP solution given to patients, and here we are the first to describe the safety and potential efficacy of AgNP in one such patient. AgNP ingestion was safe and associated with dramatic, complete, and sustained regression of head and neck squamous cell cancer, including all metastases to the liver and lung. This occurred in the absence of any other proven anticancer therapy.

## 2 | CASE REPORT

In March 2014, a 77-year-old male was seen with 6 months of worsening left nasal epistaxis and drainage. Past medical history was significant for type 2 diabetes, emphysema, and a 60 pack-year smoking history with tobacco cessation in 1984. He reported that the symptoms began after a fall during which he hit his nose. Imaging performed to rule out nasal fracture incidentally revealed a left sinonasal mass. Biopsy revealed poorly differentiated squamous carcinoma, focally positive for p16 (45%), and he was staged T4N0M0. He underwent PCC induction chemotherapy for 12 weeks, from April to July of 2014, consisting of Carboplatin (AUC of 2), Paclitaxel (80 mg/m<sup>2</sup>), and Cetuximab (400 mg/m<sup>2</sup> loading dose followed by 250 mg/m<sup>2</sup> for 3 weeks, subsequently decreased to 200 mg/m<sup>2</sup>) which only resulted in disease stability. He subsequently proceeded to volumetric modulated arc therapy for a total of 70 Gy in 35 fractions with concurrent Carboplatin for 6 weeks, completed in September 2014.

In December 2014, Positron Emission Tomography (PET)-CT was consistent with local recurrence of disease involving the medullary bone with nodal metastases. Biopsy in January 2015 revealed squamous cell carcinoma with marked treatment effect, and he was staged T4N2M0. Left parotidectomy, left neck dissection, bifrontal craniotomy approach for resection of an anterior skull-based tumor, and split calvarial cranioplasty to reconstruct tumor-infiltrated frontal bone was performed in January 2015. He subsequently underwent repeat radiation with a total dose of 60 Gray in

30 fractions to the left parotid bed and left neck. He received concurrent weekly Carboplatin (AUC of 2) from February to April 2015, for a total of 6 weeks. PET scan in May 2015, 1 month after chemoradiation, was compatible with recurrence in the left nasal bone. He was treated with stereotactic radiation therapy to the ethmoid sinus area with a total of 45 Gray in 5 fractions. He received concurrent weekly Cetuximab (250 mg/m<sup>2</sup>) for 3 weeks resulting in partial tumor response. MRI of the orbit, face, and neck in June 2015 was consistent with local progression in the left nasoethmoidal region. He subsequently underwent anterior skull base resection, partial rhinectomy, and frontoethmoidectomy with anterolateral thigh and vastus lateralis muscle reconstruction in July 2015. Pathology from this resection again demonstrated poorly differentiated squamous cell carcinoma.

In August 2015, PET-CT showed development of distant metastases, including multiple pulmonary nodules, right hilar lymphadenopathy, and a right hepatic mass. He was also found to have increased uptake in areas of previous operative sites, as well as in multiple nodal areas in the neck, including a right level three node. MRI of the face and neck confirmed the level three node and also revealed enhancement at the left lateral margin of the craniofacial flap concerning for local recurrence. CT of the chest also showed presence of a right pulmonary nodule. Based on a history of multiple recurrences in the setting of image findings highly suspicious for malignancy, a decision was made not to biopsy what appeared to be likely pulmonary and hepatic metastases. At that time, he was recommended to transition to hospice as he was found to be a poor candidate for salvage therapy given his decline in functional capacity and multiple recurrences despite aggressive anticancer therapy. A timeline summarizing the patient's disease state and corresponding treatment regimen is provided in Figure 1.

After the time of diagnosis of metastatic disease, the patient began to manufacture and consume an AgNP solution, with the following method of production. Twelve ounces of distilled water is placed in a glass container containing two bars of 99.99% pure silver. Three 9-V radio batteries are hooked in series, producing a positive lead at one end and a negative lead at the other, resulting in a total output of 27 V of electricity. A current is applied until the metal content of the water measures 0.09-0.15 ppm using a water

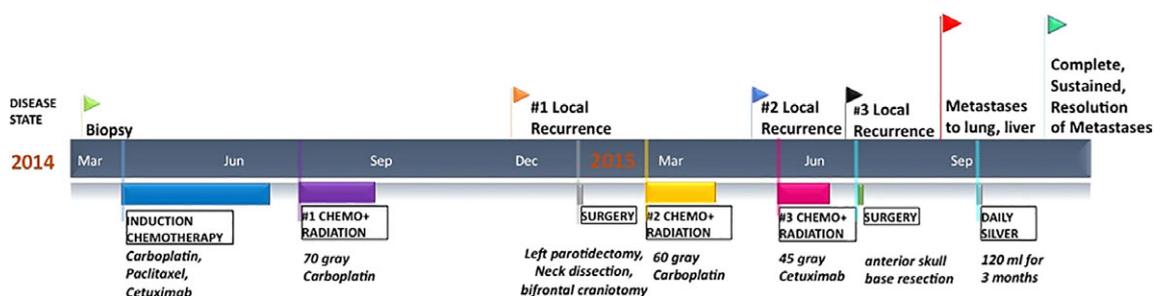


FIGURE 1 Timeline of disease state and treatment course of patient

tester, and this process averages 1 hour in duration. The resulting solution is strained with a mesh cloth to filter out remaining silver precipitate and the product is subsequently stored in a dark glass bottle.

He ingested 120 mL of the solution daily for 3 months during which time he had significant clinical improvement. The patient was seen at our facility with a completely normal functional status and feeling much better than when he had started hospice. Repeat PET-CT in November 2015, 3 months after pre-hospice imaging and after ingesting AgNP solution, showed complete disappearance of all pulmonary and liver metastases as well as of previously seen nodes in the neck (Figures 2 and 3). This recovery and complete resolution of cancer at all sites persisted for 36 months and is ongoing.

MRI of the face and skull base showed a 1.4 cm × 1.9 cm level III lymph node. PET/CT images demonstrating hepatic and lung metastases were both performed at and reported by National Cancer Institute (NCI)-designated academic Comprehensive Cancer Centers with advanced radiology research programs. Pre- and post-AgNP images were compared by a nuclear medicine radiologist to confirm that the same patient had been imaged by identifying consistent and unique anatomic variants and post treatment changes. The findings that were described in the official radiology report included an intensely fluorodeoxyglucose (FDG) avid recurrence site over the left frontal bone, multiple nodes in the neck, bilateral hilar adenopathy with pulmonary nodules. There was a large right hepatic metastasis noted as well. The report from

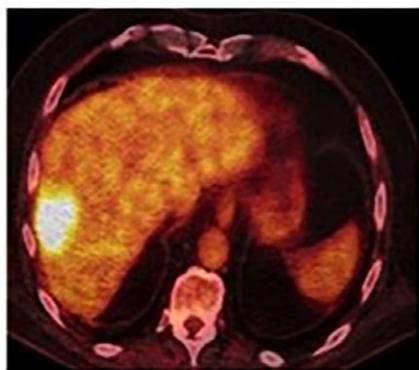
both radiologists described these masses as metastases. Independent review by our nuclear medicine radiologist concurred that the only plausible explanation for these masses was metastatic disease.

Electron microscopy of the silver solution revealed bimodal AgNP size distributions: 3 and 12 nm (Figure 4). Inductively coupled plasma mass spectrometry showed the basal blood silver ion concentrations of 32 ng/g. One hour after ingesting 60 mL of silver solution, it rose to 46 ng/g. Patient serum was analyzed and intact nanoparticles were not identified. Thus, we could not isolate the circulating AgNP form.

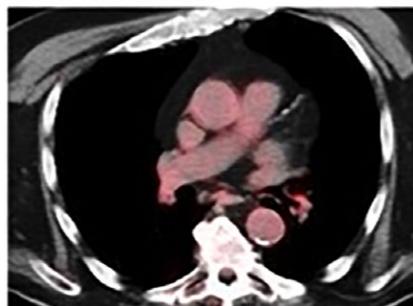
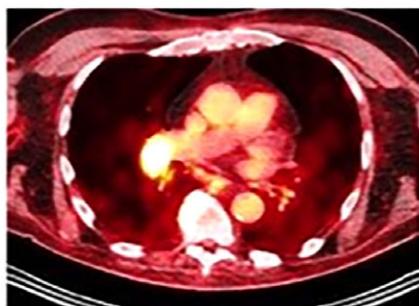
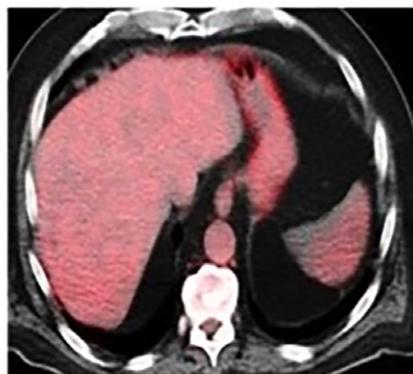
Analysis of urine showed no AgNP or detectable nanoparticle fragments. AgNP solution was also exposed to simulated gastric fluid, in which they aggregated into larger nanoparticles according to UV-Vis absorption. At this time, the patient continues to ingest the silver solution daily and does not report any adverse side effects or toxicities.

His Eastern Cooperative Oncology Group (ECOG) performance status improved to 0 from 3 at the time that he was diagnosed with metastases. He underwent restaging scans at 4 additional time points and has no radiographic evidence of lung nodules, liver masses, or any lymphadenopathy suspicious for cancer. He demonstrates normal renal and liver function, no skin discoloration and there is no evidence of myelosuppression on repeated testing. During this period, he underwent facial reconstruction surgery with flap repair and wiring of left medial canthus. He had no problems with anesthesia or wound healing.

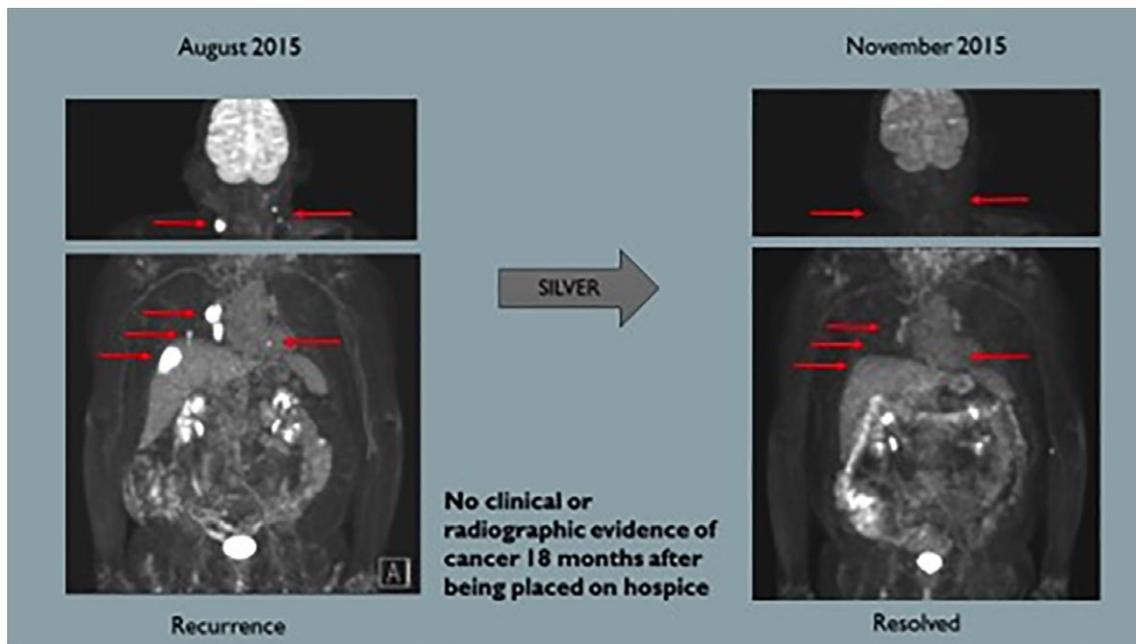
**August 2015**



**November 2015**



**FIGURE 2** PET scans from August 2015 show increased FDG uptake in the liver and right hilar lymph node suspicious for metastases (left). Repeat PET in November 2015 after consumption of silver therapy shows complete resolution of these FDG avid areas (right)



**FIGURE 3** Radiographic appearance of metastases at initiation of hospice and subsequent resolution after AgNP therapy

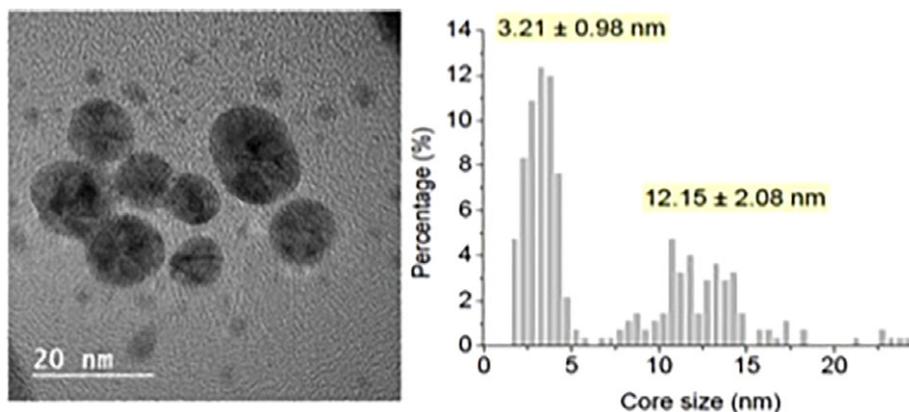
### 3 | DISCUSSION

In the 20th century, colloidal silver was available in food stores and marketed for a spectrum of infectious etiologies and multiple diseases, including cancer, HIV, and diabetes. It was further promoted as an essential mineral that enhances immunity, resulting in a decreased risk of cancer, although no scientific studies ever substantiated this claim. In 1992, the Food and Drug Administration removed colloidal silver from the over-the-counter market given inadequate data regarding its effectiveness and potential risks.<sup>7</sup> However, distribution of colloidal silver for consumption and instructions on preparation of such a solution remains widely available over the Internet, and continues to be promoted for a variety of conditions.

Silver's purported health benefits have been described for millennia, yet there is a lack of data on the medical implications of silver consumption in patients with cancer. In the 5th century

BCE, Herodotus described kings using silver containers to keep water fresh, whereas Avicenna used it to treat halitosis and palpitations.<sup>8</sup> Topical silver use has persisted through modern times as it is safe and effective for wound healing and ophthalmia neonatorum.<sup>9</sup> Oral toxic ingestion of silver shows a spectrum of symptoms, although the degree of potential harm and the length of exposure required to cause such adverse effects remains unclear.<sup>7–9</sup> Medical literature on the proven efficacy and associated risks for oral ingestion remains lacking.

AgNP activity against several cancer cell lines has been evaluated. These AgNP have been found to have antiproliferative properties while simultaneously serving as a vehicle for chemotherapy delivery to neoplastic cells.<sup>10</sup> In addition to the effect on p53, preclinical studies also suggest a possible mechanism of action against cancer by autophagy activation and accumulation of p62 which leads to defective autophagy.<sup>11</sup> The use of AgNP to eradicate a variety of human



**FIGURE 4** Electron microscopy of the silver solution (left) and bimodal distribution of nanoparticle size (right)

cancer cell lines, including lung cancer, leukemia, cervical cancer, and breast cancer, has proven to be promising.<sup>10,12–14</sup> However, there remains limited data examining the efficacy of this compound in patients with cancer.

Spontaneous regression of cancer is a rare phenomenon that has previously been documented, although mechanisms remain unclear. We consider the possibility of spontaneous regression in a patient with recurrent and aggressive head and neck cancer, although recognize this phenomenon cannot be confirmed due to lack of biopsy proven metastasis. If this case indeed represents spontaneous regression, to the best of our knowledge, we present the first such case involving distant metastatic head and neck cancer with such an outcome.

Spontaneous regression of malignancy is extremely rare and was first defined as the disappearance of a tumor without treatment or in the absence of a treatment known to be capable of regression.<sup>15</sup> In a review of 741 cases of spontaneous regression from 1900 to 1987, only 14 were found in the head and neck.<sup>16</sup> Of these cases, 5 were adenoid cystic carcinoma, 3 were squamous cell carcinoma without further specification of location, and the remainder lacked pathologic identification. Furthermore, a review of the outcomes of 808 patients with untreated head and neck cancer explicitly mentioned no cases of spontaneous regression.<sup>17</sup> The literature thus supports the idea that this phenomenon remains extremely rare in head and neck cancer.<sup>17</sup> After these review articles were published, there has been one report of spontaneous regression of squamous cell carcinoma of the tongue with lymph node metastases.<sup>18</sup> However, our patient receiving AgNP would, to the best of our knowledge, be the first reported case of spontaneous regression of head and neck cancer involving distant metastases.

A limitation of our work is the lack of biopsy confirming the presence of distant disease. However, an alternate diagnosis was found to be highly unlikely on radiographic review in the setting of an aggressive cancer with multiple recurrences. This led to a clinical decision at the time to defer pathological confirmation. Another limitation is that we have not yet identified the active form of AgNP in the serum, by which we may confirm activity in cancer cell lines and animal experiments.

#### 4 | CONCLUSION

In conclusion, the close temporal relationship of this patient's AgNP ingestion with complete and sustained regression of cancer suggests, though is not conclusive, that AgNP may exert some anticancer effect. Given these dramatic results that may be attributed to AgNP in conjunction with strong preclinical data, further testing of AgNP should be done to confirm its safety and efficacy in head and neck cancer.

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#### DISCLOSURE OF INTERESTS

The authors have nothing to disclose.

#### ORCID

Jasmine Singh  <https://orcid.org/0000-0001-6994-8527>

Saad A. Khan  <https://orcid.org/0000-0002-3440-9774>

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