

REVIEW

Autologous fat grafting in the face and neck: Multinational trends and knowledge of the safety, applications, and indications considering oncologic risk potential

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Abstract

Background: Autologous fat grafting (AFG) is evolving in both aesthetic and reconstructive applications, since the body of evidence for its use has expanded. The earliest controversies were evident in lipofilling for oncological breast reconstruction, and to this day, some countries do not allow it for fear of inducing tumorigenesis in an oncologically ablated field.

Methods: We sought to review contemporary harvesting and processing techniques for AFG in the craniofacial region, therefore distributed a survey to evaluate the clinical impact of oncological risk across four European countries.

Results: We found no significant geographical differences between the German-speaking and the English groups concerning their harvesting and processing technique. Half of our respondents discuss the possibility of pro-oncologic behavior of AFG.

Conclusion: AFG harvesting and processing techniques do not considerably vary by geography. Further studies should evaluate oncologic risk potential of AFG in head and neck tumor sites, especially because there is no excellent article regarding this phenomenon.

Level of Evidence: V

KEYWORDS

face, fat, grafting, head and neck cancer, oncologic risk with fat grafting, oncological safety

1 | INTRODUCTION

Autologous fat grafting (AFG) is used both in aesthetic and reconstructive surgery. Neuber described fat transfer in retractile scarring and published successful outcomes.¹ In recent decades, this technique has been used increasingly since the development of modern liposuction techniques in the 1980s by Illouz.^{2,3} The technique of harvesting

and processing, expanded applications and fat transfer is now commonly used in the head/face and neck.^{4,5} Coleman provided a comprehensive description of techniques in the 1990s, and in recent years the scientific basis of the regenerative effects of fat grafts is progressing.^{6,7}

Adipose tissue has notable plasticity and has endocrine function.⁸ A lipoaspirate of fat tissue contains an aqueous fraction, the stromal vascular fraction (SVF), which is a combination of preadipocytes, endothelial

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precursor cells, endothelial cells, macrophages, smooth muscle cells, lymphocytes, pericytes, and adipose-derived stem cells (ASCs).⁹ The latter have the potential to differentiate into numerous cell lines comparable with mesenchymal stem cells.^{9,10} ASCs are involved in biologic pathways of inflammation and tumor environment.⁷ ASCs have been ascertained to promote angiogenesis and further showed elevated pro-oncologic behavior in xenografts.^{10,11} The applications also have expanded beyond physical “contouring and space-filling” to regenerative applications that address radiation injury, abnormal scarring, improving aged skin, and managing varieties of skin injury such as burns.^{2,9,12}

The worldwide incidence of head and neck cancer (HNC) is more than 550 000 cases with around 300 000 annual deaths. About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC). HNSCC is the sixth leading cancer by incidence worldwide.^{13,14} About one third of these patients present with low stage disease (T1-2, N0), therefore radiation or surgery protocols are available for treatment. Higher stage disease in HNC requires postoperative chemoradiotherapy¹³ resulting in treatment sequelae like a cosmetic burden,¹⁵ trismus, radiotherapy-induced neck fibrosis,¹⁶ and radiodermatitis, further skin irregularities, and lymphedema.¹⁷ AFG can address these complications after successful treatment. The safety of AFG is largely accepted, but attitudes differ where and the anatomical region to be treated has previously been ablated for cancer.⁸

Unlike breast surgery, it is not clear what current attitudes and trends are in facial fat grafting in the postcancer treatment patient, for example, postradiation injury, contour defect, or chronic neck lymphedema. We aimed to try ascertaining attitudes in this respect and whether these attitudes are reflected in the evidence base for these procedures. We recognize there are no English or German published guidance, health care system based or otherwise, to guide the treating teams.

2 | MATERIALS AND METHODS

2.1 | Autologous fat grafting

2.1.1 | Applications and Indications of autologous fat grafting

Fat grafting has a number of monikers and this article will use the term AFG. Applications of AFG are broad and treatable regions are various. A variety of clinical problems have been treated using fat, including postoncological contour defects, scar therapy, connective tissue disease, postradiation skin injury, chronic lymphoedema, facial and body asymmetries of the soft tissues and in complex/simple burns.^{12,18} Ultrastructural analysis of radio-damaged tissue showed a significant reduction of the capillary bed, where AFG has shown to enhance tissue hydration, the induction of blood vessel formation and increased local regeneration of damaged tissue.¹⁹ Furthermore, AFG can be of use in the treatment of the microangiopathic patient.^{19,20} AFG, therefore, is beneficial for patients with volume loss due to the natural process of ageing, disease, trauma, congenital defects and it improves skin quality, tissue quality, and scars and further gives enlarged volume in the treated region.²¹

In HNC, squamous cell carcinoma HNSCC is the most common and frequently requires surgical ablation plus radiotherapy. This oncologic treatment can often lead to major functional impairment, lymphoedema, and radiation-induced soft tissue changes inducing neck lymphedema and radiation injury and a restriction of function, and in facial cancer ablation, contour defects.^{22,23}

Fat grafting first gathered prominence in the aesthetic area,²⁴ and subsequent study showed it had a favorable complication profile compared to synthetic filler materials.^{25,26}

However, there remains a weak consensus on the optimal conditions of fat aspiration, processing, and injection that confers a greater “take” in aesthetic applications.^{25,27-29} Further, the amount of infiltrated fat in the face is not yet standardized.²⁴ Moreover, due to the chronicity of radiation injury in HNC treatment, the optimal time of treatment is not clear, and what is the exact change in the irradiated skin microenvironment.^{2,30}

2.1.2 | Fat tissue, harvesting techniques, and processing of fat graft

Adipose tissue is remarkably complex and has a profound role in nutrient homeostasis and is, due to adipose-derived serum factors like adipin, TNF- α and leptin seen as a separate endocrine organ.³¹ Fat tissue has a necessary role in thermogenesis and insulation and protects important organs like the eyes mechanically.⁸ Fat tissue consists of a high quantity of cell types. Aspirated fat contains an aqueous fraction, the stromal vascular fraction (SVF).⁹ SVF contains a number of regenerative cells, in high numbers of ASCs, which can differentiate into adipocytes, fibroblasts, neurons, and muscles.^{8,9} Zuk et al found regenerative and stem cells in the SVF of fat.³² These SVF cells have been shown to have regenerative effects, like angiogenesis and reduction of inflammation in facial aesthetics. There are reports on regenerative effects on elastin and collagen fibers and an elevation of capillary density.³³

Every step in the process of AFG from the choice of the donor site, donor site preparation, to harvesting over processing to injection has the potential to influence graft outcome and volume retention.²⁹ Tuin et al analyzed 35 studies to identify the optimal processing technique. Their outcome was adipocyte viability, ASC survival and growth factors in vitro, the volume of the graft in animal studies and volume retention in human studies. They discovered no superior processing technique could be identified based on clinical outcome.³⁴ Lee et al found no differences in histology and weight with high vs low aspiration pressure in lipoaspirates injected in nude mice. Shear stress had a high impact on graft viability, therefore slowly injected fat grafts outperformed injection with high shear stress.³⁵

2.1.3 | Risks and oncologic potential of AFG

Fat grafting does carry a risk of intraluminal injection causing necrosis and infarct of the end organ tissue, which in the head and neck can be devastating and there are numerous reports of blindness, facial skin

loss, fat embolic syndrome, and cerebral infarct.³⁶⁻³⁸ Although AFG is used as a successful technique for aesthetic and reconstructive approaches, the oncologic safety stays unclear and is discussed controversially in literature.^{6,10,39} Due to oncologic risk potential of AFG in head and neck, Karmali et al who solely addressed this phenomenon as a sub topic, found no evidence for an association with cancer recurrence.⁴⁰

The evidence overall is lacking, and there is no specific research respectively addressing the oncologic risk profile of AFG in the head, face, and neck. Some publications concentrated on the general complications of AFG in the head, face, and neck, and stated a low rate of minor complications.^{5,41,42} Since there is no specifically addressed interest in oncologic potential of AFG in head and neck, it is necessary to orientate toward given evidence. ASCs have been shown to, in vitro, harbor pro-oncological and regenerative influences.³⁹ However, fat grafting and ASCs have not been shown to drive cancer growth in clinical reality, several studies with big cohorts showed no evidence for an elevation in oncological risk in AFG.⁴³⁻⁴⁵ Donnenberg et al suggested that ASCs support growth in active breast cancer cells. Silva et al found no evidence for clinically relevant elevations in tumor size, proliferation, histologic grade, or metastasis in AFG breast reconstruction in an animal model.⁴⁶ To the contrary, Mazur et al found no indication for a higher breast cancer risk in ASCs augmented fat in postcancer mastectomy and radiation patients.⁴⁷

Given the evidence, there seems to be a gap between in vivo and clinical studies. Whereas Yu, Muehlberg and Karnoub et al published rapidly growing tumor cell lines in the cultural combination with murine ASCs, clinical studies seem to show no evidence of cancer growth in AFG treated regions.^{39,48-50}

2.2 | AFG Survey

We conducted a survey to ascertain if there are differences in surgical cultural beliefs toward the safety of fat grafting in patients treated for head, neck, and facial cancer. A German online survey-softwaretool ©soscisurvey.de⁵¹ was used and distributed by email, and via national associations, to head and neck surgeons working in Germany, Switzerland, Austria and UK in the field of Plastic surgery, maxillofacial surgery and Otorhinolaryngology. The participants had the option to take the survey in German or English. Questions centered around the applications, indications, safety, and their personal preferences for AFG (Table 1). We chiefly aimed to determine if a wider European attitude to AFG in the head and neck mirrored that in breast reconstructive practices post cancer fat grafting.

3 | RESULTS

In our survey, there were 24 German and 21 English-speaking respondents.

TABLE 1 Autologous fat grafting survey questionnaire ©Soscisurvey.de, a free tool for online surveys

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Do you have experience with autologous fat grafting of the head/neck and face? | (A) Yes (B) No |
| How many of these procedures do you perform annually? | (A) under 10 (B) 10-50 (C) 50 and more |
| Do you use fat grafting for Aesthetic facial contouring? | (A) Yes (B) No |
| Do you use fat grafting for Benign acquired pathology such as HIV lipodystrophy, craniofacial anomalies, facial differences, or scar treatment? | (A) Yes (B) No |
| Do you use fat grafting for post cancer facial contouring, post cancer radiation treatment for facial/neck function? | (A) Yes (B) No |
| In your practice, please rank the main indications for fat grafting ¹⁻³ ? | (A) Aesthetic facial contouring (B) Benign acquired pathology such as HIV lipodystrophy, craniofacial anomalies, facial differences, scar treatment (C) Post cancer facial contouring, post cancer radiation treatment for facial/neck function? |
| What technique do you typically use to harvest your fat? | (A) vacuum aspiration as low negative pressure aspiration (B) Syringe aspiration: (a) Fine needle <0.7 mm (b) Cannula >1 mm; (c) surgical excision |
| How do you process the fat before you infiltrate it? | (A) Centrifuge (B) Manual (free text to describe) |
| Do you discuss with patients the theory of adipose derived stem cells potentiating neoplasia in a patient treated for facial, head, and neck cancer? | (A) Yes (B) No |
| Do you see an elevation of cancer risk as a possible adverse effect of autologous fat grafting in treated cancer patients? | (A) Yes (B) No |
| Have you ever experienced a cancer recurrence or a newly developed cancer in a facial region, where autologous fat has been injected before? | (A) Yes (B) No |
| Are you aware of any studies or reports of cancer recurrence following fat grafting? | (A) Yes (B) No |

Most of our responses came from Plastic and reconstructive surgeons [43/45; 95.5%] (see Figure 1), two Otorhinolaryngologists participated in and completed our questionnaire.

Nearly all of the participants declared experience with autologous fat grafting [42/45; 93.6%] whereas only three colleagues [3/45; 6.6%] had no experience with fat grafting. As shown in Figures 2, 38% [17/45; 37.7%] of the responders stated an AFG-use under 10 times a year, nearly half [21/45; 46.6%] stated the usage of 10 to 50 times per year and 14% [6/45; 13.3%] were frequent users of fat grafting (>50/year).

We observed common usage for aesthetic in 84% of respondents [38/45; 84.4%]. Further, a representative part of the participating colleagues [28/36; 62.2%] uses AFG for benign acquired pathologies such as HIV lipodystrophy, craniofacial anomalies, facial asymmetries, or scar treatment. Of particular interest, nearly two-thirds of our sample [28/36; 62.2%] do use AFG for postcancer facial contouring or radiation-induced fibrosis treatment for facial/neck function.

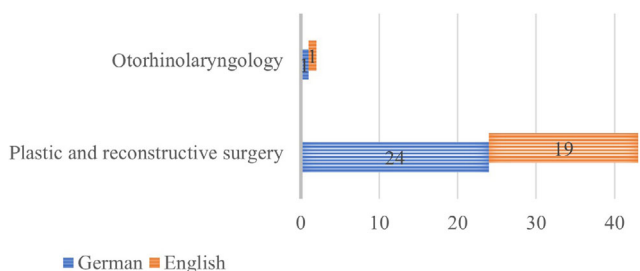
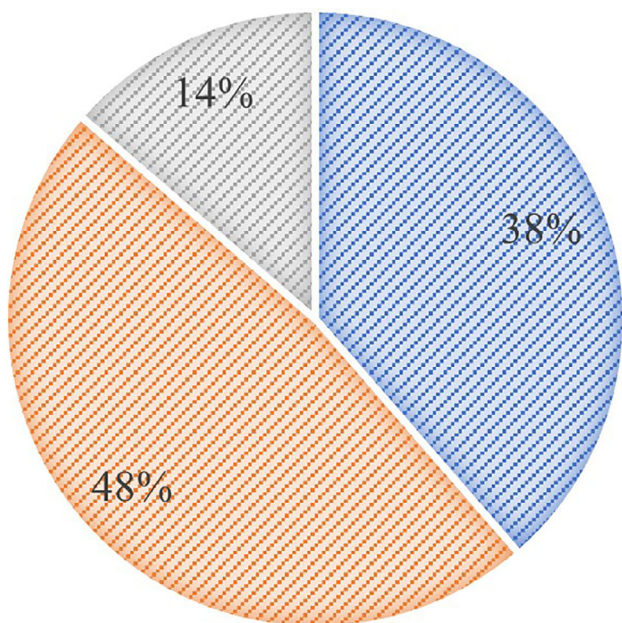


FIGURE 1 Respondents language and specialty



- Under 10 times a year
- Between 10 and 50 times a year
- 50 and more times a year

FIGURE 2 Annually performed autologous fat grafting

As presented in Figure 3, we asked how the participating surgeons rank the indications for AFG in their practice. Based on 37 valid answers in the survey, 60% deemed “aesthetic facial contouring” as the most important AFG application [22/37; 59.6%], a further 25% [9/37; 24.3%] ranked “postcancer facial contouring, postcancer radiation treatment for facial/neck function” their most common indication.

Concerning harvest technique (see Figure 4), the majority use Syringe aspiration with a fine needle/cannula 1 mm or greater [24/45; 53%], by the use of Vacuum aspiration with low pressure [17/45; 37.7%]. A few surgeons favor syringe aspiration with fine needle with a lower diameter than 0.7 mm [4/45; 9%]. Interestingly, nobody of our survey cohort works with surgical excision in AFG applications [0/45; 0%].

Nearly half of our colleagues process their harvested tissue by centrifugation [20/43; 46.5%], and the remainder (54%) had variable practices (see Table 2).

As demonstrated in Figure 5, nearly half of our survey participants [20/42; 47.6%] do not discuss the scientific conjecture around

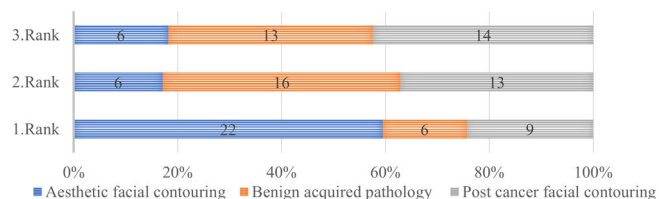
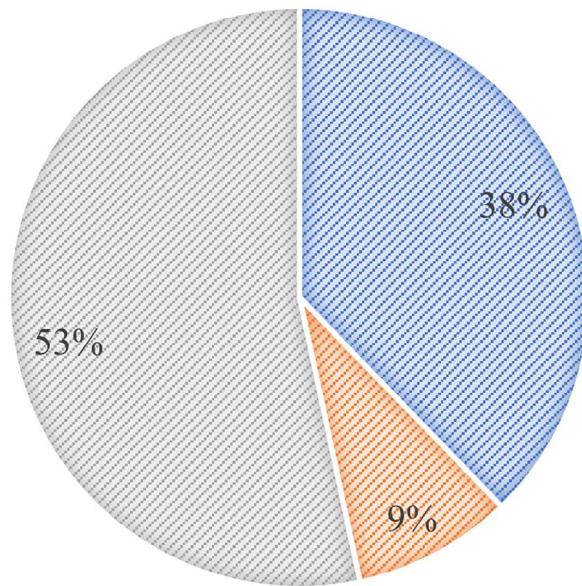


FIGURE 3 Ranks for applications of autologous fat grafting



- Vacuum aspiration with low pressure
- Syringe aspiration-fine needle < 0.7 mm
- Syringe aspiration > 1 mm

FIGURE 4 Autologous fat grafting harvesting techniques

possible oncological stimulation and neoplastic potentiation by ASCs, in the fat graft matrix. This correlates with the fact that most respondents do not believe there is an elevated cancer risk with fat grafting in anatomical locations where cancer has been resected, but seemingly a proportion of these clinicians do not even consider it significant enough to discuss the controversies with patients.

Similarly, almost all respondents reported they had not observed new tumor recurrence in the fat grafted bed.

4 | DISCUSSION

Our survey was conducted in four countries because there are no English or German published guidance on AFG in the head and neck to guide the treating teams. Most of our responses came from Plastic surgeons (95.5%), only two Otorhinolaryngologists completed our questionnaire. This response mismatch does not correlate with the count of active surgeons in the fields. There are 1328 active colleagues in Plastic surgery listed in UK and 1498 in Germany, UK counts 1916 ENT-surgeons, whereas Germany lists 2981 active colleagues in ENT.⁵²⁻⁵⁴ Reasonably, we assume a broader use of AFG in Plastic surgery.

TABLE 2 Autologous fat grafting processing techniques (free text)

| Free answers of processing technique | n | %-absolute |
|---------------------------------------------------|---|------------|
| Sedimentation and passive separation by gravity | 6 | 16.2% |
| PureGraft | 3 | 8.1% |
| Decant liquid parts-no centrifuge | 2 | 5.4% |
| Separation of fat and liquid parts in the syringe | 2 | 5.4% |
| mesh washing | 2 | 8.1% |
| Drainage of sediment and nanofat preparation | 1 | 2.7% |
| Strain and irrigate | 1 | 2.7% |

Most colleagues who participated in our survey (46.6%) state a 10 to 50 times a year use of AFG and 14% stated an AFG-use of more than 50 times a year. The frequency of usage of AFG is not yet addressed in the literature. Where the indications have expanded beyond physical “contouring and space-filling” to regenerative applications, we expect an increase of frequency of this application in use soon.^{2,9,12}

Although aesthetic applications of fat grafting in the head and neck seem to be more prominent (84% of respondents), a significant body of our survey respondents use autologous fat in the postcancer treatment setting (62%). In our opinion, this correlates with the fact, that in recent decades AFG is being used increasingly. Responsible for that is the development of modern liposuction techniques in the 1980s by Illouz,^{2,3} further Coleman provided a comprehensive description of techniques in the 1990s.^{6,7} While fat grafting first gathered prominence in the aesthetic area,²⁴ and a subsequent study showed it had a favorable complication profile compared to synthetic filler materials,^{25,26} in recent years the scientific basis of the regenerative effects of fat grafting is progressing.^{6,7}

HNC represents 3 % of all malignant neoplasms, HNSCC is responsible for 90% of these cases.¹⁴ The resulting impairments of craniofacial cancer therapy, surgical reconstruction, and radiotherapy make AFG a very promising and useful tool to deal with scars, irregularities, and radiodermatitis and chronic radiation-induced fibrosis.⁸

Due to harvesting and processing in AFG, the majority use syringe aspiration with a fine needle/cannula 1 mm or greater (53%), and Vacuum aspiration with low pressure (34%). This correlates with a necessary low negative pressure level in aspiration and lower shear stress for the tissue. The perception seems to be, the higher the negative pressure level of liposuction, the higher the level of shear stress to the adipose tissue, reducing fat graft survival.^{6,29,55}

Nearly half of our colleagues process their harvested tissue by centrifugation (46.5%), and the remainder (54%) had variable practices like sedimentation (16%) or pure graft (8%). Only two colleagues use mesh-washing techniques. Tuin et al discovered no superior processing technique could be identified based on clinical outcome.³⁴ The lower count of used washing techniques, in our opinion, may be because mesh-washing techniques are labor intensive and are linked

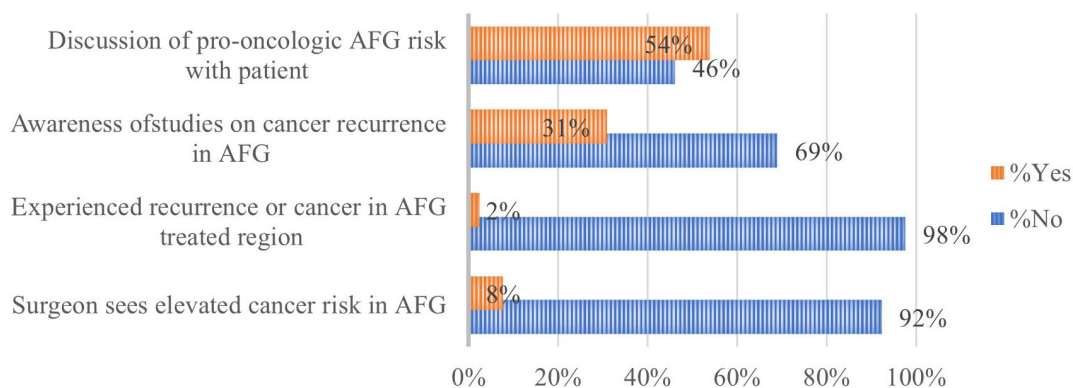


FIGURE 5 Results on elevated pro-oncologic risk in autologous fat grafting (AFG)

with a higher loss of graft material in the process, compared to the easy to use and fast centrifugation.

Nearly half of our survey participants do not discuss elevated cancer risk. On the other hand, only 31% stated knowledge of studies dealing with cancer recurrence following AFG. Moreover, most respondents have never confidently experienced cancer recurrence or newly developed cancer in a previously ablated region, following AFG in head and neck.

The evidence overall is lacking, and there is no specific research respectively addressing the oncologic risk profile of AFG in the head, face, and neck. Due to oncologic risk potential of AFG in head and neck, Karmali et al who solely addressed this phenomenon as a sub topic, found no evidence for an association with cancer recurrence.⁴⁰ Since there is no specifically addressed interest in oncologic potential of AFG in head and neck, it is necessary to orientate toward given evidence.

In several mastectomy studies, fat grafting and ASCs have not been shown to drive cancer growth in clinical reality, several studies with big cohorts showed no evidence for an elevation in oncological risk in AFG.⁴³⁻⁴⁵ Further, studies found no significant evidence for clinically relevant elevations in tumor size, proliferation, histologic grade, or metastasis in AFG breast reconstruction. Most of the current studies dealing with the oncologic risk of AFG refer to breast cancer, further longitudinal shared data sets would be desirable to evaluate a possible pro-oncologic behavior of AFG in the face, head, and neck.

In conclusion, AFG applications, indications, harvesting, and processing techniques do not considerably vary by geography given our data.

And currently, there are no evidence-based studies which would authorize a valid recommendation due to pro-oncological risk of AFG in treated HNC tumor sites. There is a good case to suspect a different behavior of ASCs in breast cancer cells vs HNSCC. Perhaps, we should not consider discussing this complex area of oncogenesis with patients as there is no elevated risk from what we know. However, the bulk of data is for breast carcinoma, which is a different disease to HNSCC, and different tumors could conceivably interact in a different way to ASCs.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Lukas Fiedler: writing, survey design. GER, dispatch GER and analysis GER/EN, revision. Daniel B Saleh: survey design EN, dispatch UK, editing. Alicia Mukrowsky: writing, selection of publications.

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